13ª EDIZIONE
Progetto CANOA

CARCINOMA MAMMARIO:

QUALI NOVITA' PER IL 2023?

"Saper leggere" uno studio clinico per migliorare la pratica clinica

Antibody-drug Conjugates nel Carcinoma mammario

L'inizio di una storia infinita?

Davide Massa

I.O.V.
ISTITUTO ONCOLOGICO VENETO
I.R.C.C.S.

Disclosures

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- **Eli Lilly: travel expenses**

Outline

ADC: the beginning of a never ending story?

- ADC platform: components and mechanisms of action
- The beginning: anti-HER2 and TROP2
- … a never ending story?
    - Fine-tuning the ADC platform
    - Biomarker-driven ADC selection
    - Rational combinatiorial strategies: ADC-combos

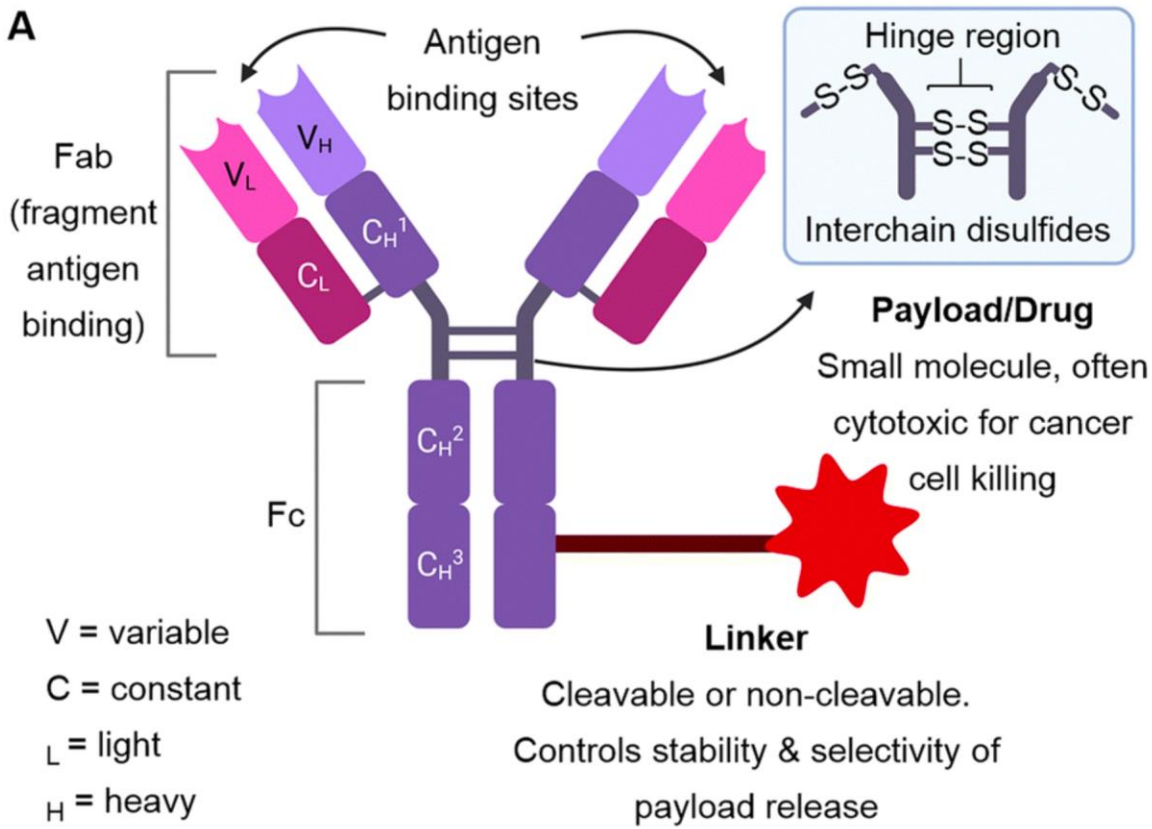
Outline

ADC: the beginning of a never ending story?

- **ADC platform: components and mechanisms of action**
- **The beginning: anti-HER2 and TROP2**
- **… a never ending story?**
  - **Fine-tuning the ADC platform**
  - **Biomarker-driven ADC selection**
  - **Rational combinatiorial strategies: ADC-combos**

ADC platform

Design principle: Improve the therapeutic index of systemic chemotherapy



Antigen

Selective distribution into tumor tissue

Antibody

Linker

Connecting payload to antibody

Payload

Apoptotic cell death

Target-antigen and Antibodies

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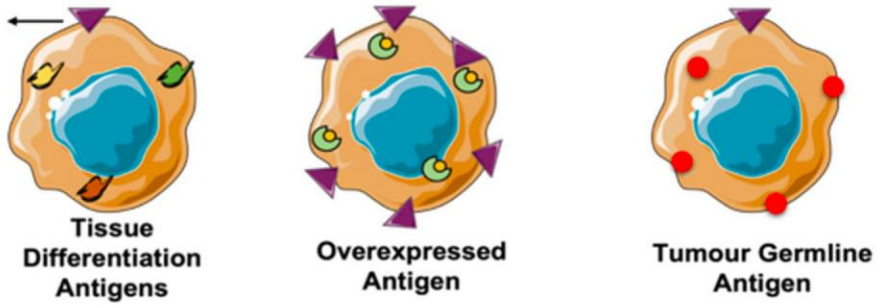
- **Surface expression**
- **Tumor specific antigens / tumor associated antigens**
- **Normal tissue expression**: on target, off-tumor toxicity
- **Internalization properties:** ADC transport into the cell + lysosome processing and degradation influence payload activity
- **Oncogene role**: can influence activity, but not required



Drago J. Nat Rev Clin Oncol 2021; Tolcher Annals 2016

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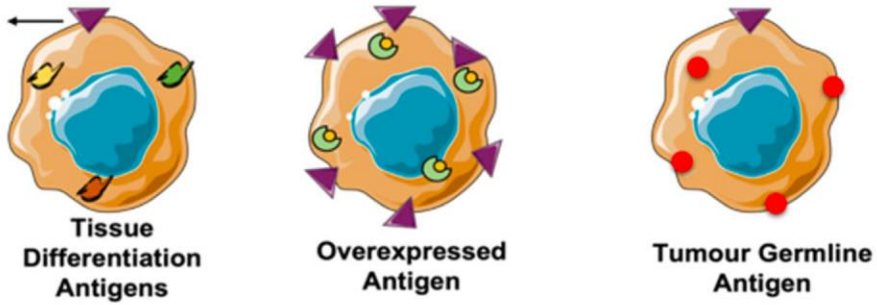


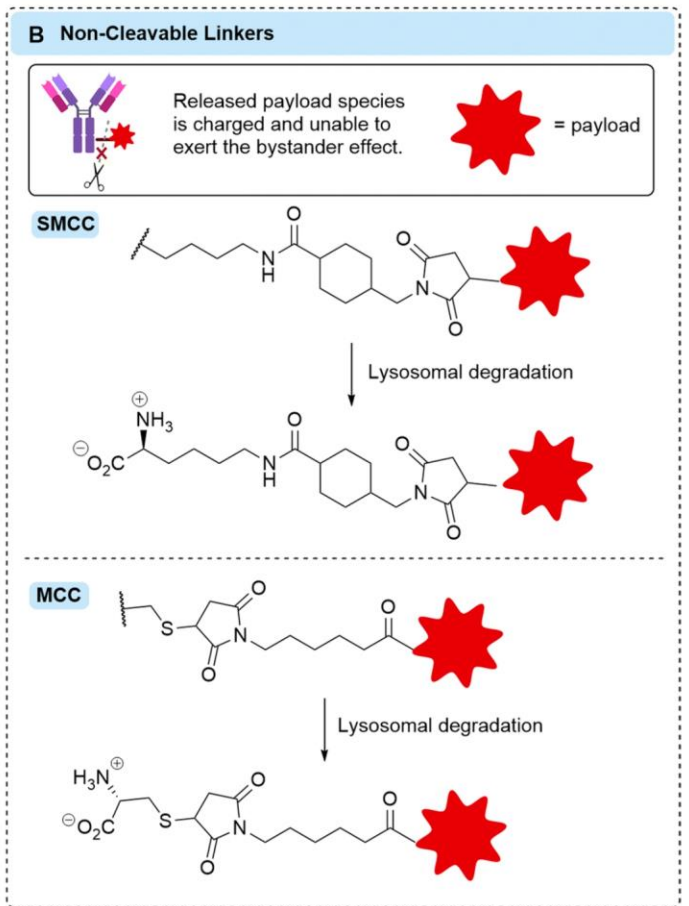
- **Antibody type**: serum half-life, complement fixation and FcR-binding (IgG1 more balanced, IgG3 have low half-life!)
- **Target specificity**: reduced interaction with other antigens
- **Reduced antigenicity** (humanized or fully human)
- **functional activity:** ADCC, ADCP, CDC
- mAb as large proteins: **limited solid tumor penetration**

Antibodies	IgG1	IgG2	IgG3	IgG4
Serum half-life	21 days	21 days	7–21 days	21 days
C1q binding	Yes	Yes	Yes	No
Fcγ avidity	High	Low	High	Moderate

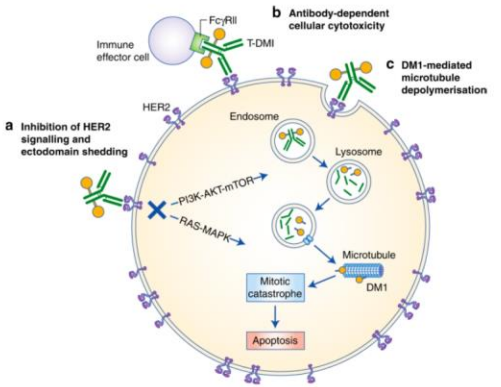
Drago J. Nat Rev Clin Oncol 2021; Tolcher Annals 2016

Linker

- ***Non-cleavable***: <u>plasma stability</u> **but requires lysosomal degradation, retention of charged payload and impact on <u>cell permeability</u>**



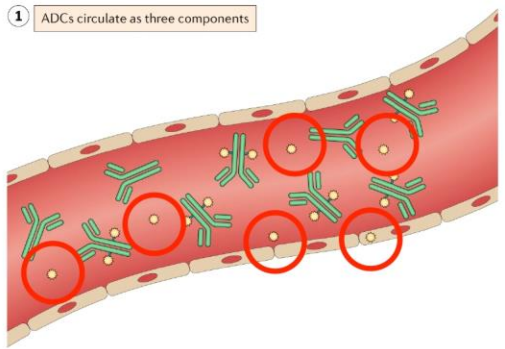
TDM-1

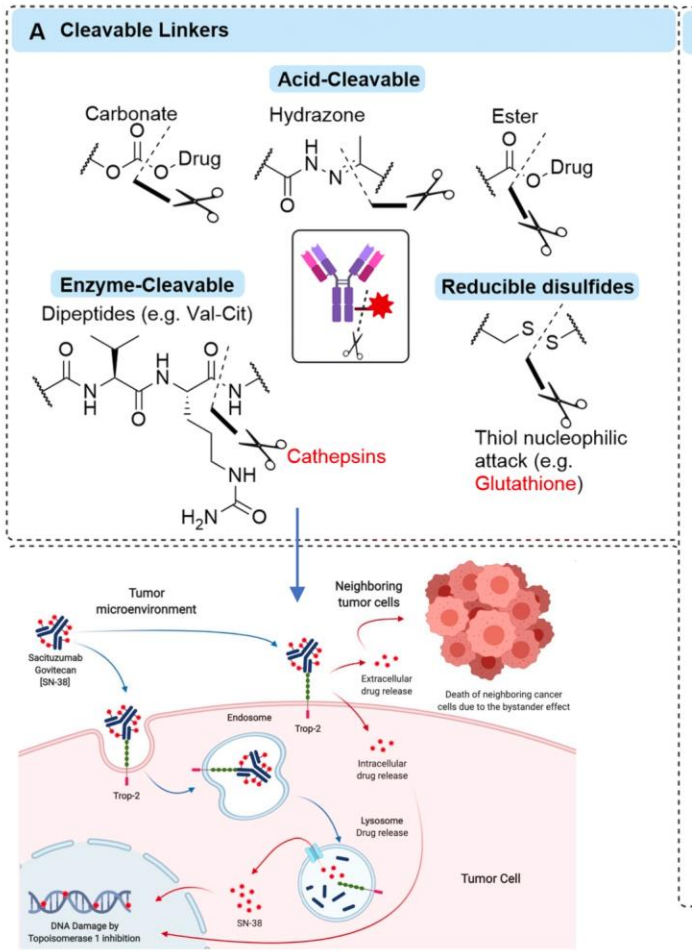


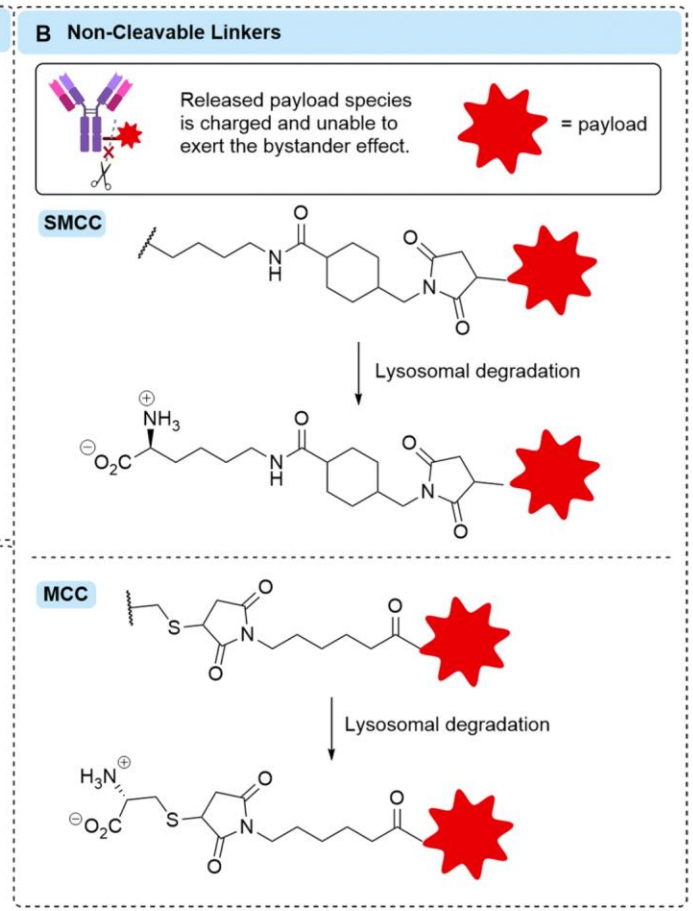
Ashman - 10.1039/D2CS00446A

Linker

- *Non-cleavable*: plasma stability but requires lysosomal degradation, retention of charged payload and impact on cell permeability
- *Cleavable*: higher plasma instability (10-100x increase in circulating unconjugated payload for SG/TDxD compared to TDM-1) but potential for payload release in the TME and transmembrane diffusion (bystander effect)







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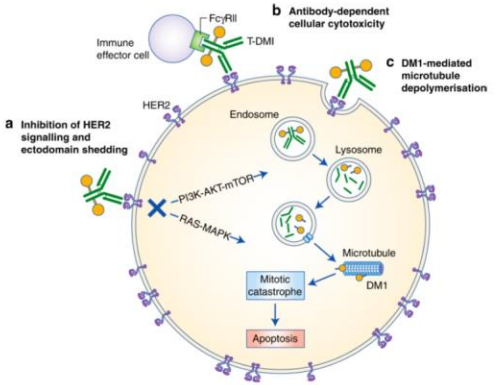
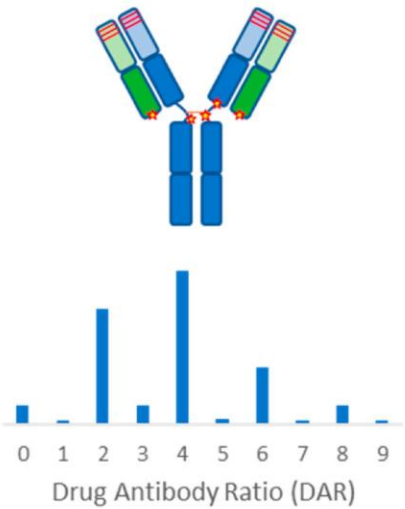


Ashman - 10.1039/D2CS00446A; Tarantino et al. CA 2021

Linker

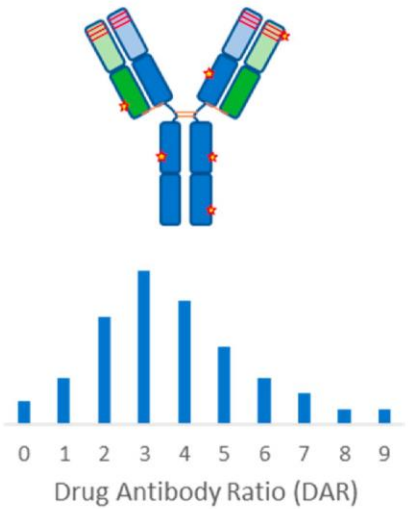
Conjugation chemistry and Drug-antibody ratio

Stochastic



(a)

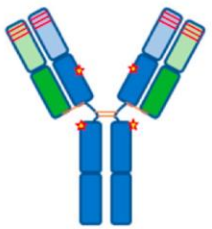
Native cysteines



(b)

Native lysines

Site-specific



⋆ = Site Specific Conjugation
Defined DAR e.g. 2, 4, 6…

- Engineered residues
- Modified glycans
- Enzymatic ligations
- Cross-linkers

(c)

- **Precise and homogenous payload**
- **Improved stability and reduced off-target payload loss**
- **Improved Therapeutic index**

Drago J. Nat Rev Clin Oncol 2021; Tolcher Annals 2016

Potency

- ***Due to large dimension of mAb, their tissue penetration is limited (Only 0.1% of Ab dose reaches cancer cells): higher potency required***

Drago et al. Nat Rev Clin Oncol 2021; Nakada et al. Chem. Pharm. Bull. 2019; Ghassan JCO 2006; Ogitani CCR 2016; Conilh et al - Journal of Hematology & Oncology 2023

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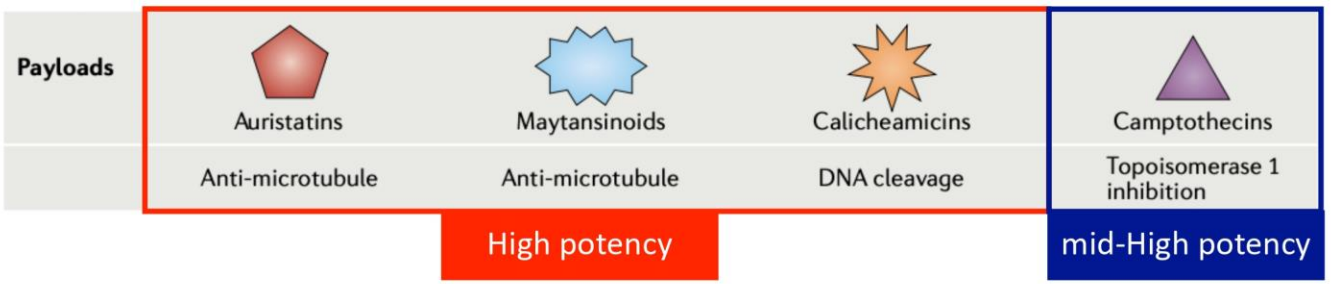

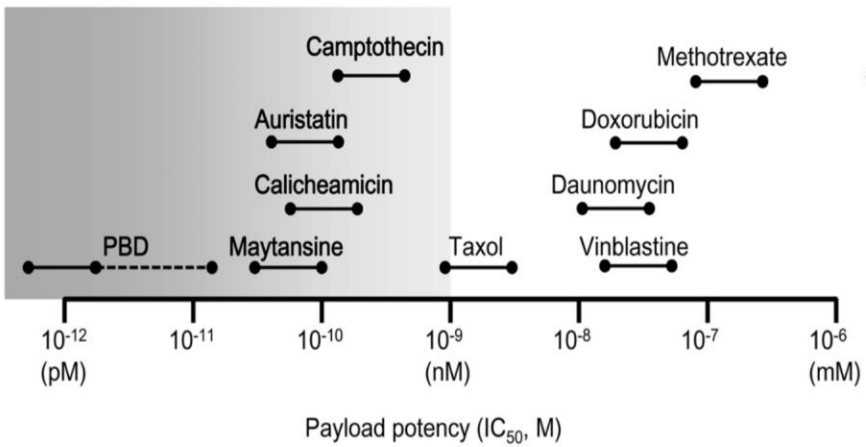

c

DNA topoisomerase I inhibition (IC_{50}, µmol/L)	
SN-38	2.78
DX-8951f	0.25
DXd	0.31

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Payload

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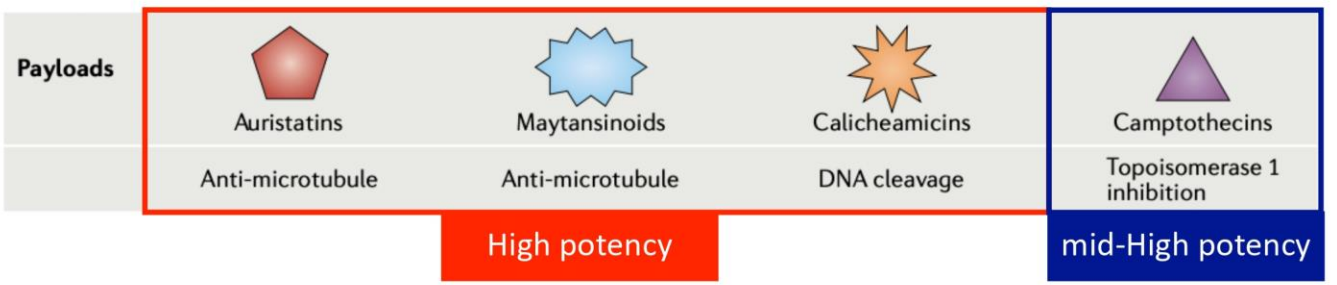
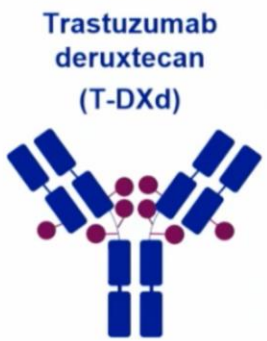


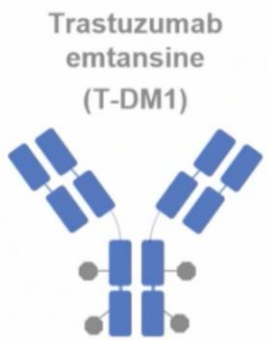
Camptothecins:

- **Mid-high potency**
- **Higher DAR**

HER2 Targeting ADCs with similar mAB Backbone



T-DXd	ADC Attributes	T-DM1
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No



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ADC platform

One of the most complex platform in oncology

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- Target antigen binding
- Tumor/normal tissue expression and Off-target toxicity
- Internalization kinetics and lysosomal trafficking
- Fc effector functions: ADCC, ADCP, CDC

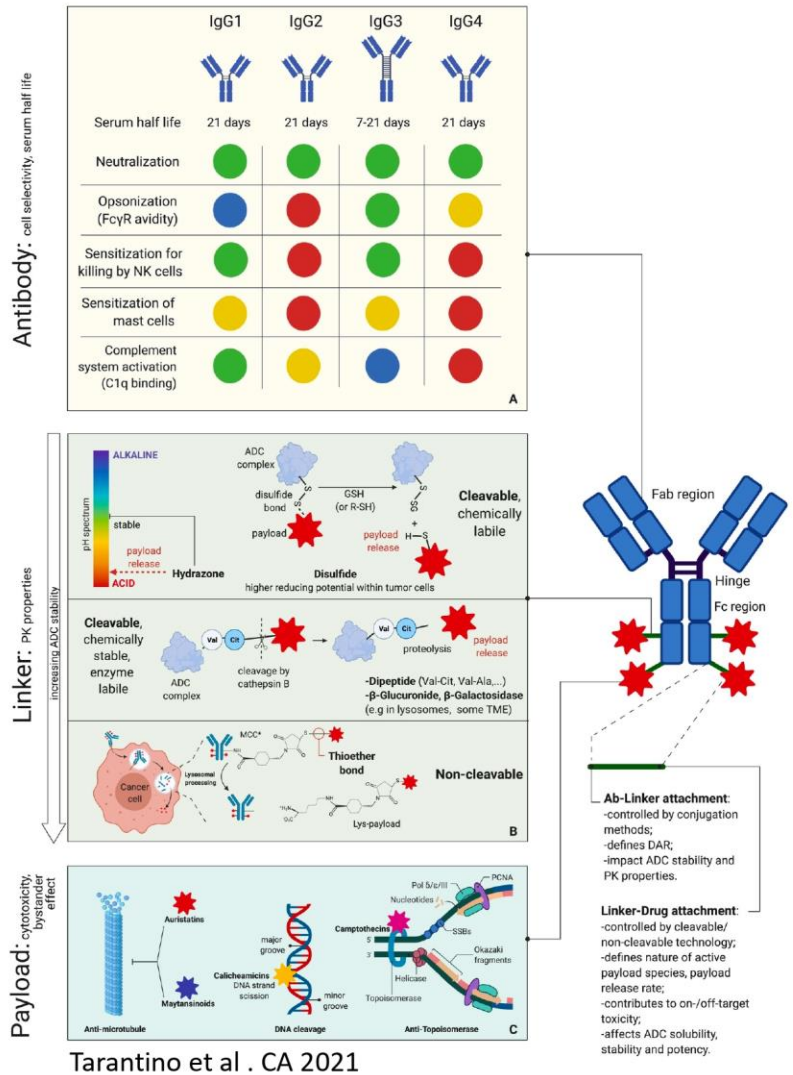
Selective distribution into tumor tissue

- Linker chemistry and Drug-antibody ratio (DAR)
- Control Stability/payload release: bystander effect and off-target toxicity

Connecting payload to antibody

- Warhead-driven cell death: Therapeutic index and Biology-driven payload choice
- Permeability and Bystander effect

Apoptotic cell death

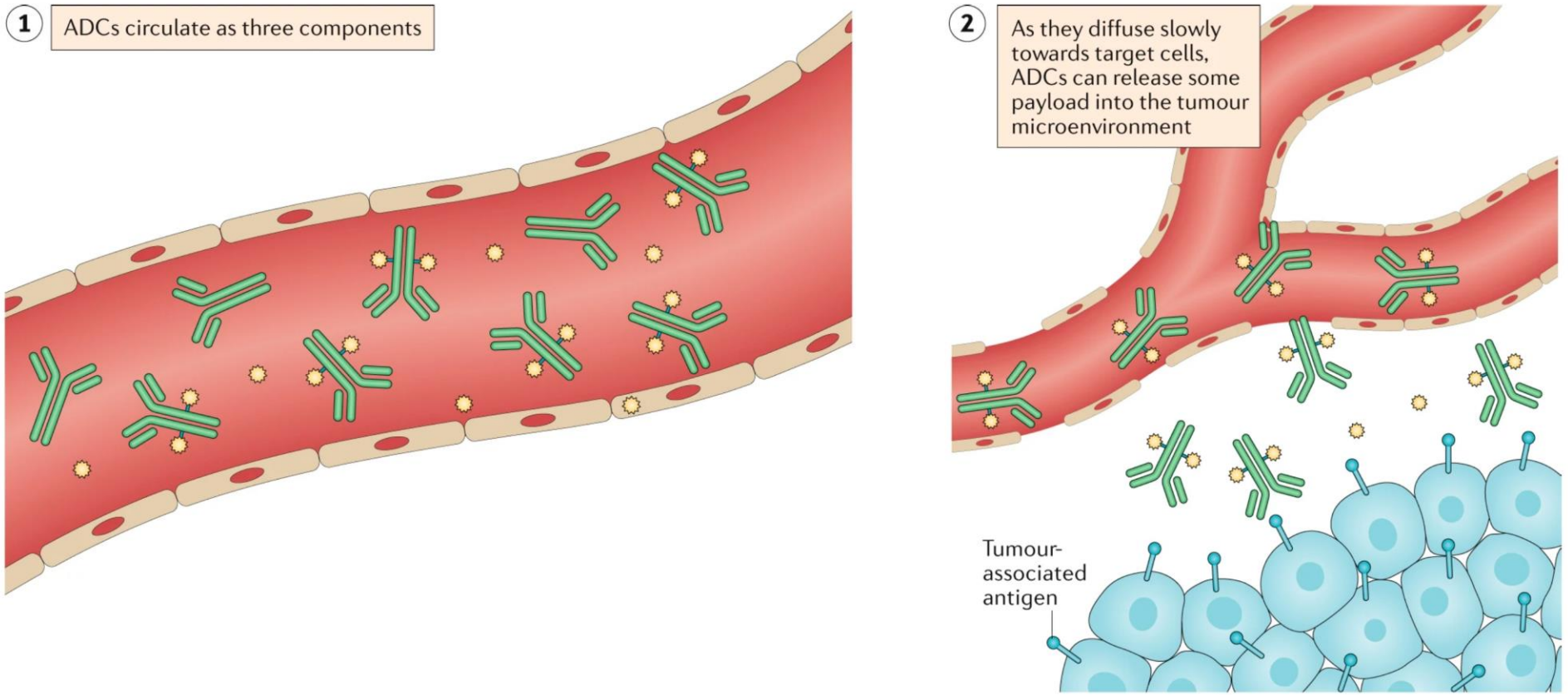


Tarantino et al . CA 2021

Mechanisms of action

ADCs as pro-drugs

- ADCs circulate as admixture of 3 components: naked Ab, free payload and intact ADC (predominant)



Mishra et al - Cancers 2022

Mechanisms of action

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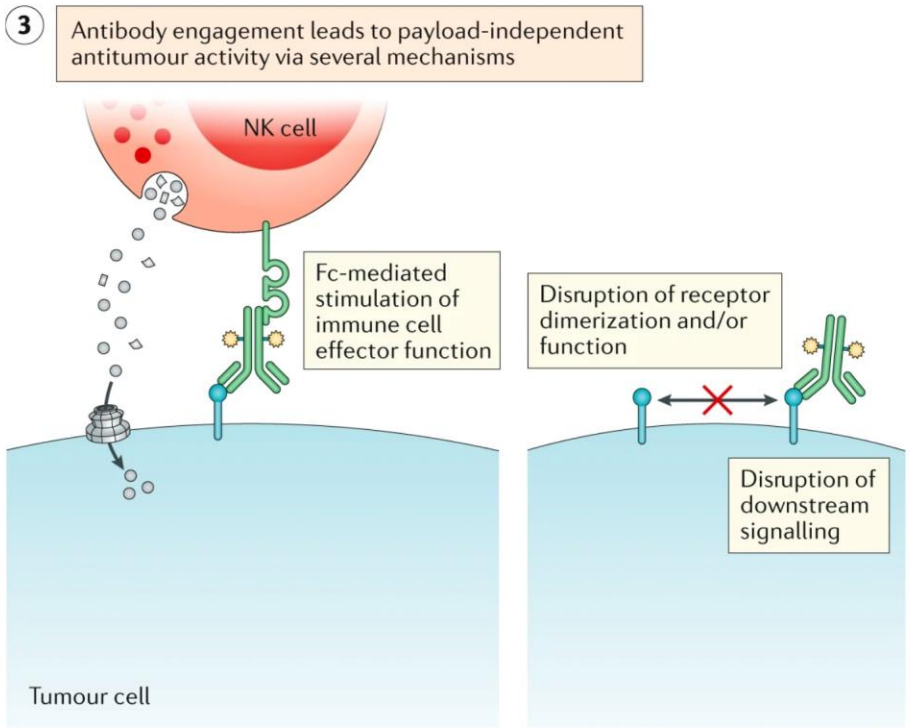
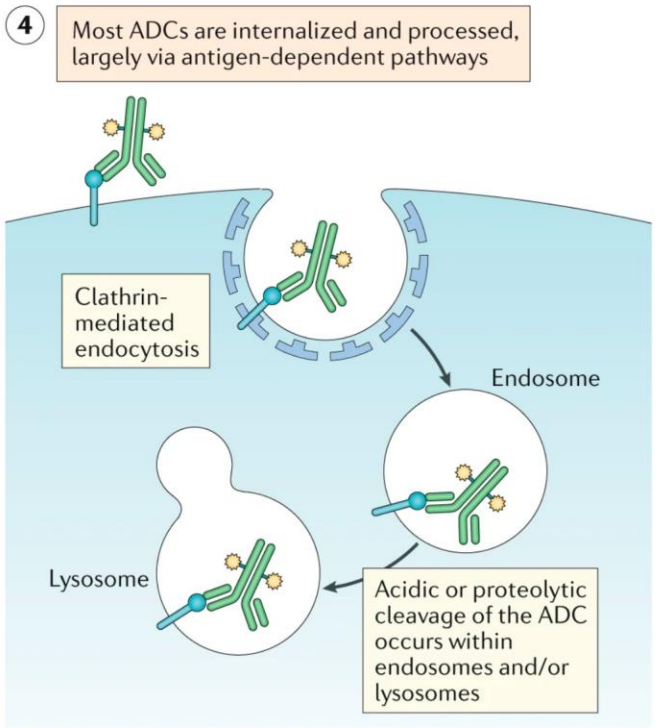
A Combined Endeavor

- Endocytosis of ADCs followed by payload release from Ab carrier into the cytoplasm - antitumor activity
- Payload-independent antitumor activity related to Fc-mediated inmune cells stimulation (ADCC..) and inhibition of antigen-related oncogenicity



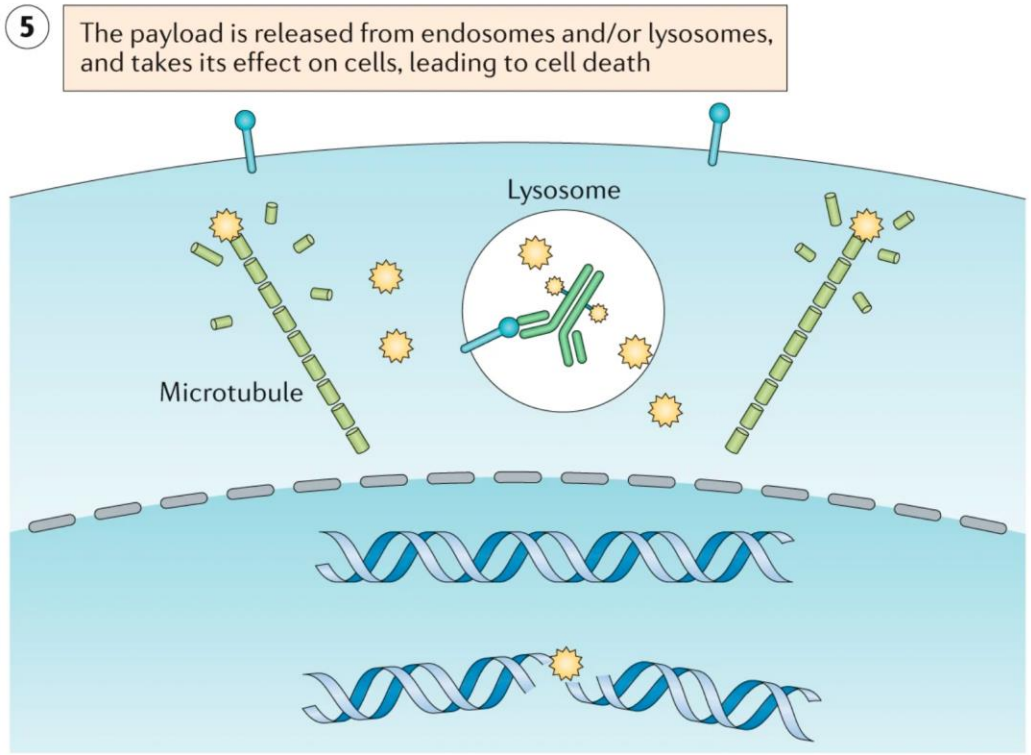


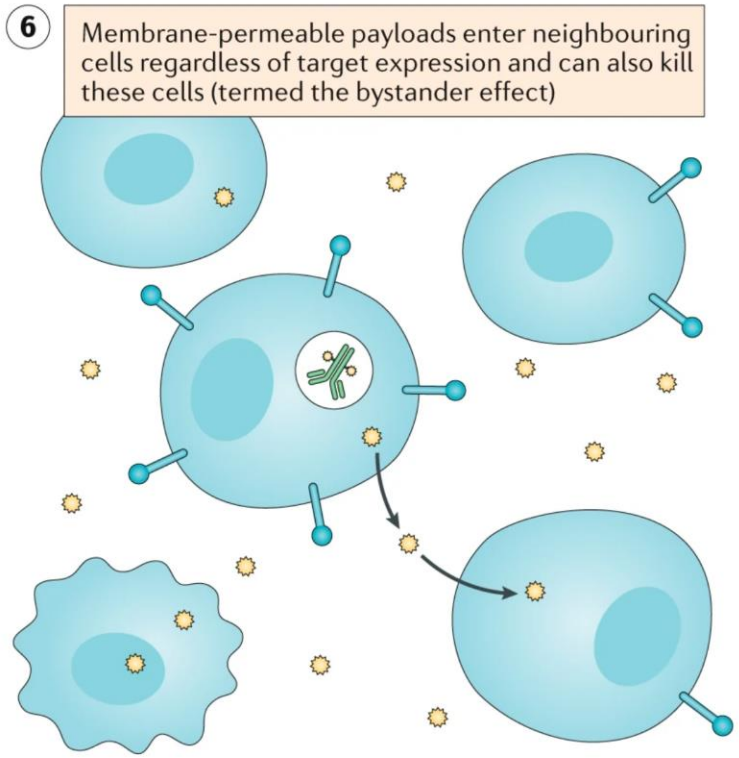
Mishra et al - Cancers 2022

Mechanisms of action

A Combined Endeavor

- **Free payload-dependent antitumor activity when payload is delivered into tumor microenviroment before or after internalization (bystander effect)**





Mishra et al - Cancers 2022

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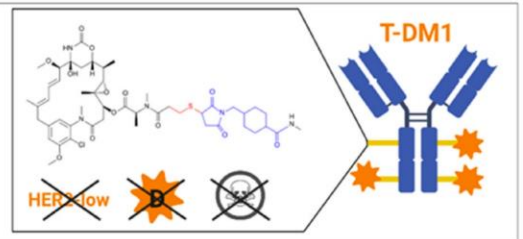
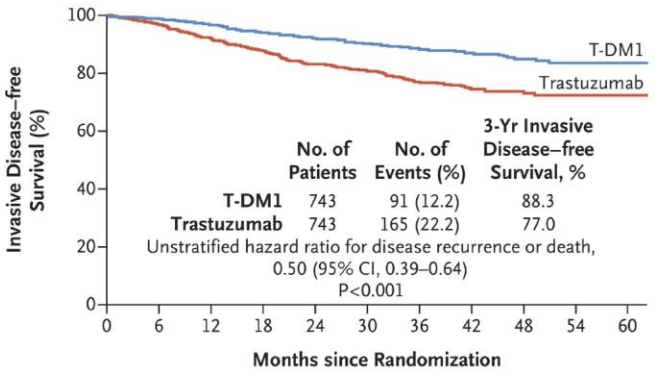
Payload action: Microtubule inhibitor
DAR: 3.5 (mean)



Corti et al - Cancers 2022

		Trial	Phase	Patients	Comparator	ORR	mPFS	mOS	Ref
TDM-1	HER2-positive	KATHERINE	III	1486	Trastuzumab		iDFS: 88% vs 77%	NR	Minckwitz et al. NEJM 2019
		TH3RESA	III	602	TPC	31.3%	6.2 vs 3.3	22.7 vs 15.8m	Krop et al Lancet 2017
		EMILIA	III	978	Lapatinib + Capecitabine	44%	9.6 vs 6.4m	30.9 vs 25.9m	Verma et al. NEJM 2012

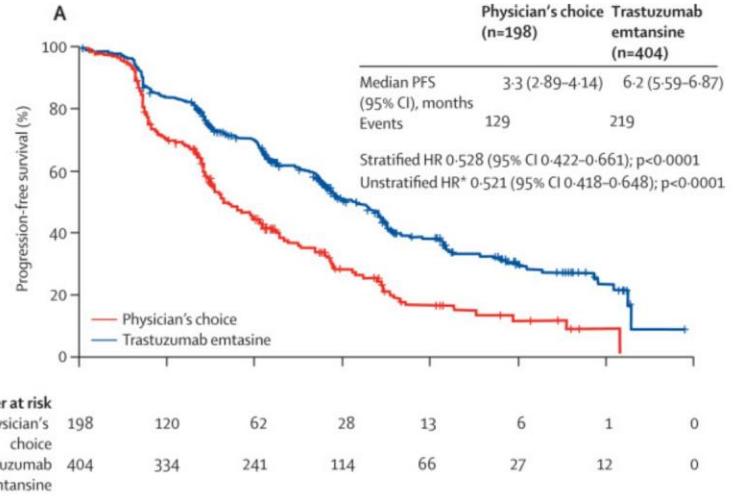
KATHERINE



No. at Risk

T-DM1	743	707	681	658	633	561	409	255	142	44	4
Trastuzumab	743	676	635	594	555	501	342	220	119	38	4

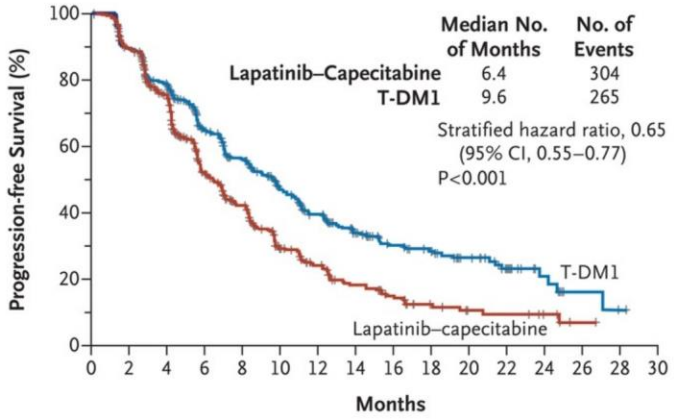
TH3RESA



Number at risk

Physician's choice	198	120	62	28	13	6	1	0
Trastuzumab emtansine	404	334	241	114	66	27	12	0

EMILIA



No. at Risk

Lapatinib–capecitabine	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

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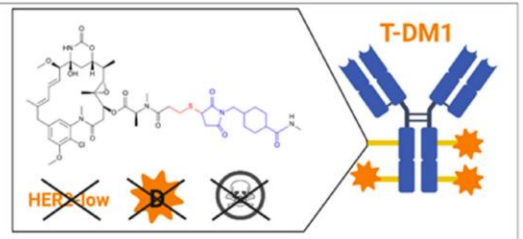

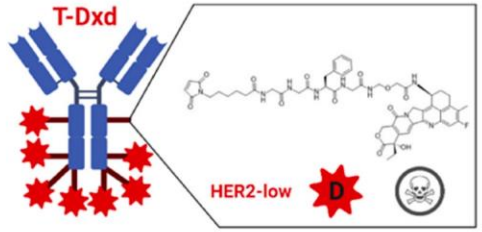

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Payload action: Topoisomerase-1 inhibitor
DAR: 8

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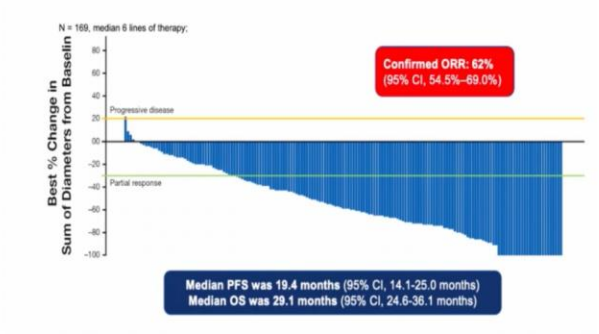
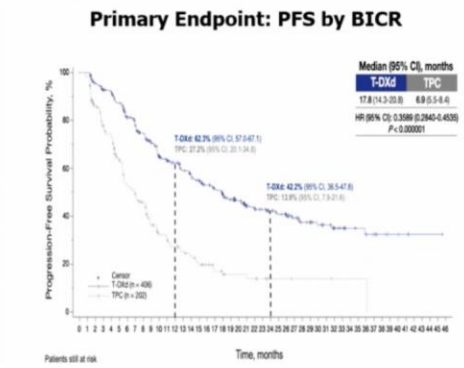
T-Dxd	HER2-positive	Destiny-Breast 01	II	184		60.9%	16.4m	NR	Modi et al. NEJM 220
		Destiny-Breast 02	III	608	TPC (Trastuzumab + Capecitabine / Lapatinib + Capecitabine)	69.7%	17.8m vs 6.9m	39.2m vs 26.5m	Krop et al. SABCS 2022
		Destiny-Breast 03	III	524	TDM-1	79.7%	12m PFS: 75.8% vs 34.1%	12m OS: 94.1% vs 85.9%	Cortes et al. NEJM 2022
	HER2-low	Destiny-Breast 04	III	557 (HR+ 88.7%)	TPC (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel)	HR+: 52.6% HR-: 50.0%	HR+: 10.1 vs 5.4 HR-: 8.5m vs 2.9m	HR+: 23.9 vs 17.5 HR-: 18.2m vs 8.3m	Modi et al. NEJM 2022

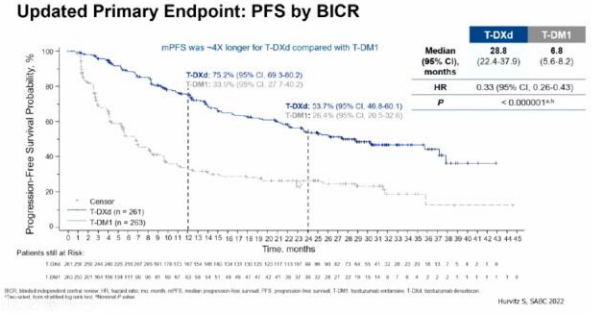
Destiny-Breast 01



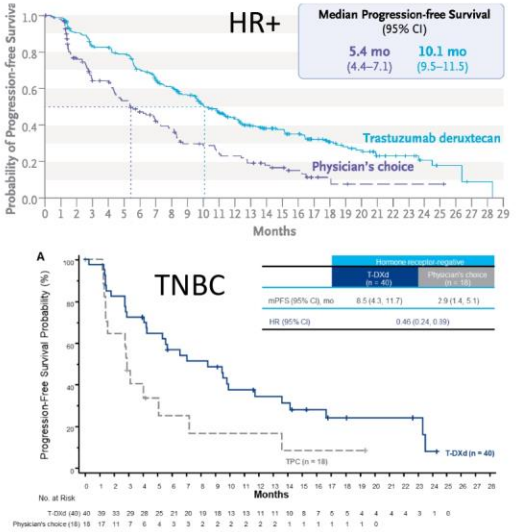
Destiny-Breast 02



Destiny-Breast 03



Destiny-Breast 04



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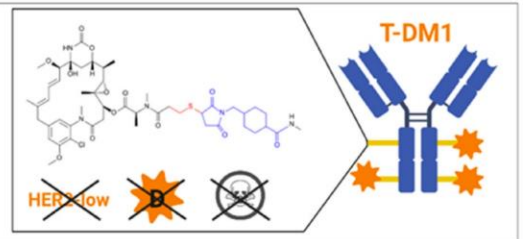
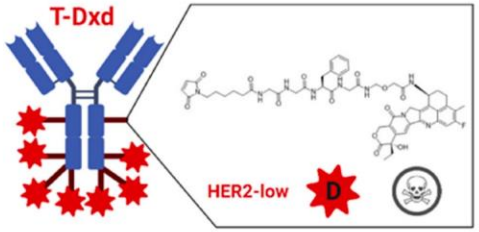
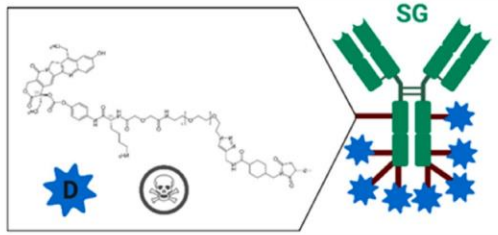
DAR: 3.5 (mean)





Target Antigen: HER2 (trastuzumab vehicle)
mAb isotype: IgG1
Linker type: cleavable
Payload (class): Dxd (Camptothecin)
Payload action: Topoisomerase-1 inhibitor
DAR: 8

Target Antigen: TROP2
mAb isotype: IgG1
Linker type: cleavable
Payload (class): SN-38, active metabolite of irinotecan (Camptothecin)
Payload action: Topoisomerase-1 inhibitor
DAR: 8

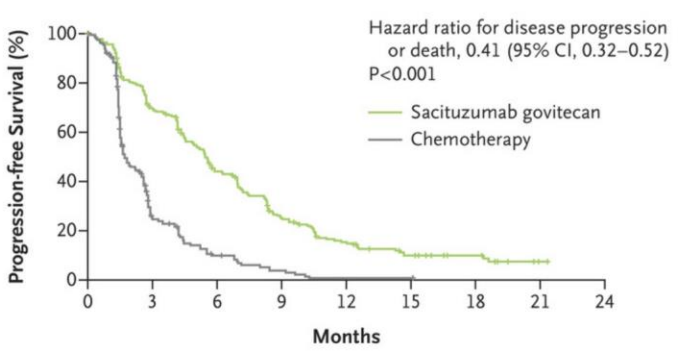


Legend: HER2-low = Targets HER2-low tumors; D = Diffusible cytotoxic moiety; = Bystander killing effect

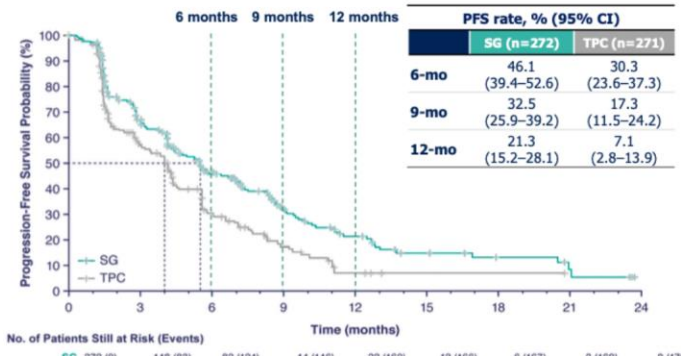
Corti et al - Cancers 2022

		Trial	Phase	Patients	Comparator	ORR	mPFS	mOS	Ref
TDM-1	HER2-positive	KATHERINE	III	1486	Trastuzumab		iDFS: 88% vs 77%	NR	Minckwitz et al. NEJM 2019
		TH3RESA	III	602	TPC	31.3%	6.2 vs 3.3	22.7 vs 15.8m	Krop et al Lancet 2017
		EMILIA	III	978	Lapatinib + Capecitabine	44%	9.6 vs 6.4m	30.9 vs 25.9m	Verma et al. NEJM 2012
T-Dxd	HER2-positive	Destiny-Breast 01	II	184		60.9%	16.4m	NR	Modi et al. NEJM 220
		Destiny-Breast 02	III	608	TPC (Trastuzumab + Capecitabine / Lapatinib + Capecitabine)	69.7%	17.8m vs 6.9m	39.2m vs 26.5m	Krop et al. SABCS 2022
		Destiny-Breast 03	III	524	TDM-1	79.7%	12m PFS: 75.8% vs 34.1%	12m OS: 94.1% vs 85.9%	Cortes et al. NEJM 2022
	HER2-low	Destiny-Breast 04	III	557 (HR+ 88.7%)	TPC (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel)	HR+: 52.6% HR-: 50.0%	HR+: 10.1 vs 5.4 HR-: 8.5m vs 2.9m	HR+: 23.9 vs 17.5 HR-: 18.2m vs 8.3m	Modi et al. NEJM 2022
SG	TNBC	Ascent	III	529	TPC (eribulin, vinorelbine, capecitabine, or gemcitabine)	35%	5.6m vs 1.7m	12.1m vs 6.7m	Bardia et al - NEJM 2021
	HR+/ HER2-	TROPICS-02	III	543	TPC (capecitabine, eribulin, vinorelbine, or gemcitabine)	21%	5.5m vs 4m	13.9 vs 12.3m	Rugo et al - ASCO 2022

Ascent



TROPICS-02



Outline

ADC: the beginning of a never ending story?

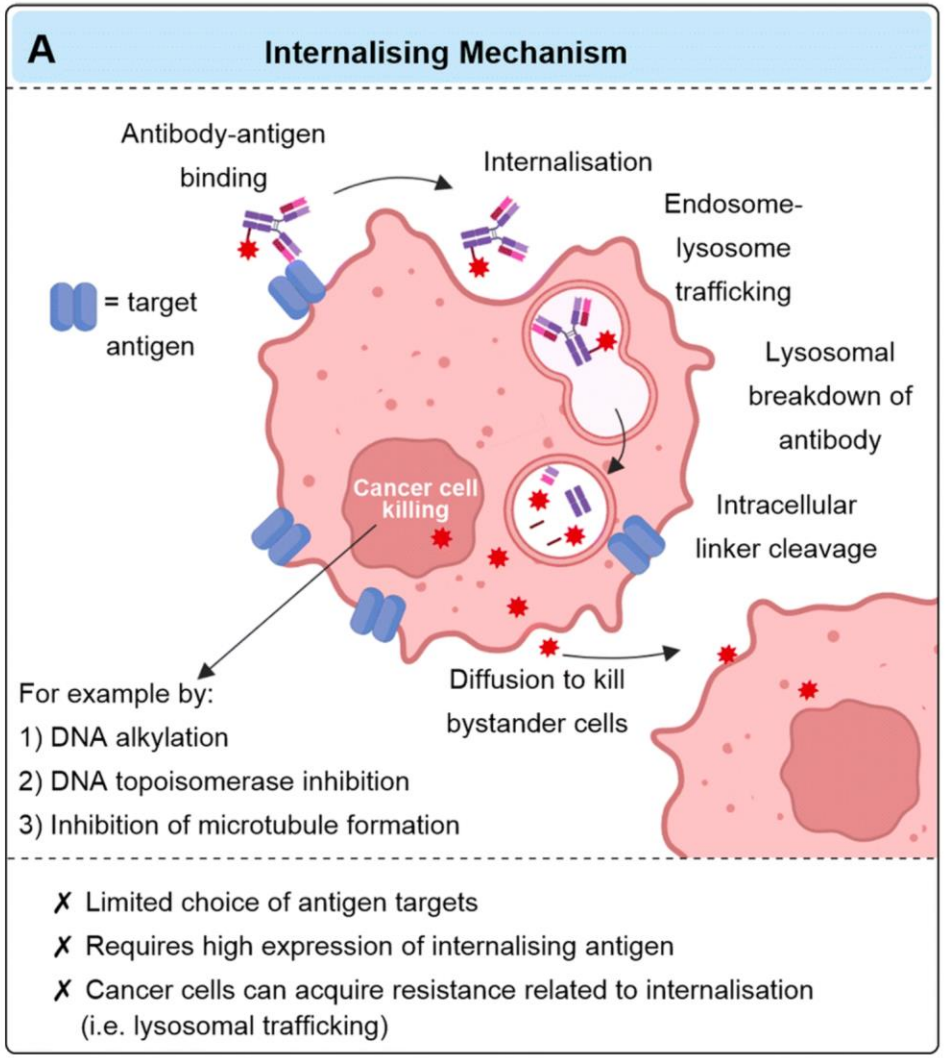
- ADC platform
- The beginning: anti-HER2 and TROP2
- … a never ending story?
    - Fine-tuning the ADC platform
    - Biomarker-driven ADC selection
    - Rational combination

New Targets

Fine-tuning the ADC platform

HER2	LIV1	B7-H3	PD-L1
TROP2	NECTIN4	CD166	CEACAM5
HER3	MESOTHELIN	ROR1	
ROR2	B7-H4	MUC1	

Target	Payload	ADC
LIV1	MMAE	Ladiratuzumab-vedotin (SGN-LIV1a)
Nectin-4	MMAE	Enfortumab vedotin
CD166	DM4	CX2009.
HER3	DXd	Patritumab Deruxtecan
ROR2		BA3021-001
ROR1	MMAE	Zilovertamab vedotin
B7-H3	DXd	DS-7300
B7-H4	TOP1i	AZD205
MUC1 (CA-6)		SAR566658.
CEACAM5	DM4	Tusamitamab ravtansine

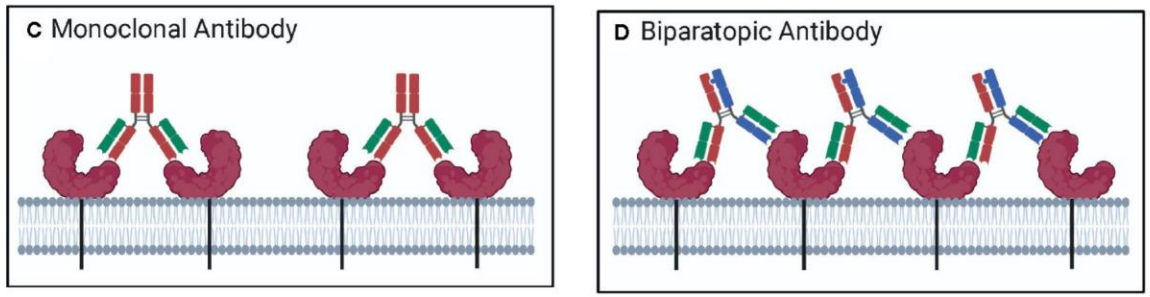


Corti Cancers 2022; Ashman - 10.1039/D2CS00446A; Modified from Tarantino - ESMO breast 2022

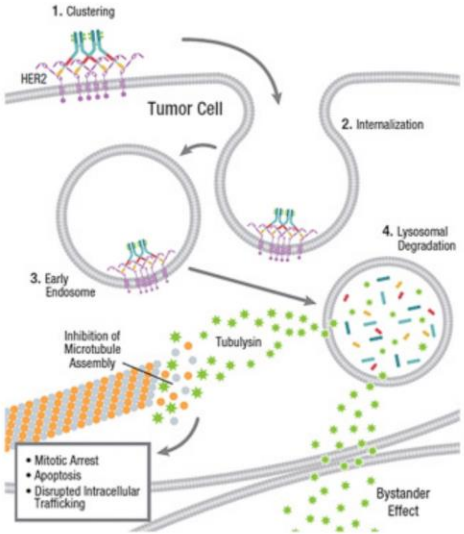
New Antibodies

Fine-tuning the ADC platform

Biparatropic-ADCs



- Higher Receptor clustering
- **Enhanced internalization**
- **Optimized payload delivery**



Swain Nat rev Drug discovery 2023 ; Li - Cancer cell 2016

New Antibodies

Fine-tuning the ADC platform

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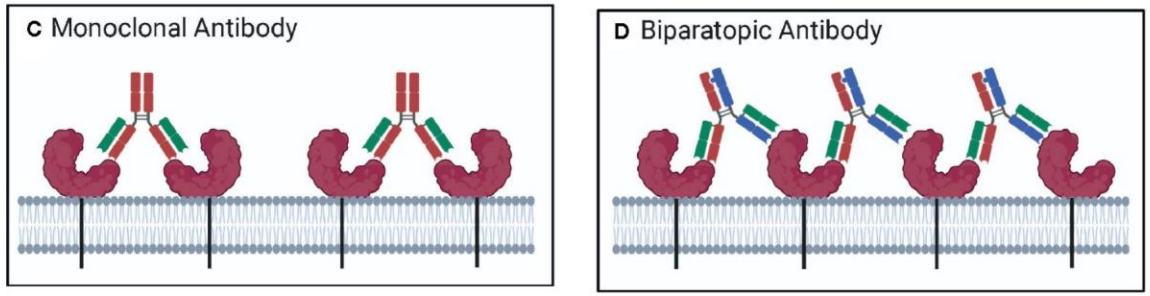
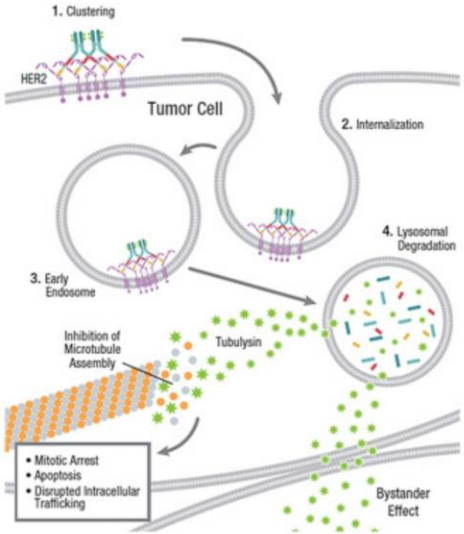
Biparatropic-ADCs





- Higher Receptor clustering
- **Enhanced internalization**
- **Optimized payload delivery**

Bispecific-ADCs

HER2-CD3 bispecific mAb

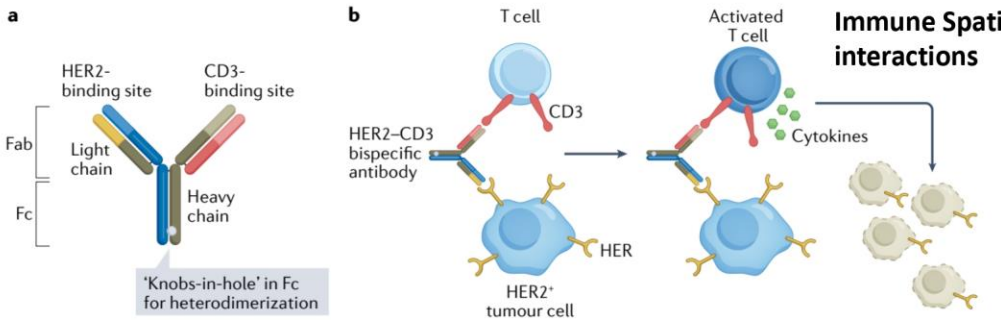


Table 3 | Immune bispecific agents under evaluation for HER2⁺ BC

Therapeutic agent (institution/company)	Tumour-associated antigen	Immune target	Phase/clinical trial ID	Reference
In vitro data only				
HER2/CD3 BsAb (Memorial Sloan Kettering Cancer Center)	HER2	CD3	Not applicable	Lopez-Albaitero et al.[225]
M-802 (Huazhong University of Science and Technology)	HER2	CD3	Not applicable	Yu et al.[176]
p95HER2×CD3 BsAb T cell (Vall d'Hebron Institute of Oncology)	$p95^{HER2}$	CD3	Not applicable	Ruiz et al.[226]
Tribody [(HER2)2×CD16] (University Hospital Schleswig-Holstein, Christian-Albrechts University)	HER2	CD16	Not applicable	Oberg et al.[227]
BsPDL1×ErbB2 (QIMR Berghofer Medical Research Institute)	HER2	PDL1	Not applicable	Mittal et al.[228]
In clinical trials				
Runimotamab/BTRC4017A (Genentech, Inc.)	HER2	CD3	Phase I/NCT03448042	Not applicable
IBI315 (Innovent Biologics (Suzhou) Co. Ltd)	HER2	PDL1	Phase I/NCT04162327	Not applicable
PRS-343 (cinrebafusp alfa) (Pieris Pharmaceuticals, Inc.)	HER2	CD137	Phase I/NCT03650348	Ku et al.[190]
SAR-443216 (Sanofi)	HER2	CD3/CD28	Phase I/NCT05013554	She et al.[229]
BDC-1001 (Bolt Biotherapeutics, Inc.)	HER2	TLR7/8	Phase I/NCT04278144	Sharma et al.[230]
NJH395 (Novartis Pharmaceuticals)	HER2	TLR7	Phase I/NCT03696771	Janku et al.[231]
SBT6050 (Silverback Therapeutics)	HER2	TLR8	Phase I/NCT04460456 Phase I/II/NCT05091528	Klemper et al.[232]
HER2Bi–aATCs/HER2BATs (University of Virginia)	HER2	CD3⁺ activated T cells	Phase I/II/NCT03272334	Lum et al.[181]
TAC01-HER2 (Triumvira Immunologics, Inc.)	HER2	CD3 and CD4 co-receptor domain	Phase I/II/NCT04727151	NCT04727151
DF-1001 (Dragonfly Therapeutics)	HER2	NK cells	Phase I/II/NCT04143711	NCT04143711
ACE1702 (Acepodia Biotech, Inc.)	HER2	NK cells	Phase I/NCT04319757	NCT04319757
BPX-603 (Bellicum Pharmaceuticals)	HER2	Dual switch CAR-T cells	Phase I/NCT04650451	NCT04650451
MT-5111 (Molecular Templates, Inc.)	HER2 scFV	De-immunized Shiga-like toxin-A subunit	Phase Ib/NCT04029922	Wainberg et al.[184]

ATC, activated T cell; BsAb, bispecific antibody; CAR-T cell, chimeric antigen receptor–T cell; NK, natural killer; TLR, Toll-like receptor.

Swain Nat rev Drug discovery 2023 ; Li - Cancer cell 2016

New Antibodies

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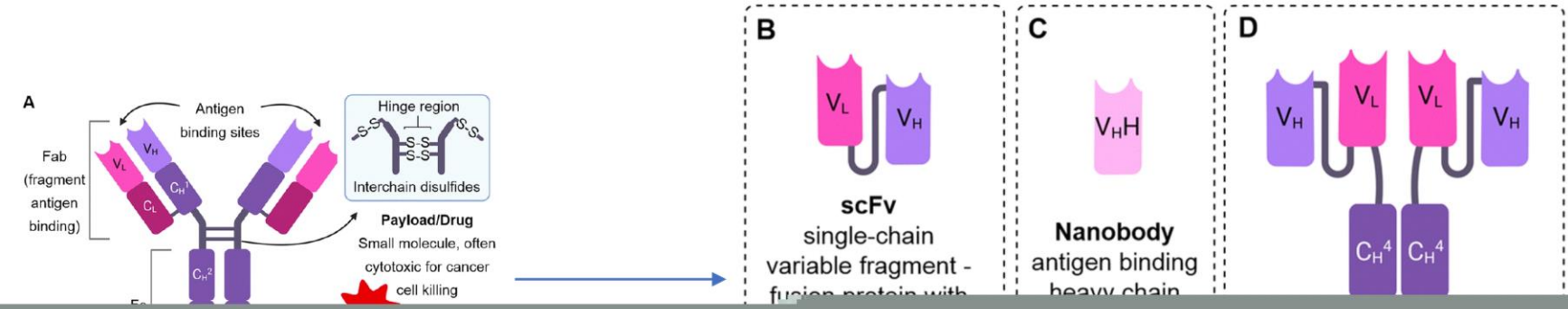
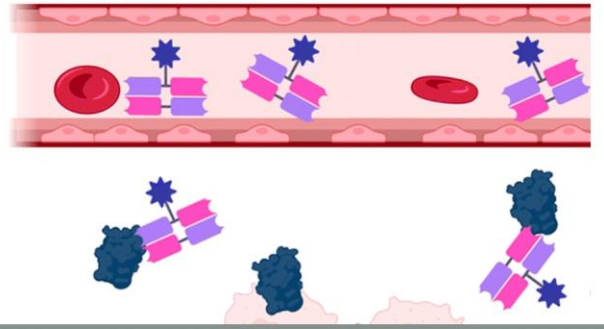
Fine-tuning the ADC platform

Alternative antibody formats

Small molecular-weight drug conjugates

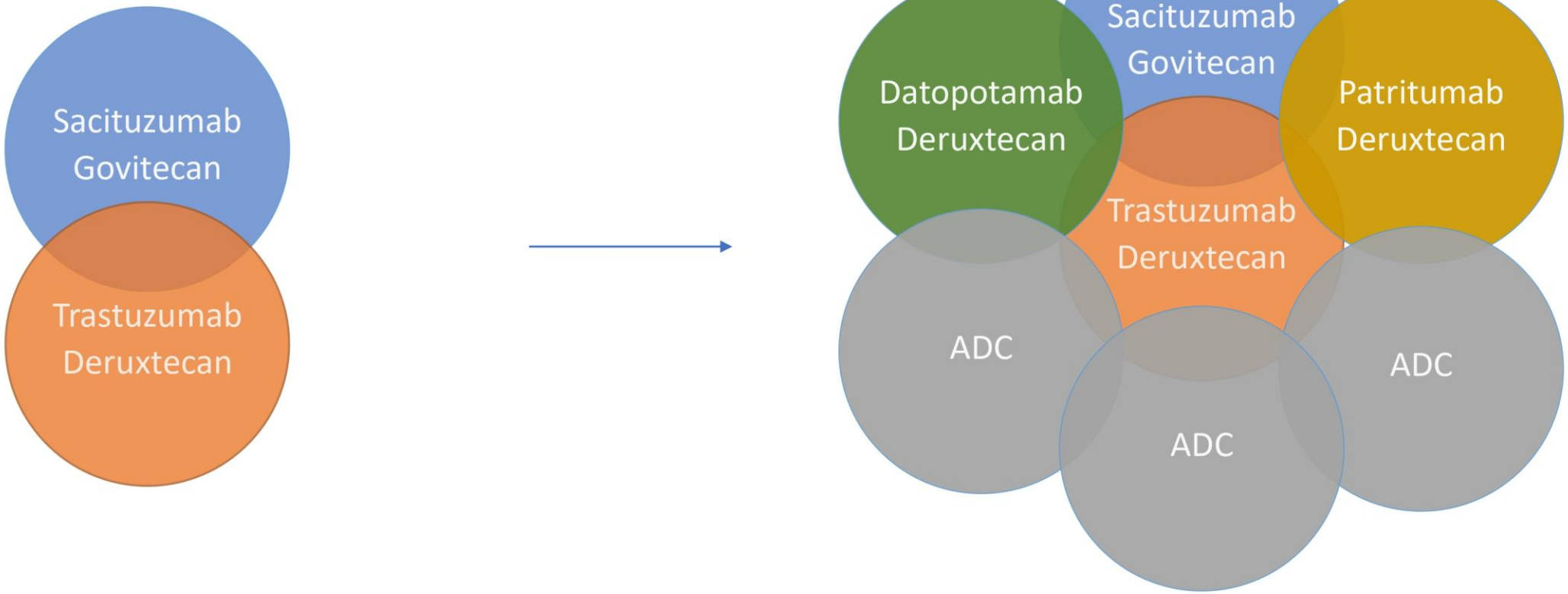


Improved tissue penetration



Biomarkers

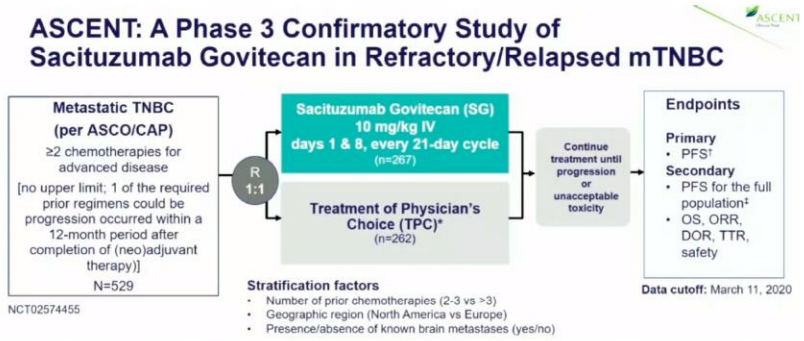
Ok but… what about Treatment prioritization and sequencing?

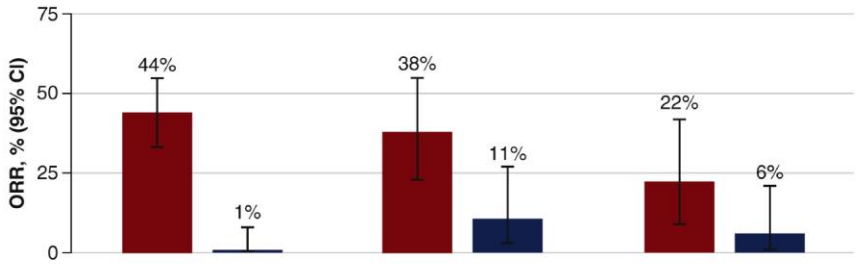


Antigen expression

TROP2 expression

ASCENT: TNBC





	Trop-2 high H-score: >200-300 (*n* = 157)		Trop-2 medium H-score: 100-200 (*n* = 74)		Trop-2 low H-score: 0 to <100 (*n* = 59)	
	SG (*n* = 85)	TPC (*n* = 72)	SG (*n* = 39)	TPC (*n* = 35)	SG (*n* = 27)	TPC (*n* = 32)
ORR, % (*n*)	44 (37)	1 (1)	38 (15)	11 (4)	22 (6)	6 (2)
95% CI	33-55	0-8	23-55	3-27	9-42	1-21

Bardia Annals 2021

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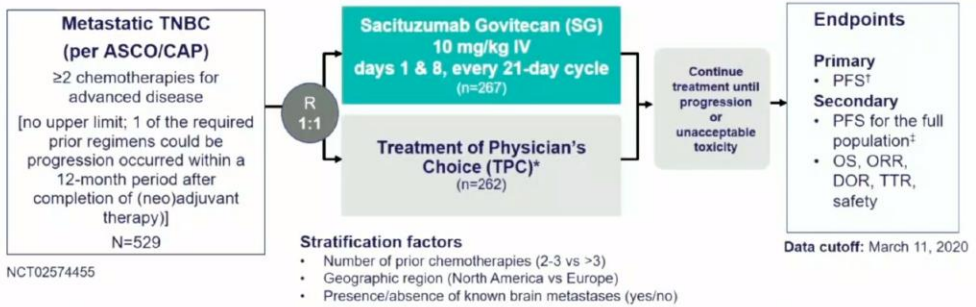
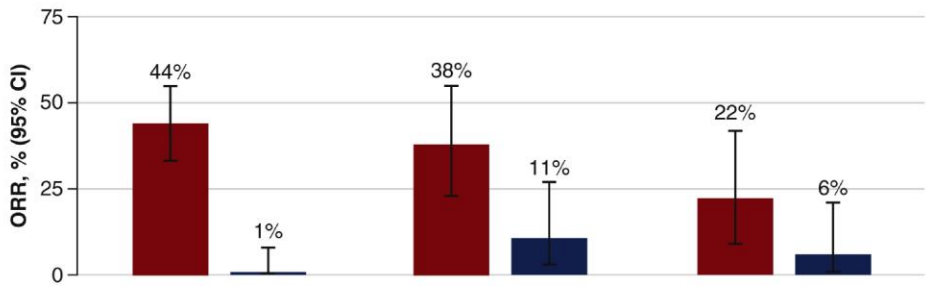
Antigen expression

TROP2 expression

ASCENT: TNBC

ASCENT: A Phase 3 Confirmatory Study of Sacituzumab Govitecan in Refractory/Relapsed mTNBC





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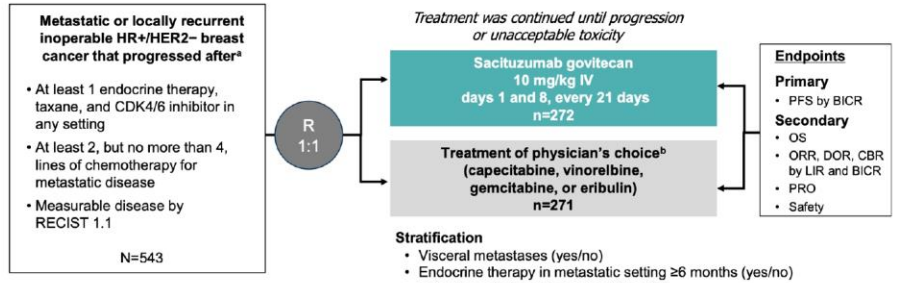
95% CI	33-55	0-8	23-55	3-27	9-42	1-21

Bardia Annals 2021

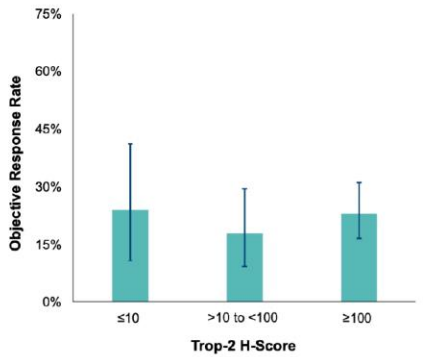
Cytotoxicity not proportional after a threshold of antigen expression is reached…?

TROPICS-02: HR+/HER2-

TROPiCS-02: A Phase 3 Study of SG in HR+/HER2− Locally Recurrent Inoperable or Metastatic Breast Cancer



Objective Response Rates



Trop-2 expression, H-score	ORR, n (%)	CBR,[a] n (%)	Median DOR, mo (95% CI)
≤10 (n=34)	8 (24)	11 (32)	7.5 (2.5-NR)
>10 to <100 (n=62)	11 (18)	17 (27)	7.4 (4.1-NR)
≥100 (n=142)	33 (23)	55 (39)	8.5 (5.9-16.9)

- Response was also observed in the small Trop-2 negative (H-score = 0, n=10) subgroup

Response to SG are observed in all Trop-2 subgroups, including those with very low Trop-2 expression (H-score ≤10)

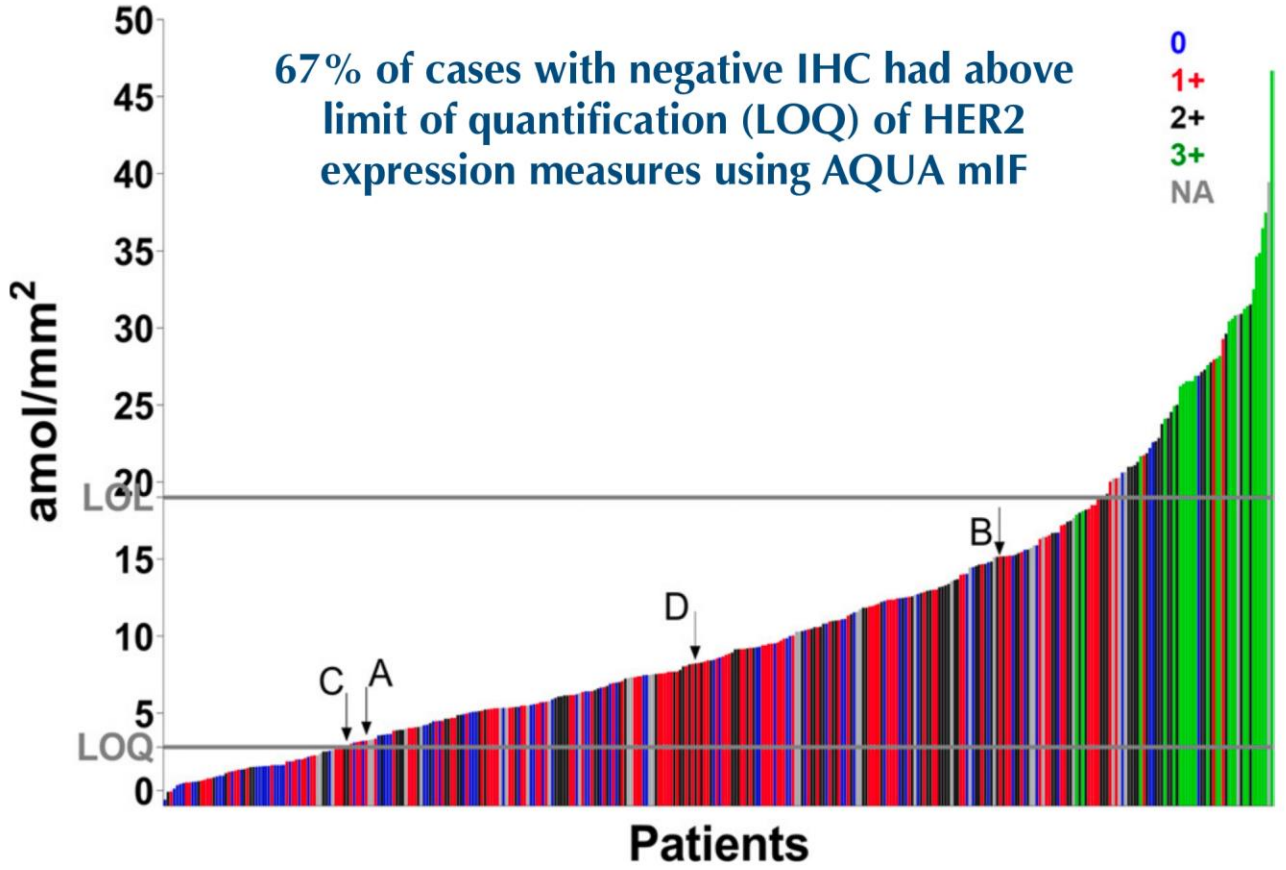
Marie et al - Cancer cell international 2022

Rugo SABCS 2022

Antigen expression

Is there a precise antigen expression threshold predictive of ADC efficacy?

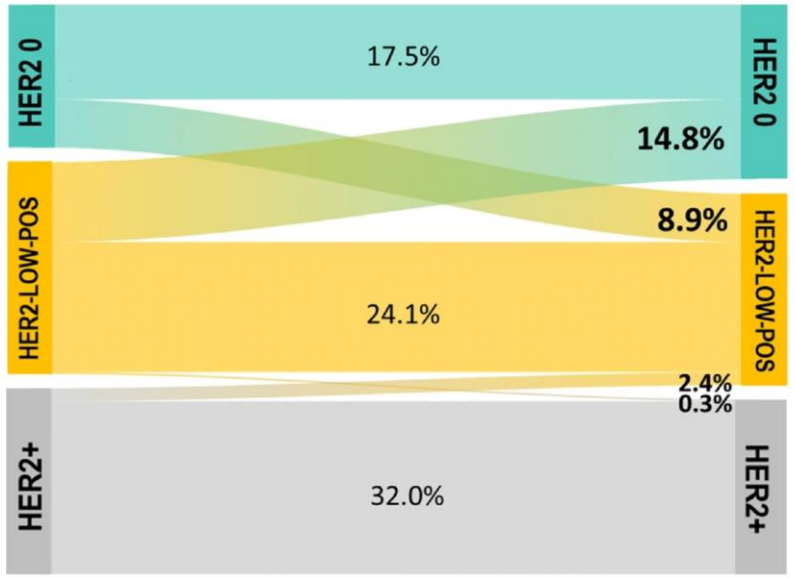
HER2 expression



Antigen selection

Temporal Heterogeneity: HER2 evolution

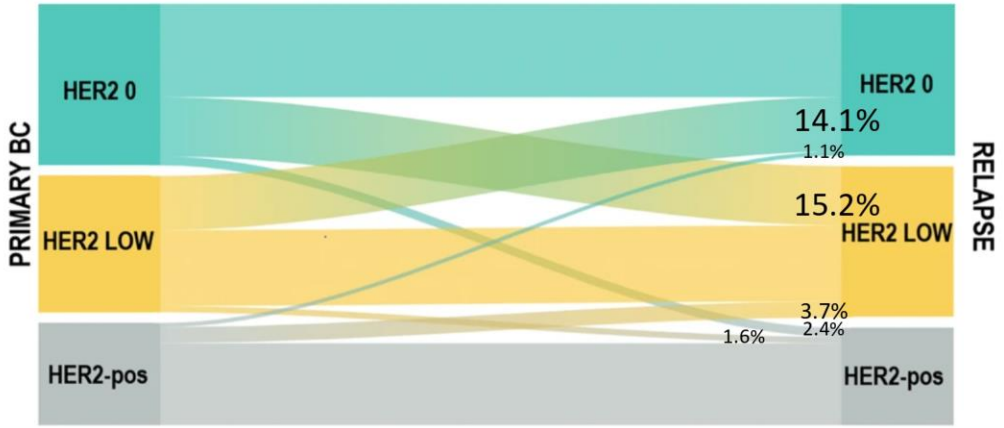
Biopsy to Residual disease after NAT



Overall rate of HER2 discordance: 26%

Miglietta et al. NPJ 2022

Primary to Recurrent



		HER2 recurrence/metastasis N,%			Total
		0	Low	Positive	
HER2 primary BC N,%	0	132 (24.1)	83 (15.2)	13 (2.4)	228 (41.7)
	Low	77 (14.1)	101 (18.5)	9 (1.6)	187 (34.2)
	Positive	6 (1.1)	20 (3.7)	106 (19.4)	132 (24.1)
Total		215 (39.3)	204 (37.3)	128 (23.4)	547 (100)

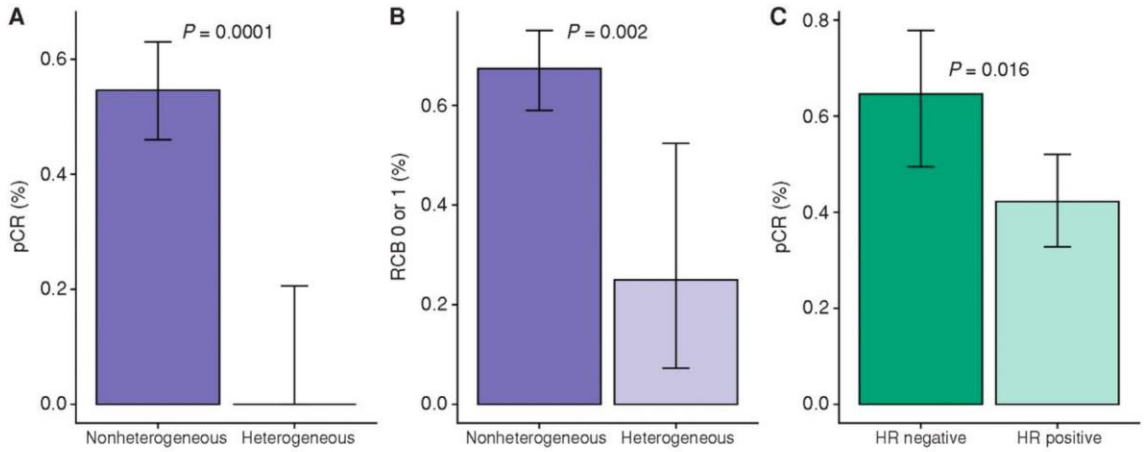
Overall rate of HER2 discordance: 38%

Miglietta et al. NPJ 2021

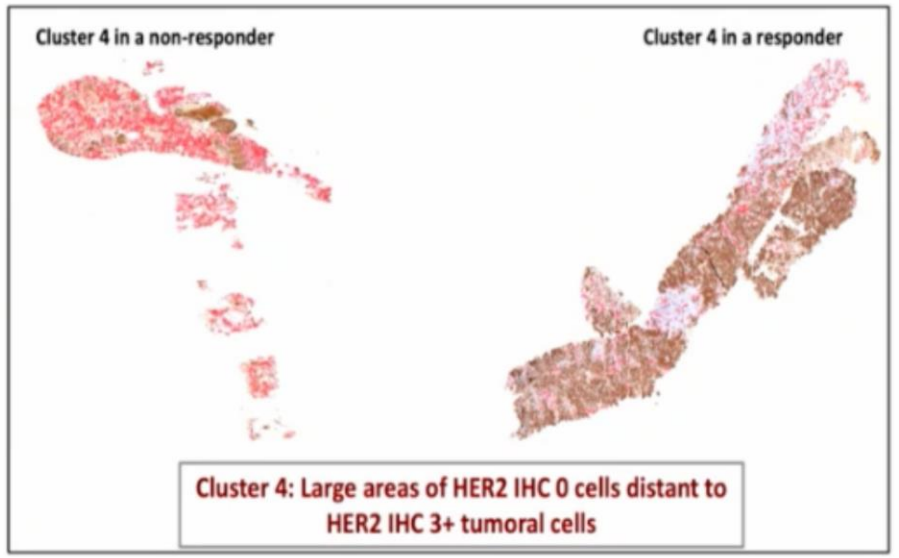
Antigen selection

Spatial characterization

Heterogeneous HER2 expression and response to TDM-1



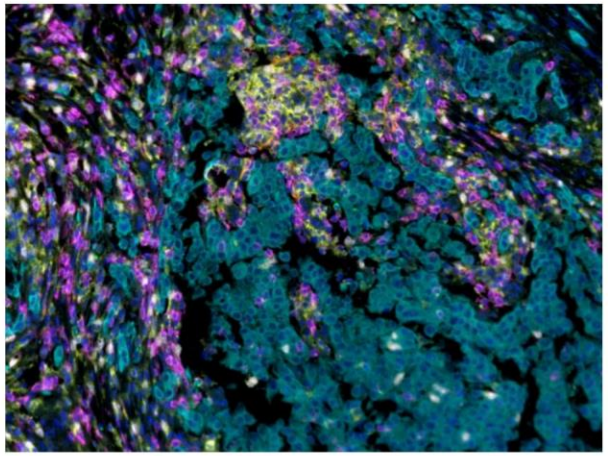
Spatial heterogeneity in HER2 antigen-expression correlates with response to T-DXd

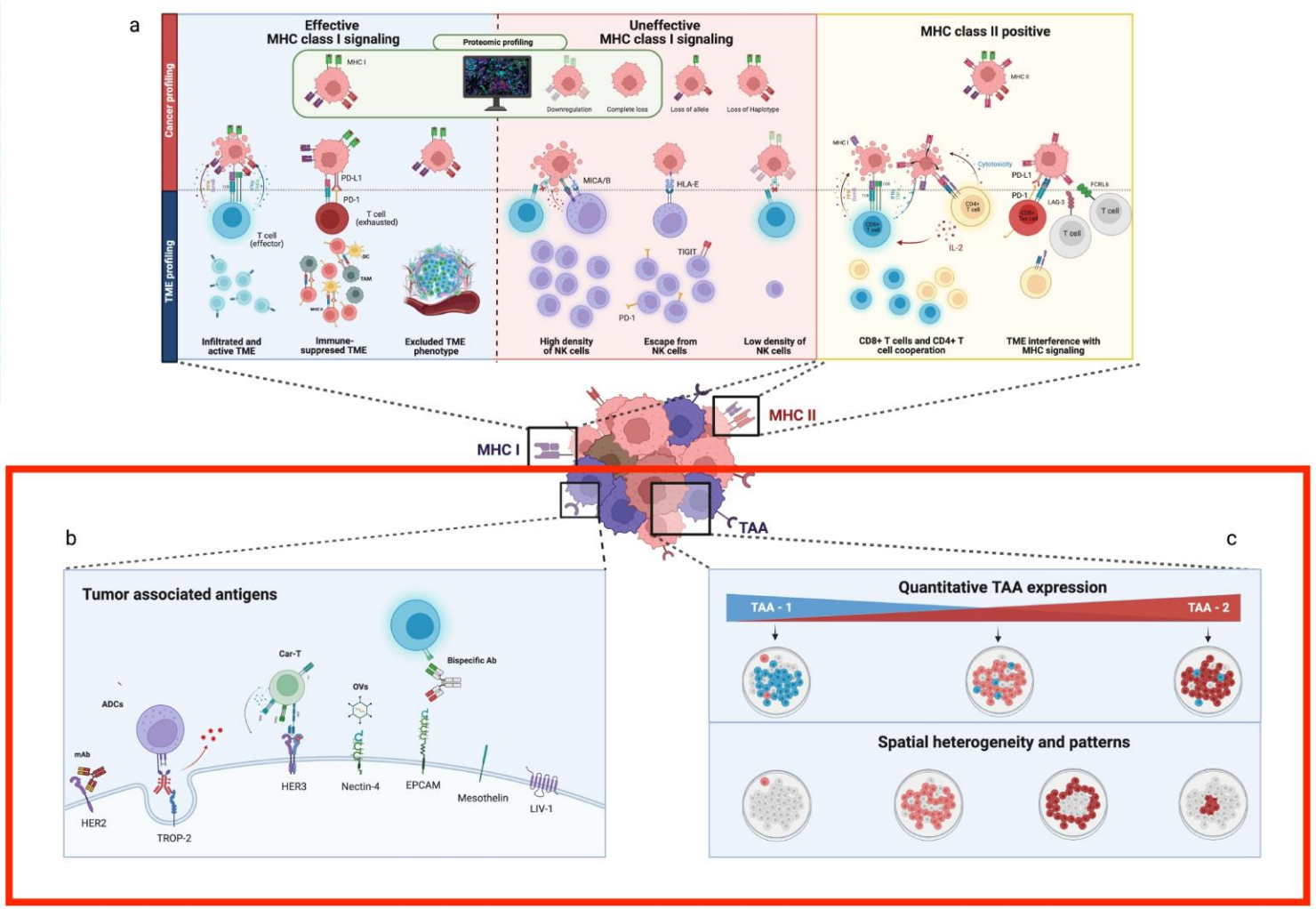


Metzger Filho Cancer Discovery 2021; Mosele et al. ESMO Breast 2022

Antigen selection

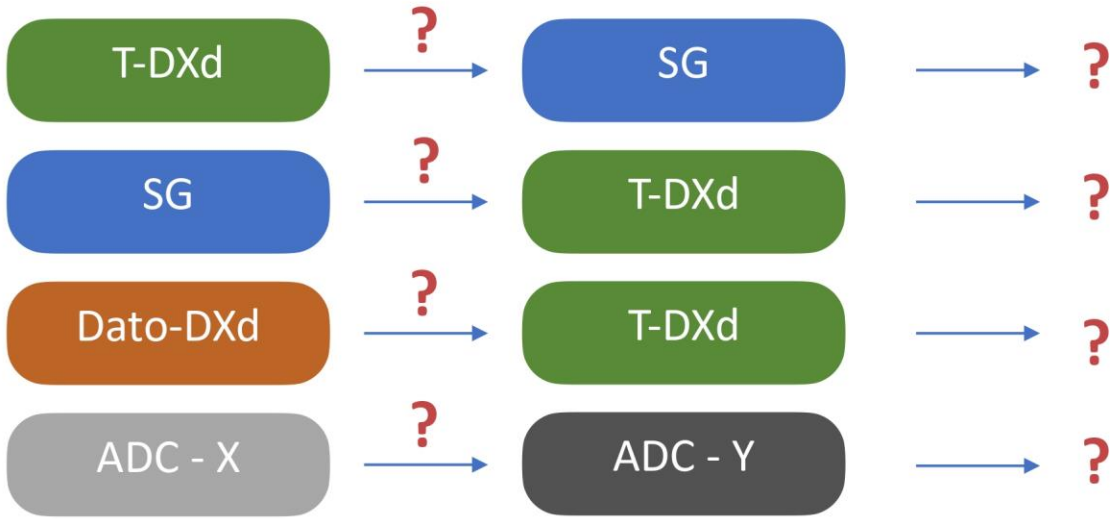
Multiplexed multi-antigen quantitative spatial characterization





ADC selection and sequencing?

Biomarker-driven ADC selection



Resistance mechanisms

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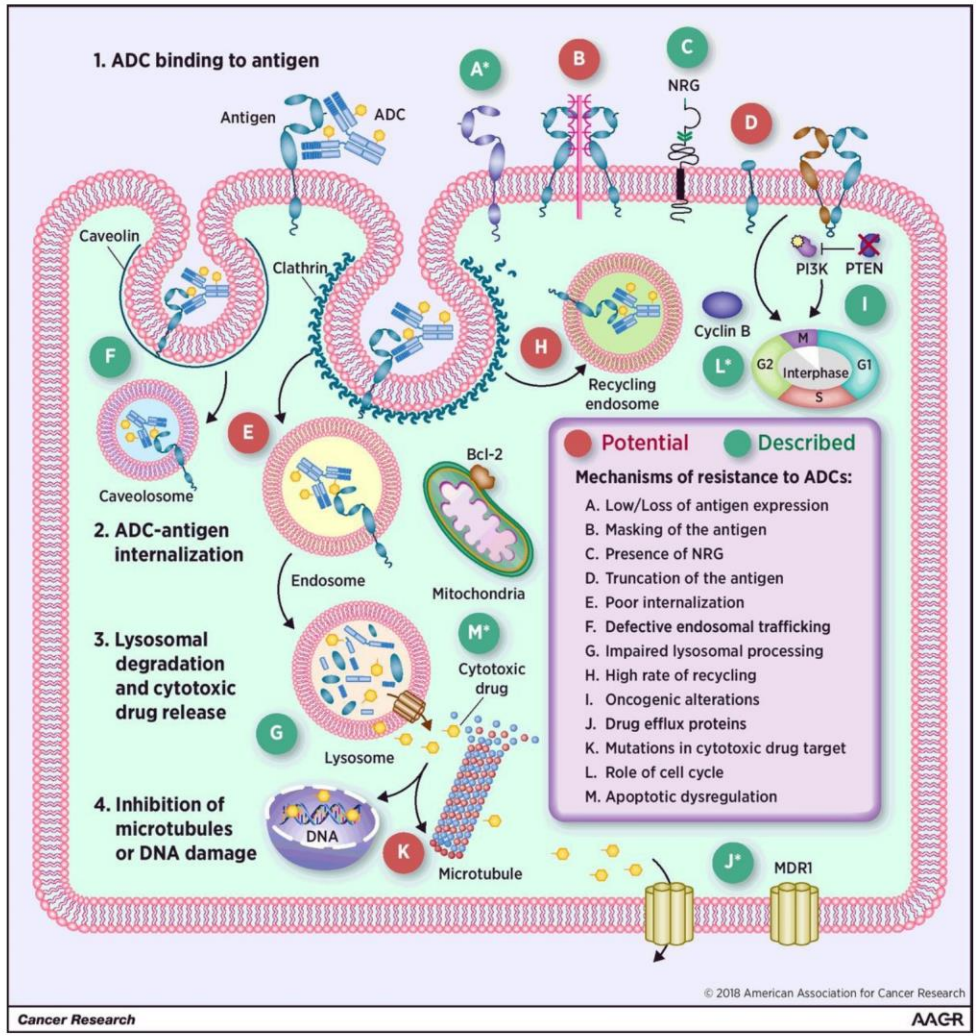
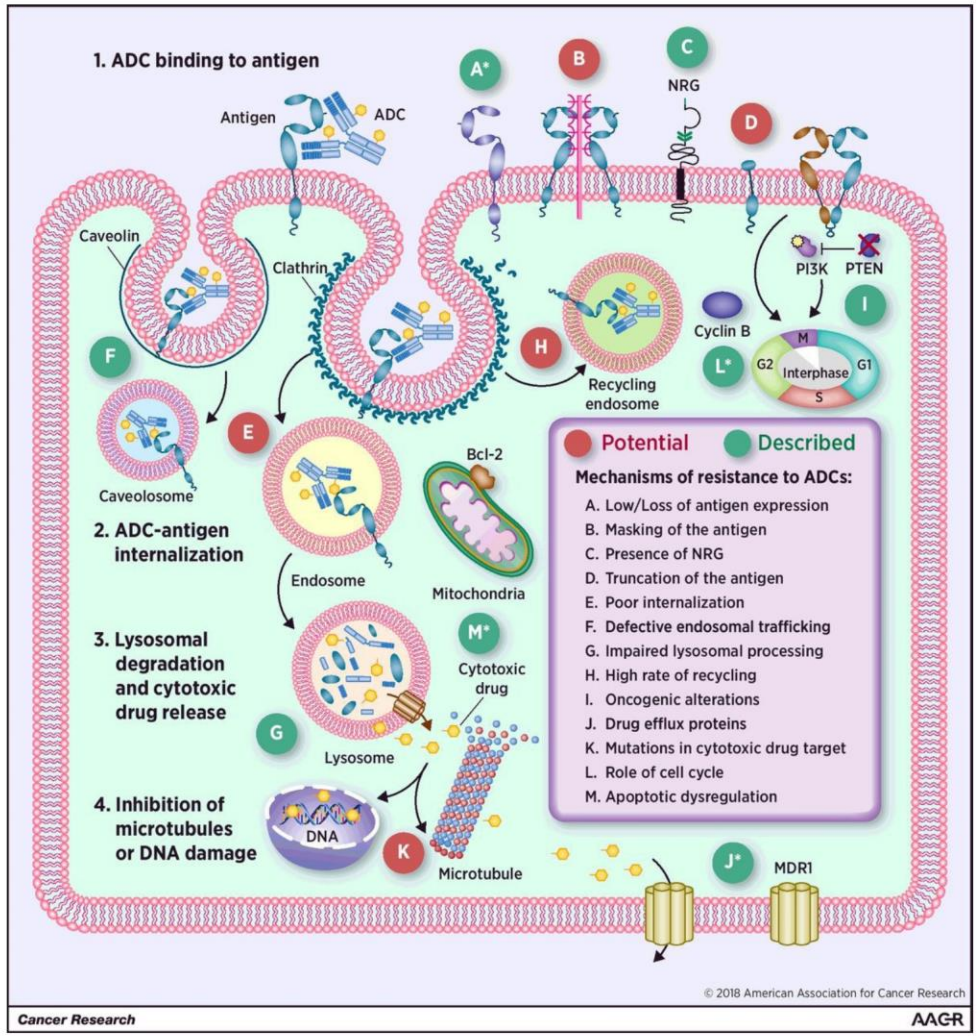


Target	Antibody	Linker	Payload	Tumor	TME
Expression	Target affinity	Stability	Mechanism	Payload sensitivity	Immune-checkpoints
Trafficking	Internalization rate	Cleavage mechanisms	Potency	Lysosome integrity	Immune-suppressive cells
Signaling	FC affinity/ADCC/ ICD		Cell permeability	MDR/PGP	Metaboolic competition
			Drug/Ab ratio	Target Addiction	Other

Resistance mechanisms



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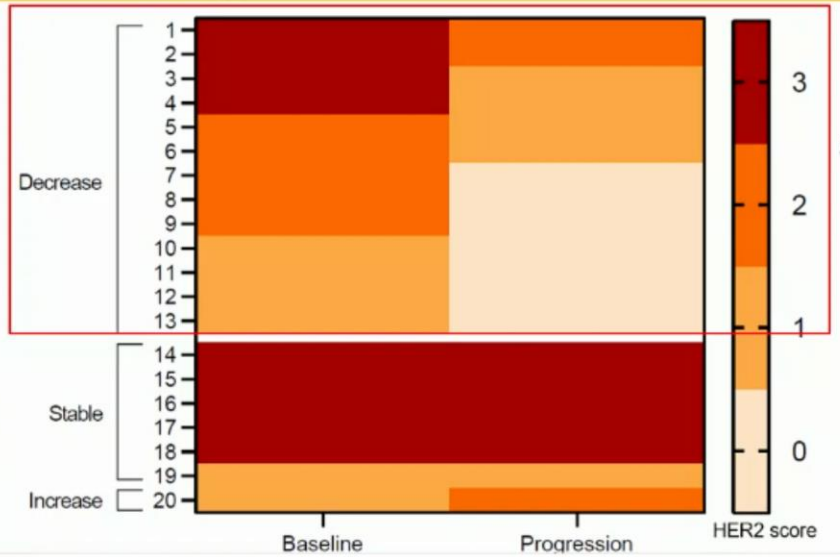
Expression	Target affinity	Stability	Mechanism	Payload sensitivity	Immune-checkpoints
Trafficking	Internalization rate	Cleavage mechanisms	Potency	Lysosome integrity	Immune-suppressive cells
Signaling	FC affinity/ADCC/ ICD		Cell permeability	MDR/PGP	Metaboolic competition
			Drug/Ab ratio	Target Addiction	Other

- 25 FFPE samples at baseline and progression: **9** HER2 IHC 3+ or IHC 2+/ISH+; **11** HER2 IHC 2+/ISH- or IHC 1+; **5** IHC 0
- HER2 status by standard IHC



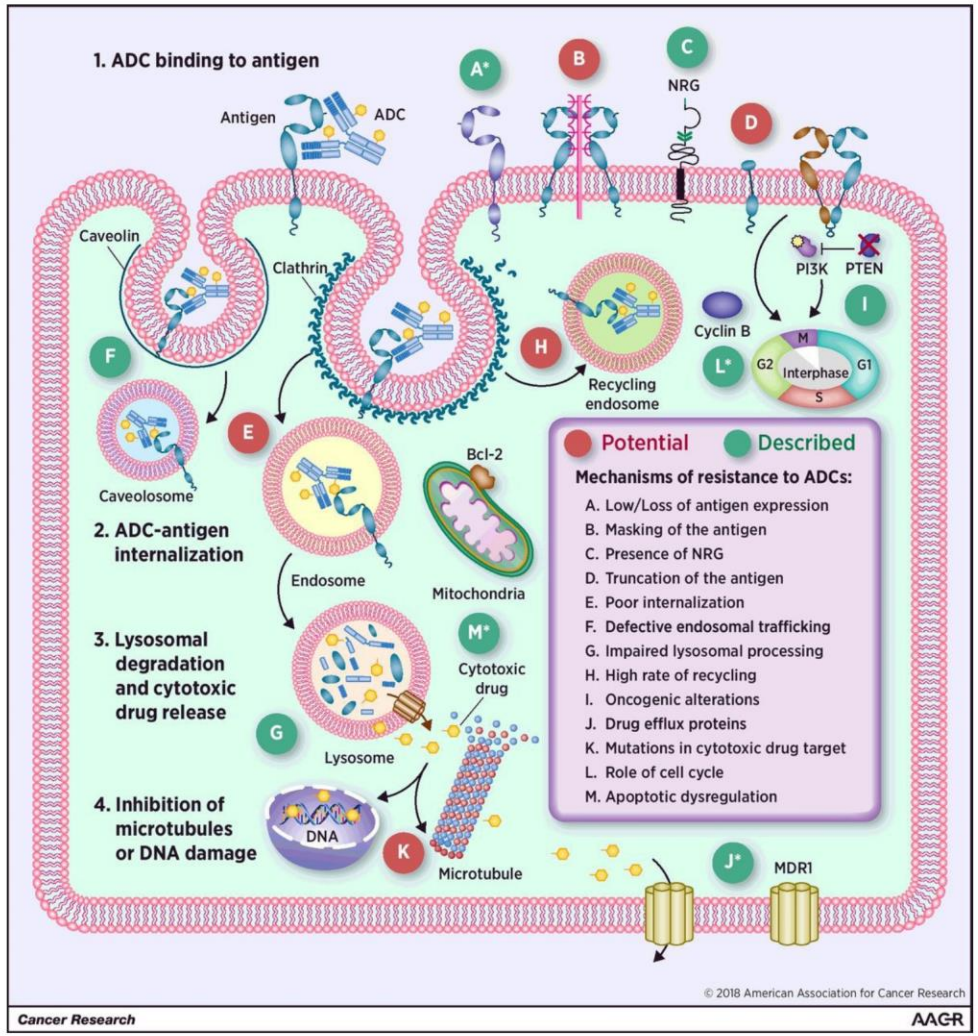
13/20 (65%)
95% CI [40.8-84.6]

13 out of 20 (65%) patients presented a decrease of HER2 expression at progression

Mosele et al, ESMO Breast 2022

Resistance mechanisms

13ª EDIZIONE
Progetto CANOA



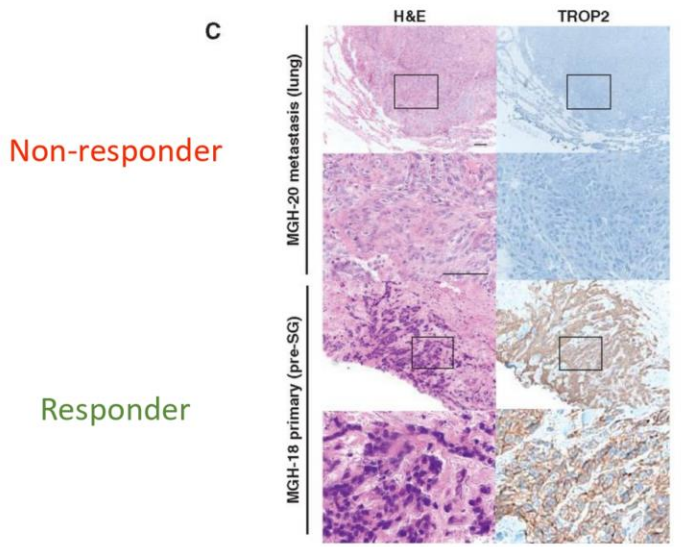
Target	Antibody	Linker	Payload	Tumor	TME
Expression	Target affinity	Stability	Mechanism	Payload sensitivity	Immune-checkpoints
Trafficking	Internalization rate	Cleavage mechanisms	Potency	Lysosome integrity	Immune-suppressive cells
Signaling	FC affinity/ADCC/ ICD		Cell permeability	MDR/PGP	Metaboolic competition
			Drug/Ab ratio	Target Addiction	Other

A

Post-progression (rapid autopsy) specimens from SG Progressors

Participant ID	Molecular subtype	Age at diagnosis	Days on IMMU-132	Days from last dose SG to death	Treatments before SG	Treatments after SG	Lesions sequenced at autopsy	Best response (per RECIST)	Extent of best response (%)
MGH-18	TNBC	41	253	138	2	2	9	PR	–45.0
MGH-19	TNBC	59	150	305	5	4	8	SD	–21.9
MGH-20	TNBC	62	34	56	4	1	6	PD	+78.0

C



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Resistance mechanisms

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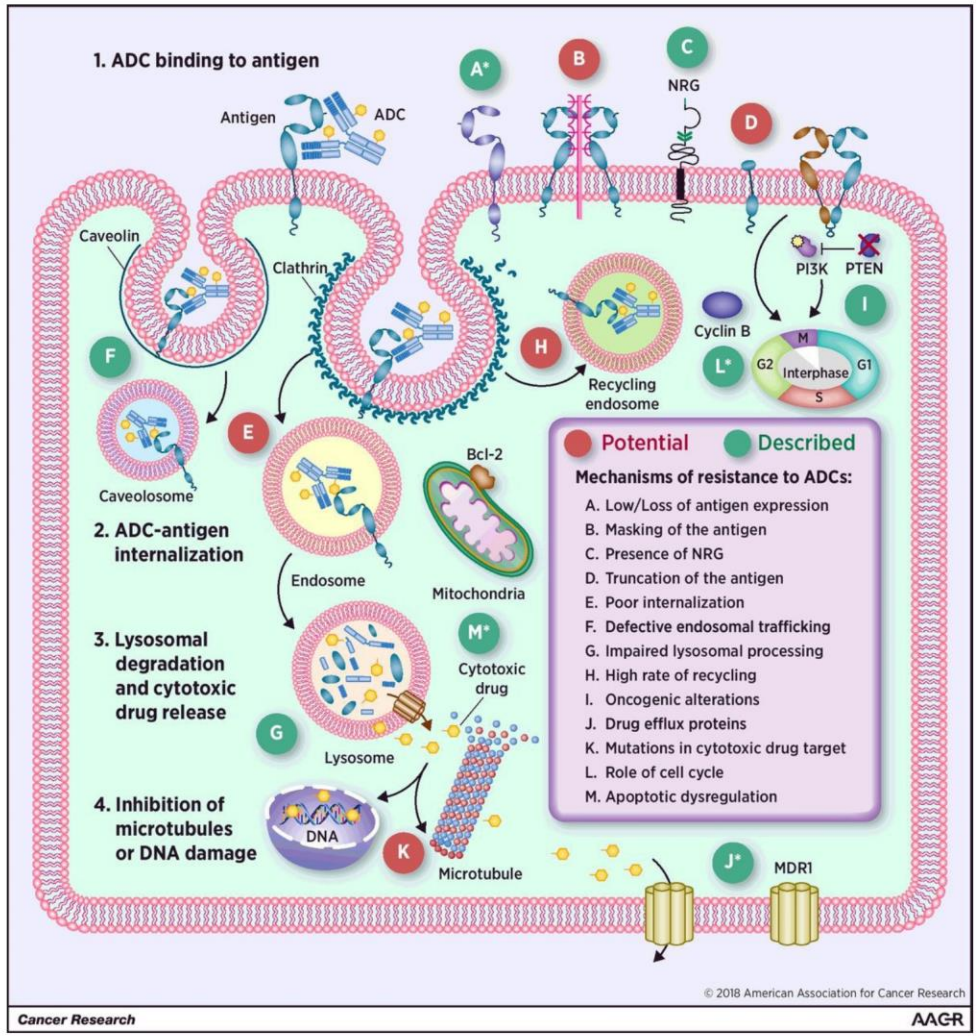

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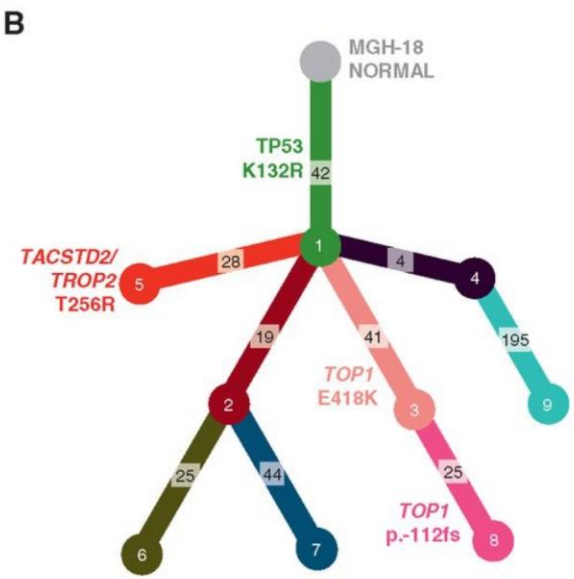
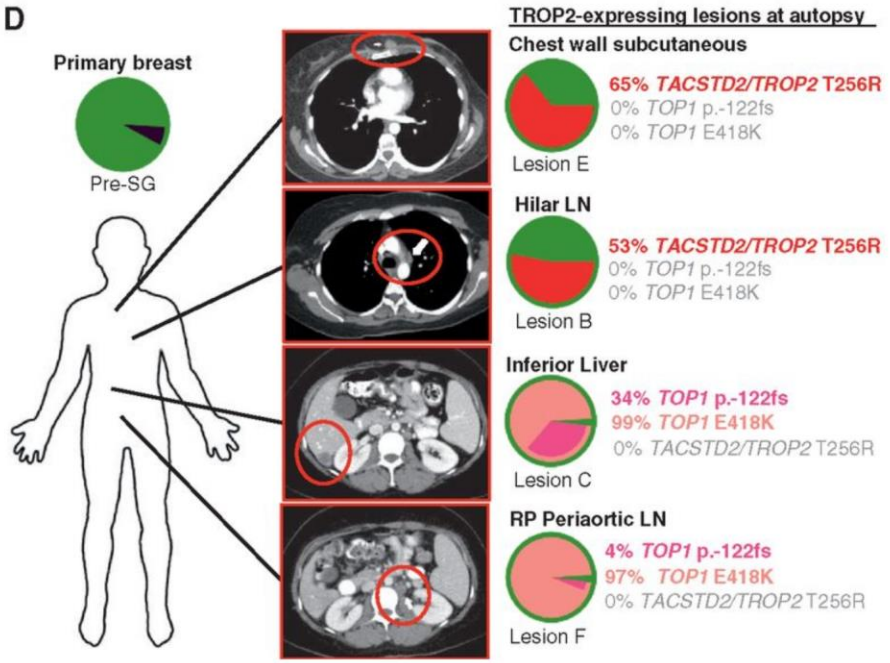
Post-progression (rapid autopsy) specimens from SG acquired progressor





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Resistance detection and ADC sequencing

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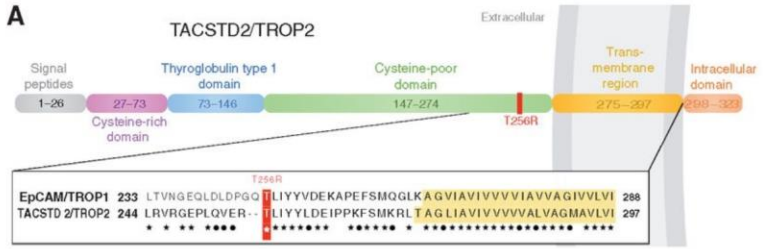
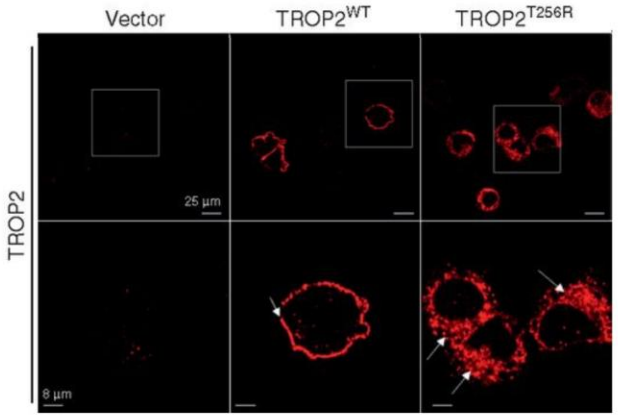
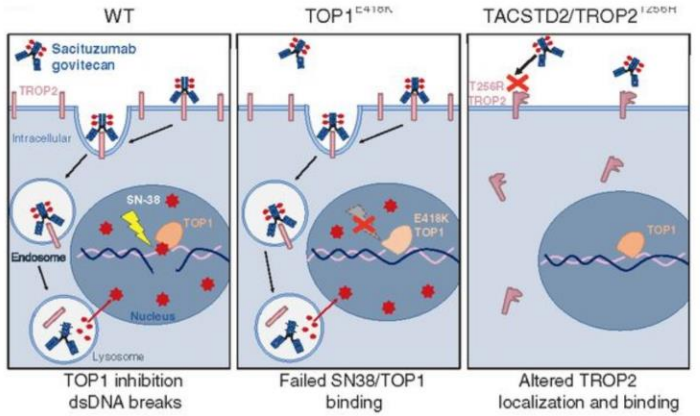
TROP2 receptor mutation



Altered TROP2 surface trafficking



Proposed resistance mechanisms



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Resistance detection and ADC sequencing

13ª EDIZIONE Progetto CANOA

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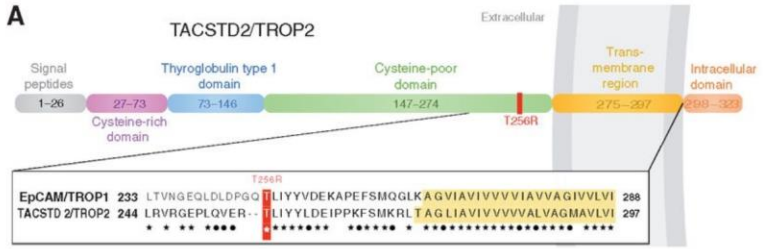

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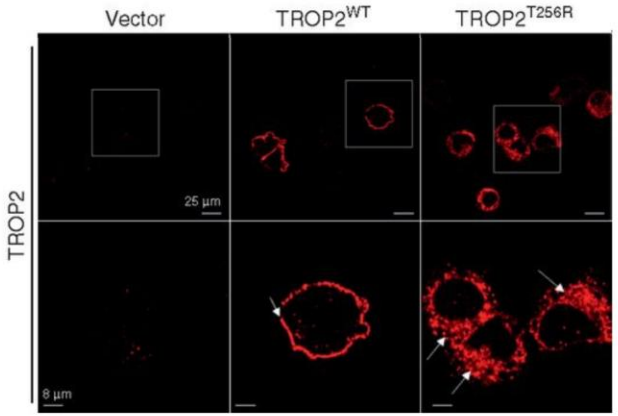

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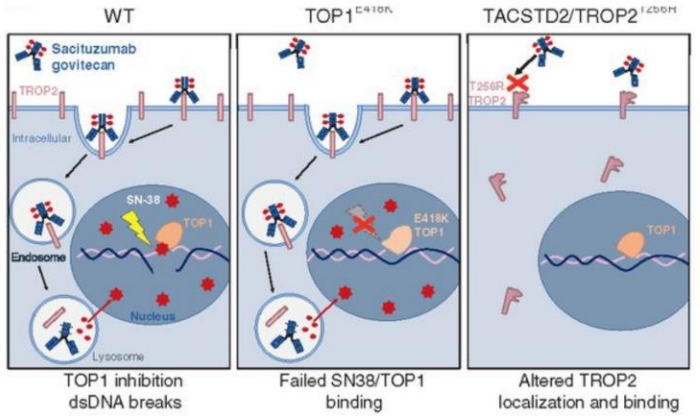

T-DXd → ?

SG

Dato-DXd

→ Tumor biopsy

ADC - X → ?

TROP2 mut → no-TROP2 ADC

TOP1 mut → ADC with non-TOP1i payload

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Combinatorial approaches

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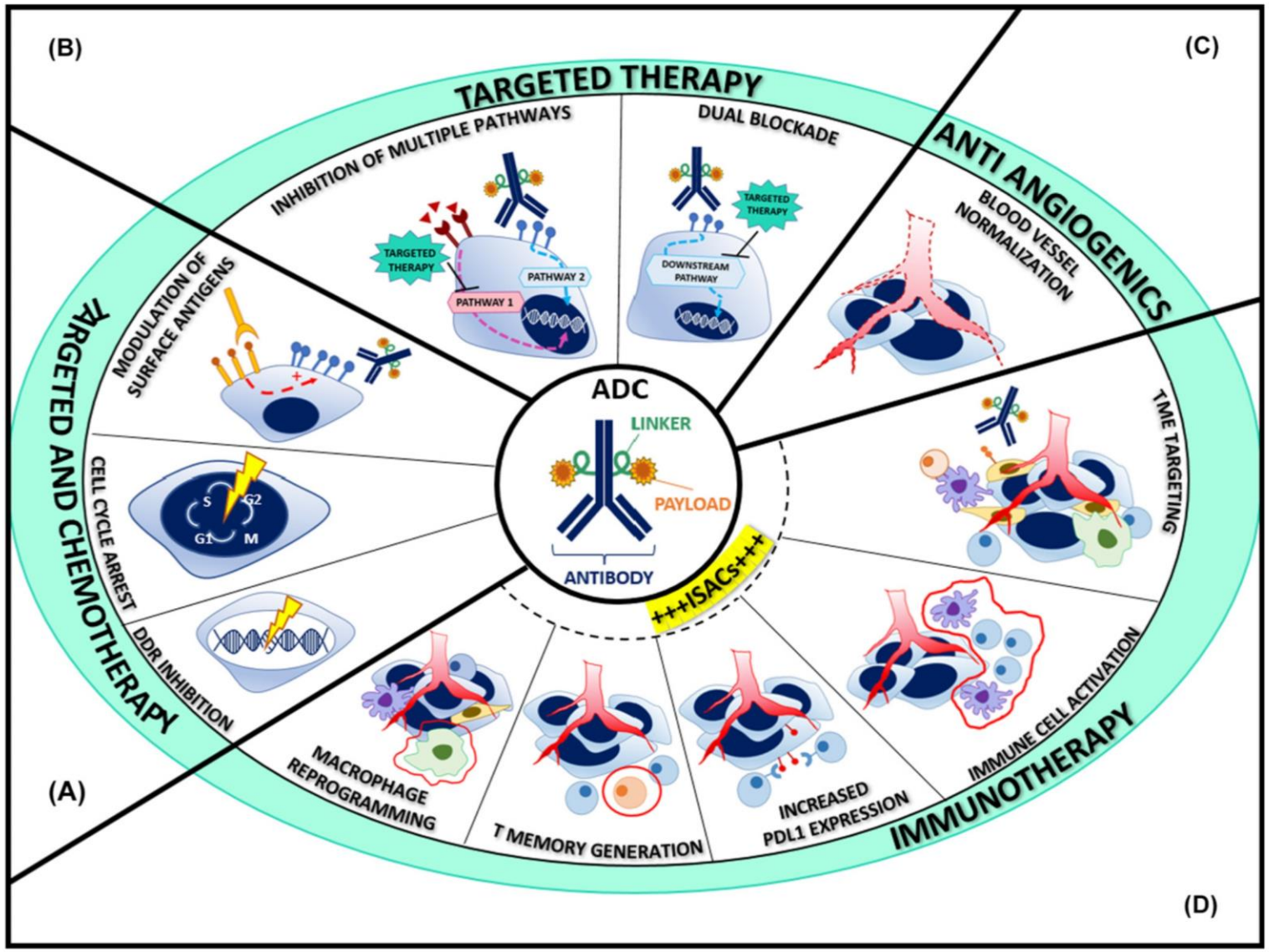

Cancer site	Combination: Chemotherapy/ Chemo-immunotherapy combinations	Targeted therapy combinations	Immunotherapy: Anti-PD1/PDL1 and anti-CTLA-4 combinations	Immunotherapy: Other combinations (e.g. monoclonal antibodies)	Anti-VEGF combinations
Breast	● ○○○○	● ○○○	●●●● ○○○○	● ○○○○	
Thyroid					
Lung	● ○○	○○	●● ○○○		
Prostate					
GI	●● ○○	○	○○○	●	
GU	● ○○	○○	●●● ○○○	○○○	
Gynecologic	●● ○○○	○○	●● ○○		●●● ○
Brain	○				
Solid tumors: General	○○○	●○○○	● ○○○		○
Hematologic: Lymphoma	●● ○○	● ○○	● ○	●●● ○	
Hematologic: Myeloma	○	● ○	○	● ○	
Hematologic: Acute leukemia	●○ ○	○ ○			

Legend

- ● Published data on combination available
- ○ Trial in progress

- ●○ TDM-1
- ●○ Trastuzumab deruxtecan
- ●○ Disitamab vedotin
- ●○ Sacituzumab govitecan
- ●○ Datopotamab deruxtecan
- ●○ Ladiratuzumab vedotin
- ●○ Tisotumab vedotin
- ●○ Telisotuzumab vedotin
- ●○ Enfortumab vedotin
- ●○ Mirvetuximab soravtansine
- ●○ BMS-986148
- ●○ Rovalpituzumab Tesirine
- ●○ Anetumab ravtansine
- ●○ Depatuxizumab mafodotin
- ●○ SGN-15
- ●○ Brentuximab vedotin
- ●○ Polatuzumab vedotin
- ●○ Pinatuzumab vedotin
- ●○ Belantamab mafodotin
- ●○ Gemtuzumab ozogamicin

Jesús Fuentes-Antrás et al. Cells 2023

Conclusions

Take home messages

- **ADC platform:** ***the most complex platform in oncology***
- **The ADC revolution:** ***new antigens, mAb, linker technology and payloads***
- **The beginning of an never ending story?** ***Yes!!!***
- ***The need for biomarker-based ADC selection and sequencing***

Grazie per l'attenzione!