Advances in Antibody-based therapies for oncology applications

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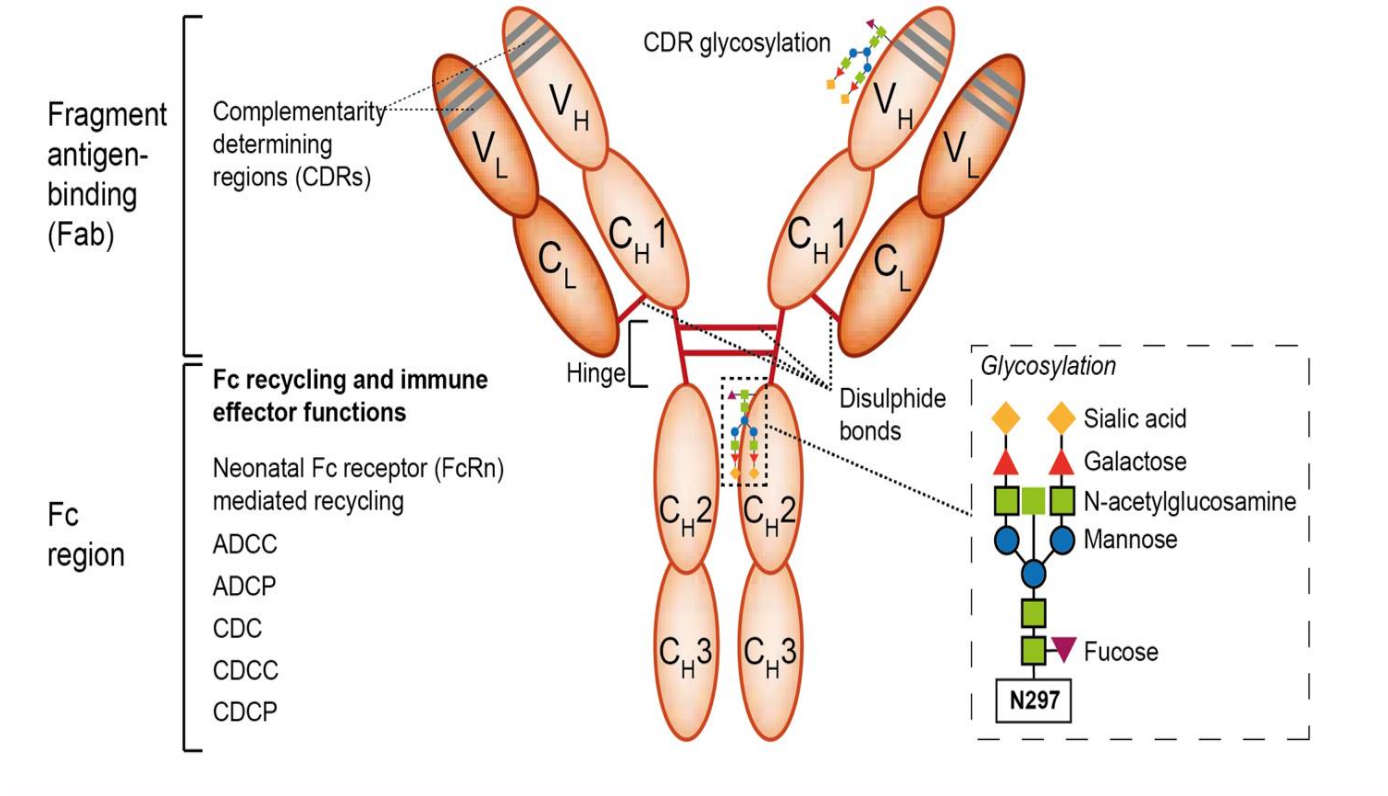
Controlled Release Society 2022 Meeting & Expo

13July2022

Outline- Evolution of Antibody-based therapies as delivery vehicles

1. Antibody-based therapies- Vision and History
2. Antibody drug conjugates (ADCs)
3. Radioconjugates
4. T-cell engagers
5. Targeted nanoparticles

Targeted therapy: harnessing the specificity and activity of monoclonal antibodies



Monoclonal antibodies offer:

1. Specific binding
2. High affinity
3. Long serum stability
4. Cellular cytoxicity

Engineering can:

1. Increase serum half-life
2. Modulate target affinity
3. Reduce immunogenicity
4. Provide appropriate pharmaceutical properties

Evolution of mAb-based therapeutics as delivery vehicles

mAb Therapies

1997

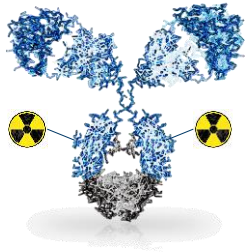
Rituxan
Rituximab

New classes

Antibody drug conjugates

2000

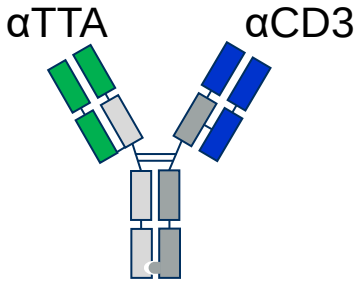
MYLOTARG™



Radioconjugates

2002

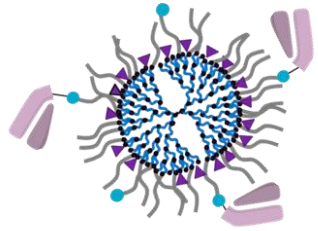
ZEVALIN®



T-cell Engagers

2014

BLINCYTO™



Targeted nanoparticles

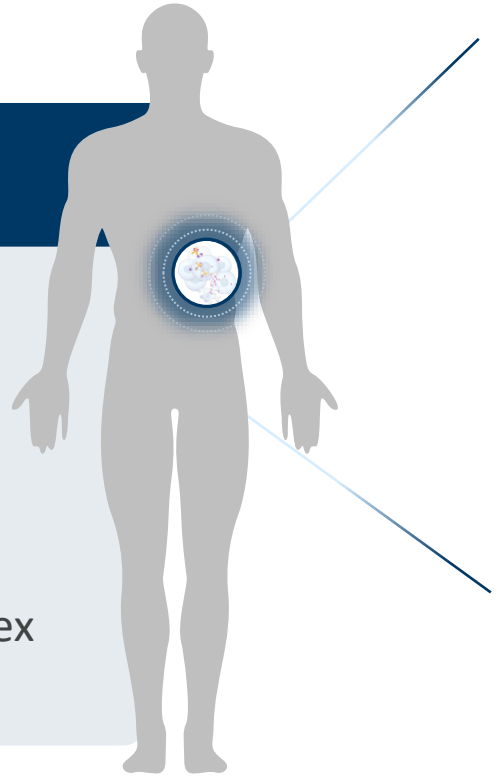
FIRST FDA APPROVAL

Outline

1. Antibody-based therapies- Vision and History
2. Antibody drug conjugates (ADCs)
3. Radioconjugates
4. T-cell engagers
5. Targeted nanoparticles

The promise of ADCs: improve the therapeutic index of systemic chemotherapy

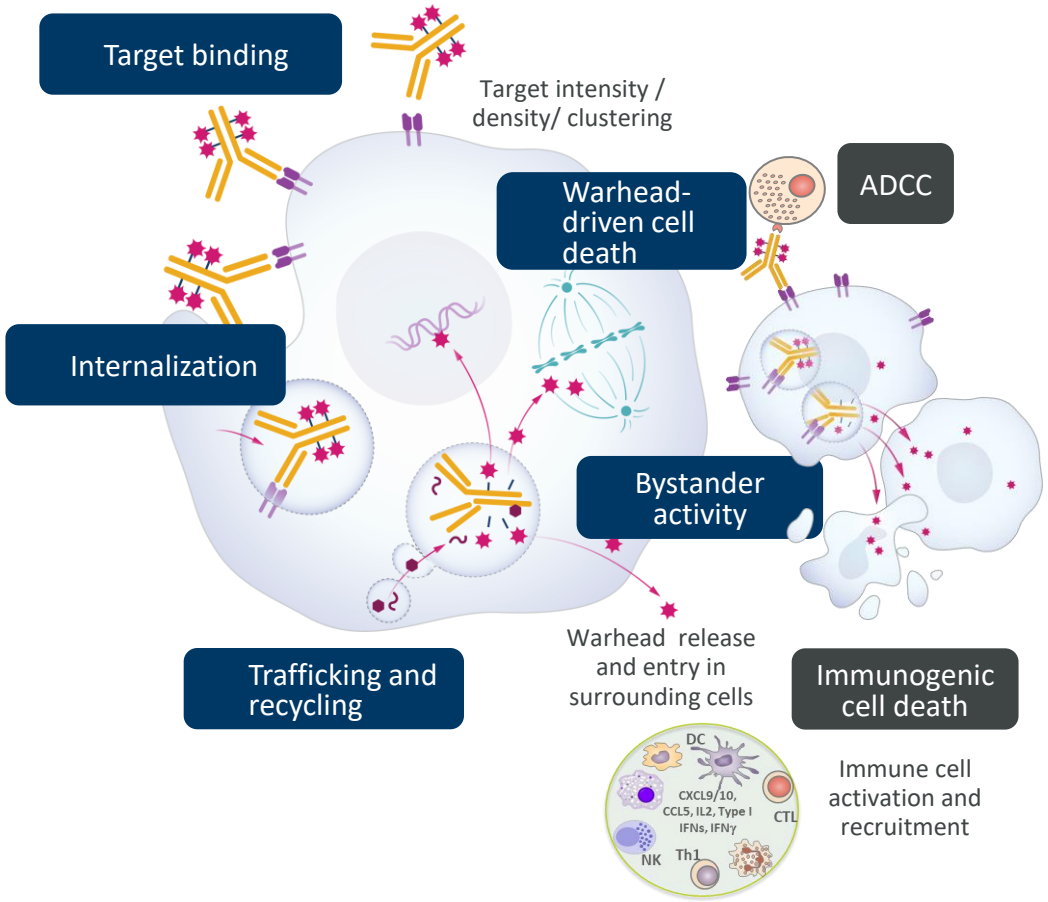
Most patients receive chemotherapy, however significant toxicities remain.



ADCs TO REPLACE CHEMOTHERAPY

- Targeted delivery to cancer cell
- Improved efficacy
- Decreased toxicity
- Increased therapeutic index

Optimized ADC technology and biology must align to build successful ADC



ADCs firmly established as a key therapeutic modality with a $30B+ projected market

11 APPROVED ADCs

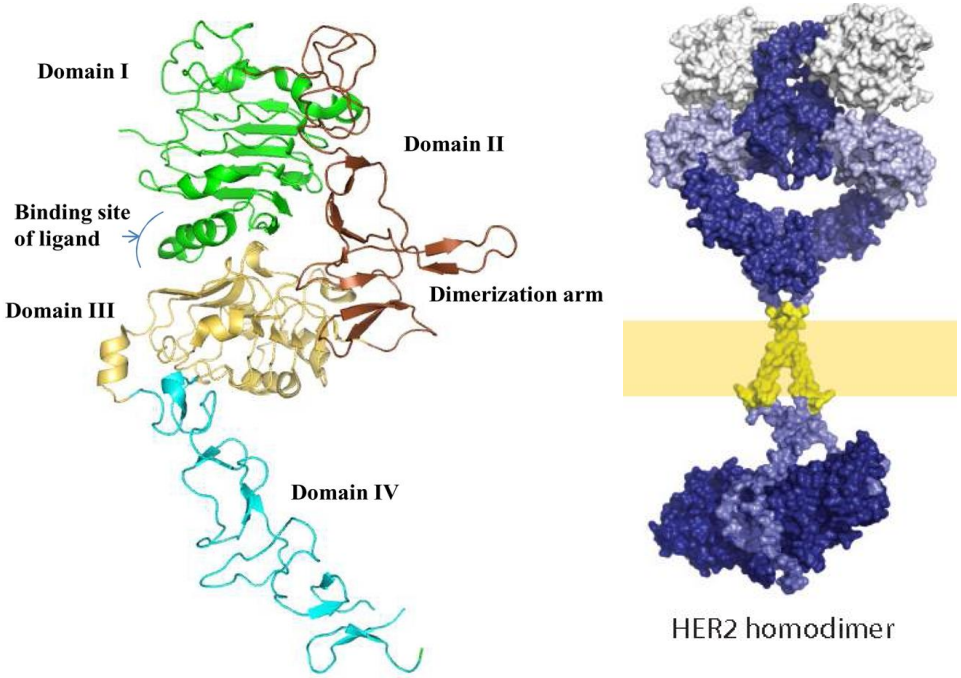
$30B+ PROJECTED TOTAL ADC MARKET

- **ADCs approved** for the treatment of various **solid and haematological** malignancies
- Successful with **multiple mechanisms of action** (MTIs, DNA cross linking, Top1 inhibitors)
- **Broad and deep responses** even in late lines
- Emerging data on **combinations with IO** (checkpoint inhibitors)

Source: GlobalData (April 12 OBU analysis)

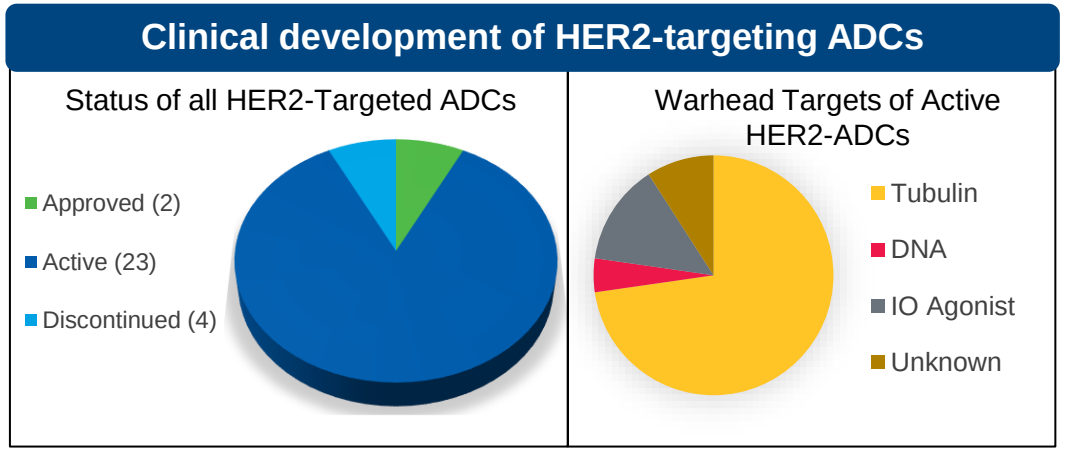
Case Study: HER2 as a preferred target for ADC development

HER2 Protein Structure



Favorable Characteristics of HER2 for an ADC

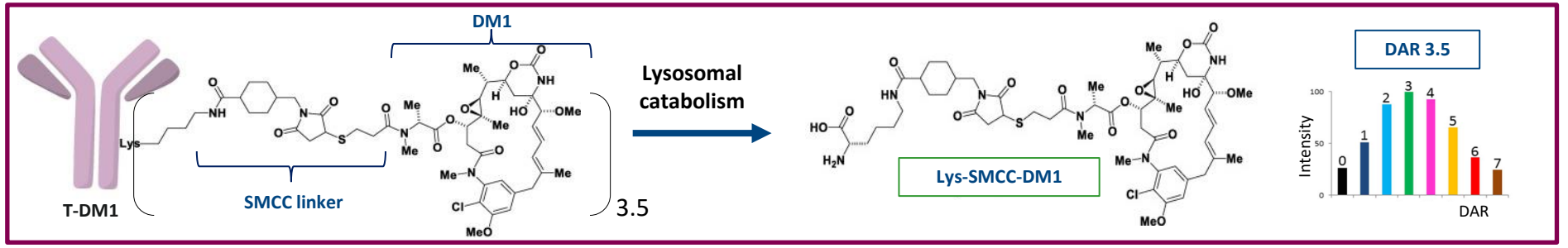
- High expression of target – amplified in many tumor types
- Upon mAb/ADC binding HER2 is internalized
- Efficient delivery of cytotoxic agent to cancer cells

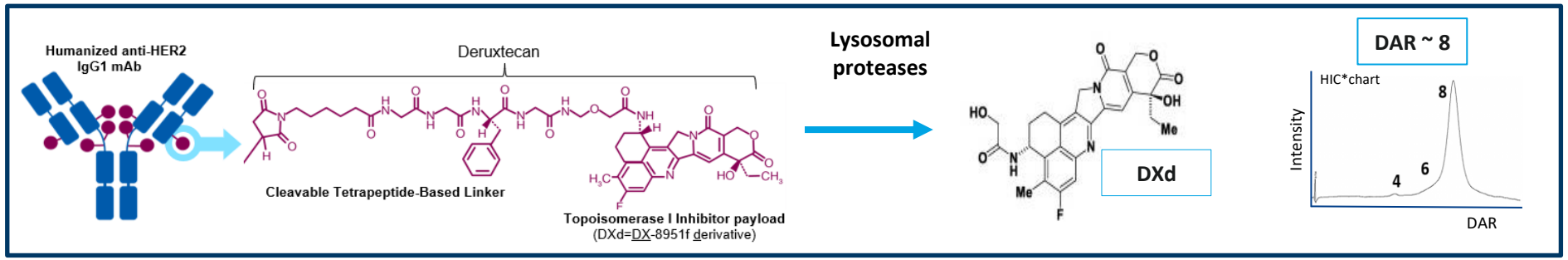


Jia He - Beacon ADC Digest, January 2021

Differences between T-DXd and T-DM1

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





T-DXd has higher DAR, and a membrane permeable payload with a different MoA

Ogitani et al. 2016. Clin Cancer Res 22(20): 5097-108

Phillips et al. 2008. Cancer Res 68(22): 9280-90

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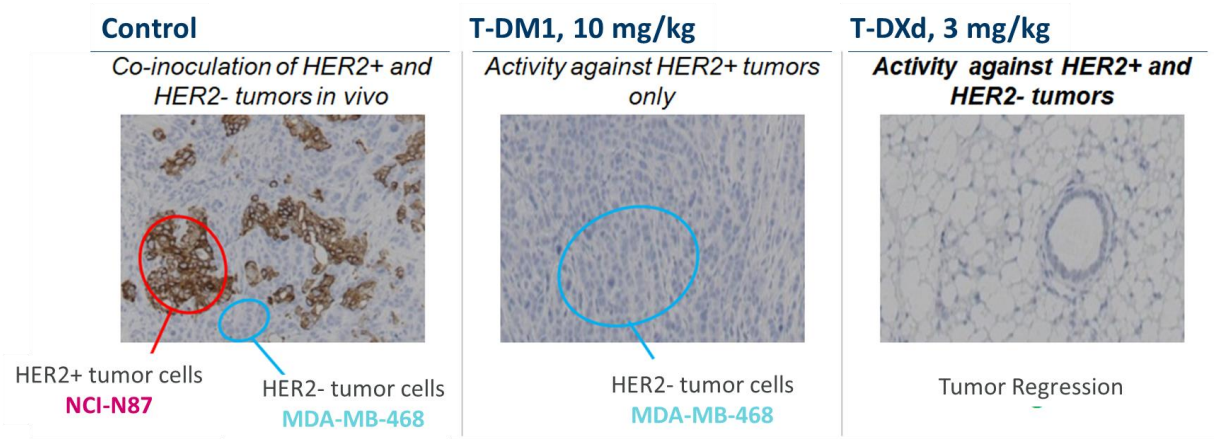
Unlike T-DM1, T-DXd elicits bystander anti-tumor effect

Highly membrane-permeable DXd payload may extend the cytotoxic effect to neighboring tumor cells.

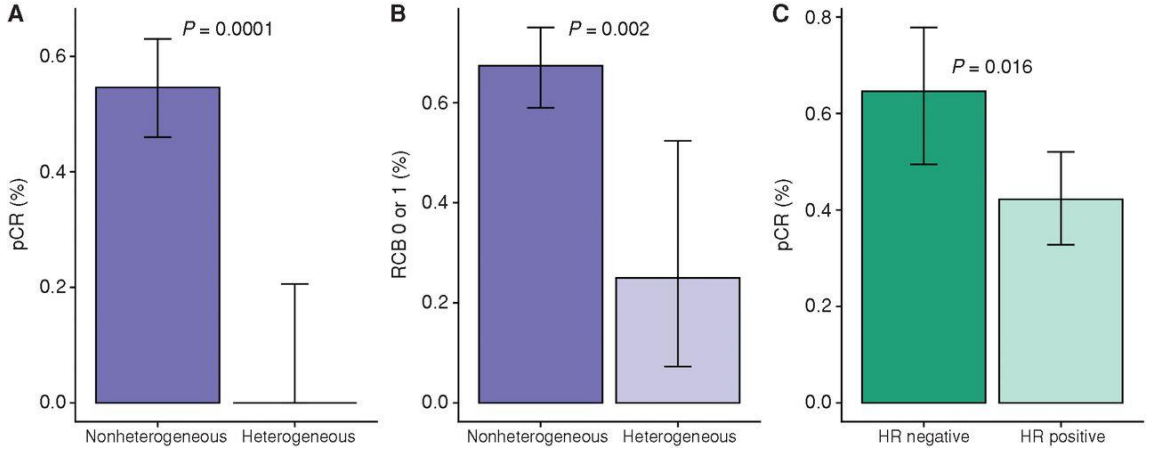
PRE-CLINICAL EVIDENCE SHOWS GREATER BYSTANDER ACTIVITY OF T-DXd vs T-DM1



Ogitani Y et al. 2016. Cancer Science 1077: 1039-1046

T-DXd was effective against HER2-negative tumor cells neighboring HER2-positive tumor cells

T-DM1 IS ONLY EFFICACIOUS IN HOMOGENEOUS TUMORS



Metzger Filho, Cancer Discovery 2021

T-DM1 showed pathological complete responses only in tumors with homogeneous HER2 expression

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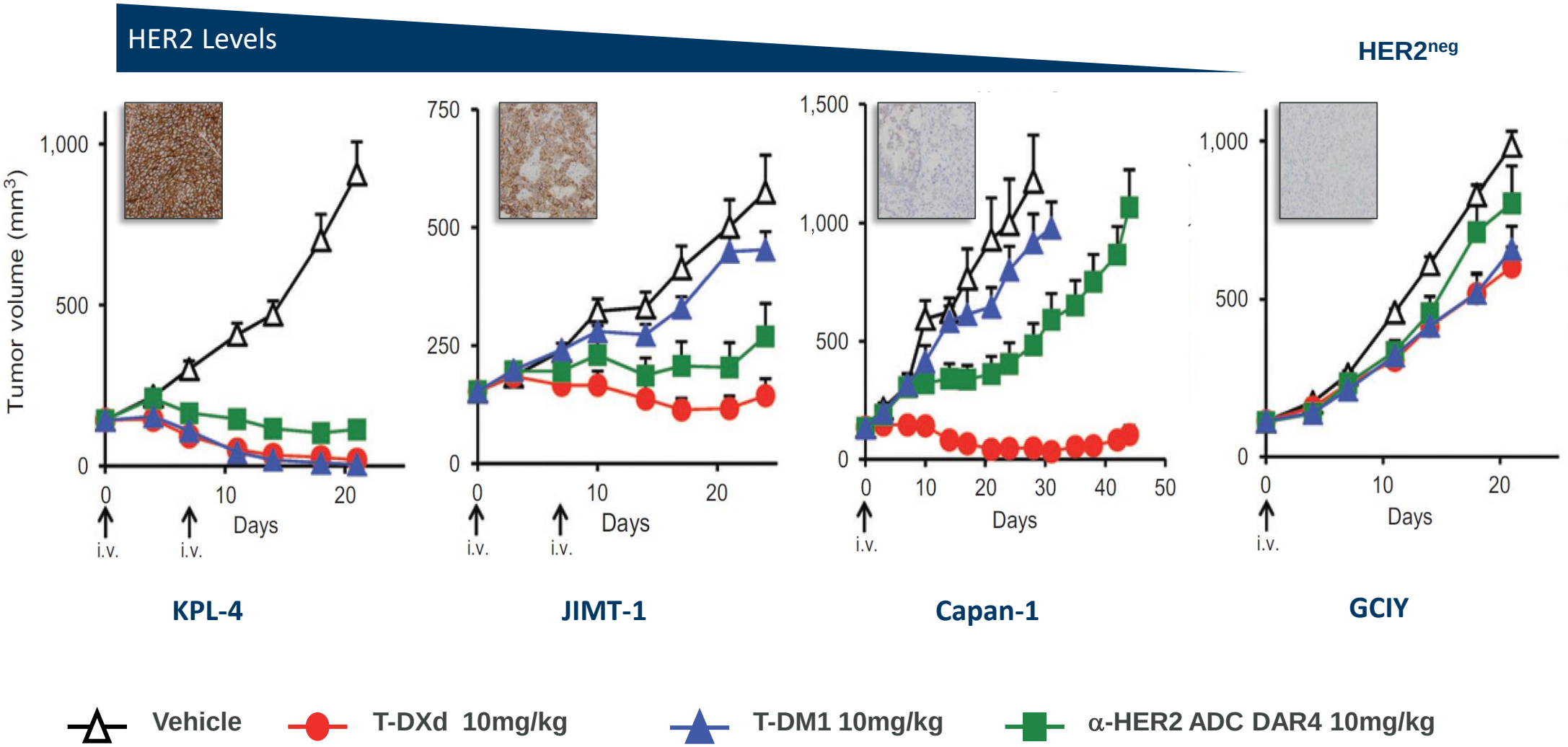
T-DXd is active in HER2-low tumor models



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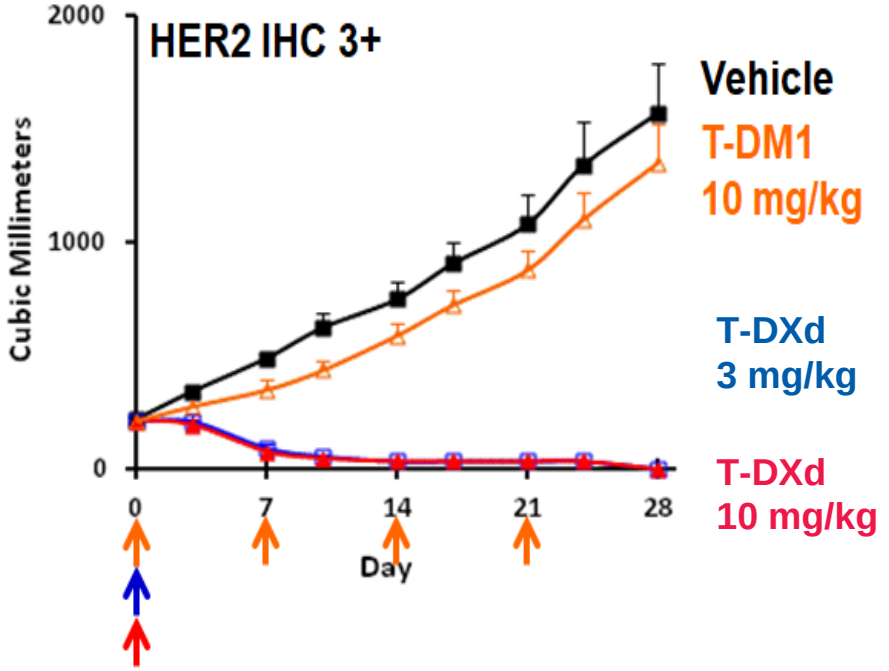
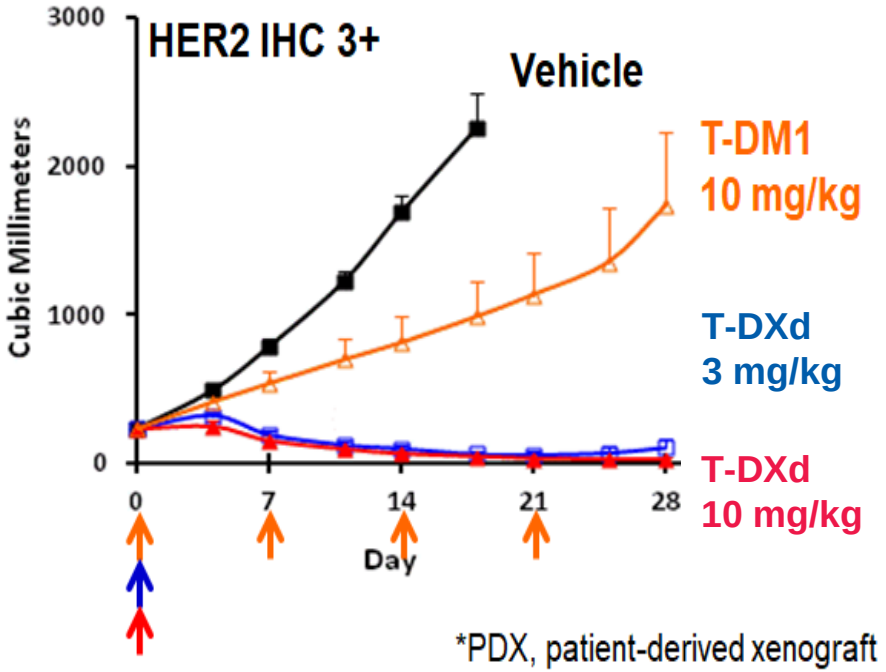
Ogitani et al. 2016. Clin Cancer Res 22(20): 5097-108

Antitumor activity against T-DM1-resistant tumors

ST1616B/TDR, breast cancer PDX*
from 13 months T-DM1-treated patient



ST1360B/TDR, breast cancer PDX
from 3 months T-DM1-treated patient



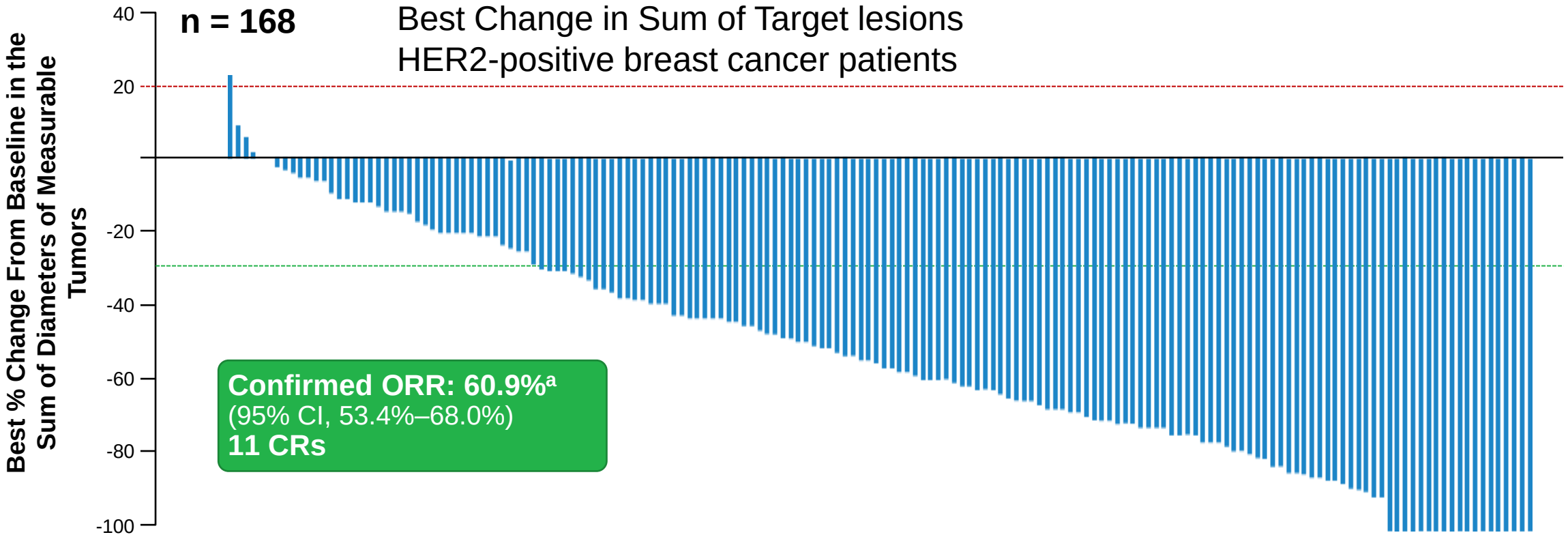
*PDX, patient-derived xenograft

T-DXd showed potent antitumor activity against T-DM1-resistant PDX tumors

Tamura-K et al, Abstract# 4585 (LBA17), ESMO 2016

T-DXd activity in patients previously treated with T-DM1

DESTINY-Breast01 An Open-Label Multicenter Phase 2 Study
Best Change in Sum of Target lesions
HER2-positive breast cancer patients



Modi S, et al. N Engl J Med. 2020; 382(7):610-621.

Data Cut off August 1, 2019
By independent central review.
The line at 20% indicates progressive disease; the line at −30% indicates partial response.
[a] Includes all patients who received T-DXd 5.4 mg/kg (intent-to-treat analysis; N=184).

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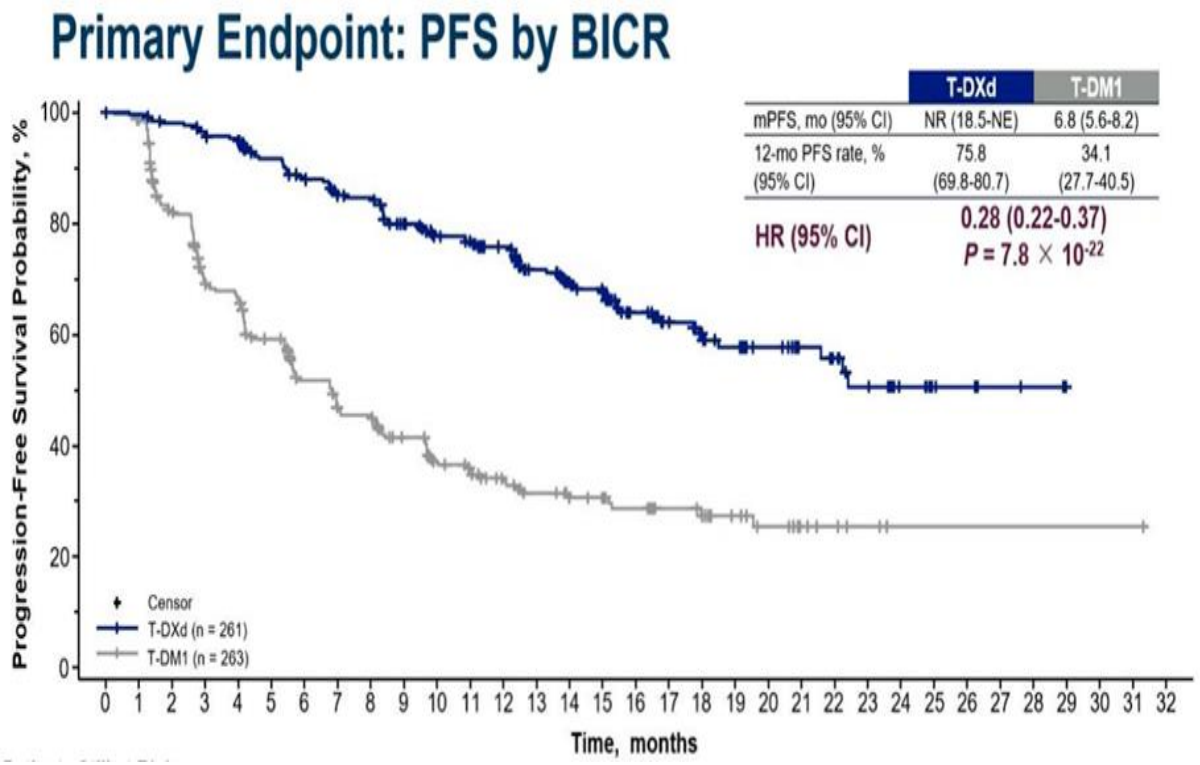
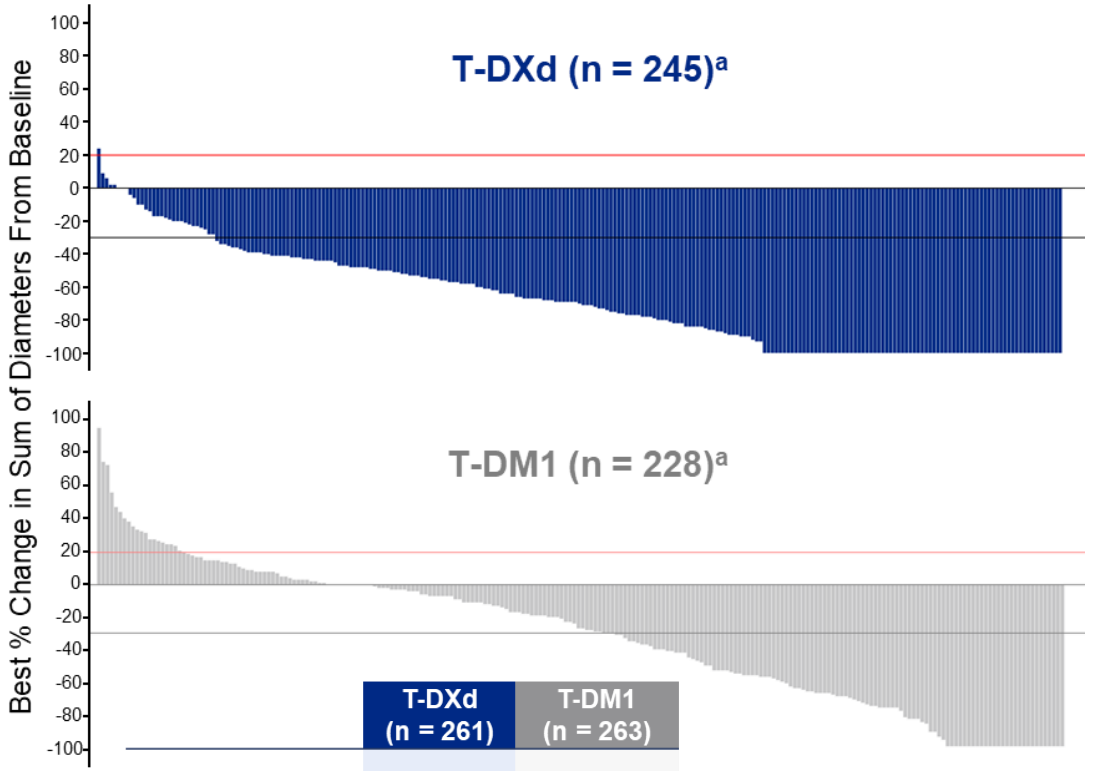
T-DXd demonstrates significant improvement in PFS compared to T-DM1

DESTINY-Breast03



	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
	$P = 7.8 \times 10^{-22}$	



	T-DXd (n = 261)	T-DM1 (n = 263)
Confirmed ORR		
n (%)[b]	208 **(79.7)**	90 **(34.2)**
[95% CI]	[74.3-84.4]	[28.5-40.3]

P < .0001

Patients with HER2-positive, unresectable or metastatic breast cancer that had progressed during or after treatment with trastuzumab and a taxane in the context of advanced or metastatic disease or that had progressed within 6 months after neoadjuvant or adjuvant treatment involving trastuzumab or a taxane

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Cortes, J et al. NEJM 24Mar2022 (DOI: 10.1056/NEJMoa2115022).

Practice-changing data at ASCO in HER2-low, HR+/HR- mBC

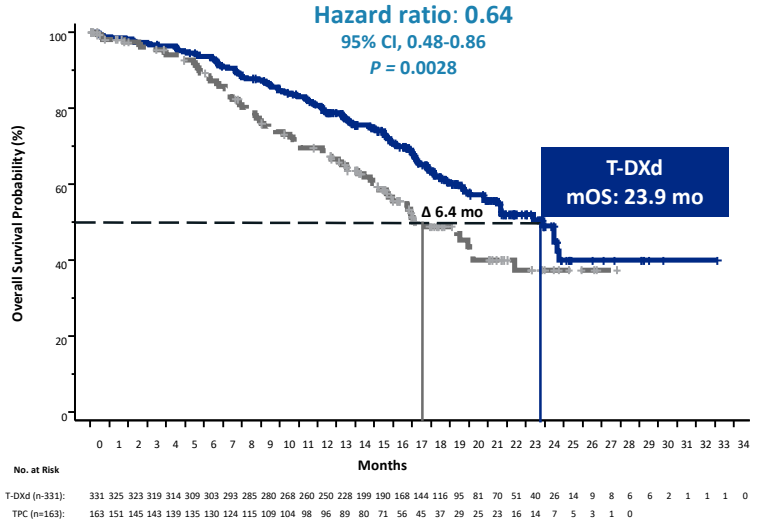
2022 ASCO ANNUAL MEETING
ADVANCING EQUITABLE CANCER CARE THROUGH INNOVATION

The NEW ENGLAND JOURNAL of MEDICINE

DESTINY-Breast04 Phase III study: Establishing T-DXd as new standard of care in HER2-low, HR+/HR- mBC

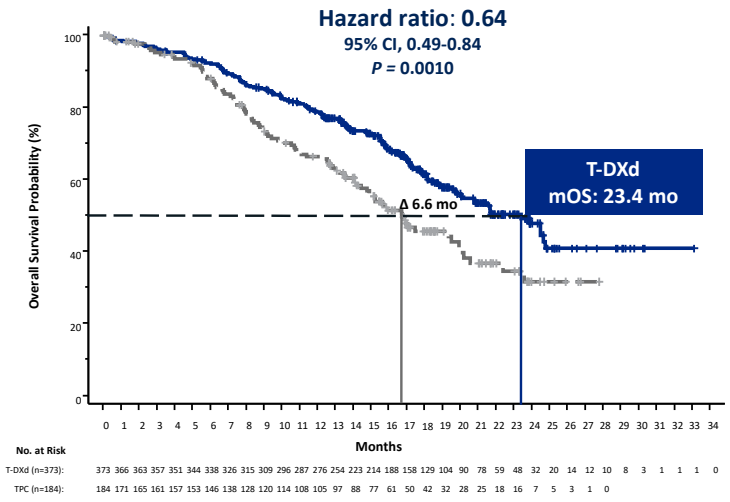
Overall Survival

Hormone receptor positive



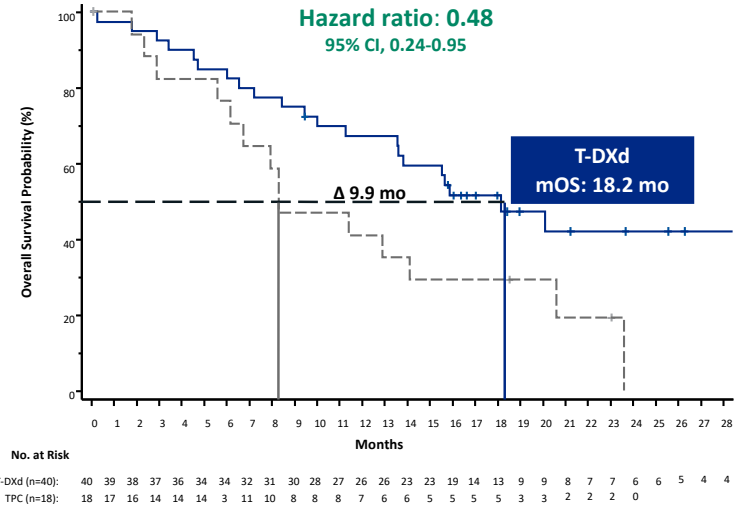
	T-DXd	TPC
mOS, mo	23.9 mo	17.5 mo
HR (95% CI)	**0.64 (0.48-0.86)**	
	***P* <0.0001**	

Intention to treat



	T-DXd	TPC
mOS, mo	23.4 mo	16.8 mo
HR (95% CI)	**0.64 (0.49-0.84)**	
	***P* <0.0010**	

Hormone receptor negative



	T-DXd	TPC
mOS, mo	18.2 mo	8.3 mo
HR (95% CI)	**0.48 (0.24-0.95)**	
	(Exploratory endpoint)	

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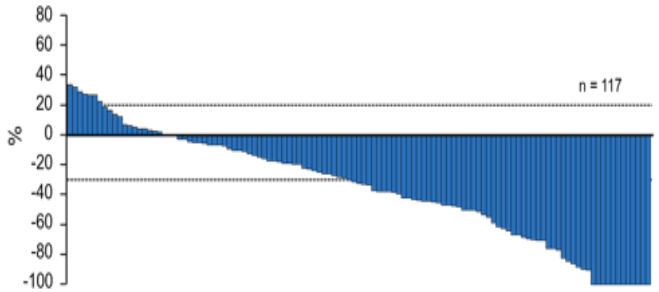
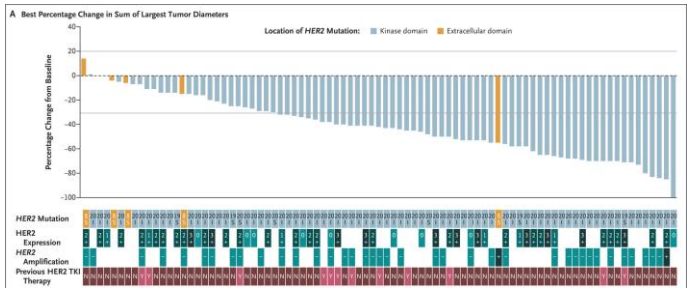
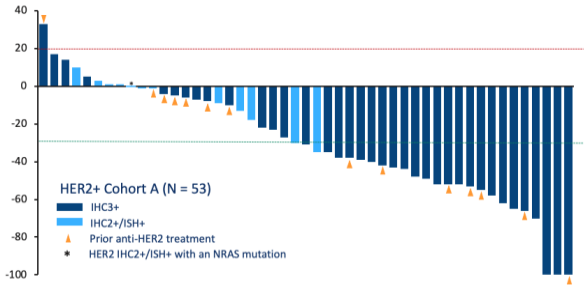
Modi, S et al. MEJM 07Jul2022 (DOI: 10.1056/NEJMoa2203690)

T-DXd is active across several tumor types

	HER2+ gastric (Approved[1])	HER2-mt lung	HER2+ CRC
T-DXd data			
	5.6m mPFS[2] **51.3% ORR** by ICR[2] **12.5 mOS** (median 2 prior LoT)[2]	**8.2m mPFS[3]** **55% ORR** (median 2 prior LoT)[3] **17.8 mOS** (median 2 prior LoT)[3]	**6.9m mPFS[5]** **45.3% ORR** (median 4 prior LoT)[5]
SOC	**Chemo. control arm** **3.5m mPFS[2]** **14.3% ORR** by ICR[2] **8.4 mOS**	**Docetaxel control arm** 4.2m mPFS[4] 12% ORR[4]	**Regorafenib** 2.0m mPFS[7] 1% ORR[7] 2012 label

Cross-trial comparisons should always be done with caution, particularly as these trials differed in setting, design, size, time period of recruitment, location of study sites, etc.

2L=second line; DRFI=distant recurrence-free survival; ICR=independent central review; IDFS=invasive disease-free survival; LoT=line of therapy; m=months; mOS=median overall survival; mPFS=median progression-free survival; ORR=objective response rate; OS=overall survival.

1. Approved based on Phase II DG-01 results: Shitara, K et al. N Engl J Med.2020; 382:2419-2430. 2. Shitara K, et al. Presented at ASCO (Virtual), 2020. Abstract #4513, Data cutoff November 08 2019; 3. Li, BT et al. N Engl J Med 2022; 386:241-251 4. Borghaei H, et al. N Engl J Med. 2015;373(17):1627–1639, Data cutoff March 18 2015 5.Siena, S et al The Lancet Onc 22(6):779-789.; 7. FDA. STIVARGA PI. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203085lbl.pdf. Accessed March 2021.

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Thoughts

We can successfully delivery cytotoxics precisely to tumor cells using Antibodies

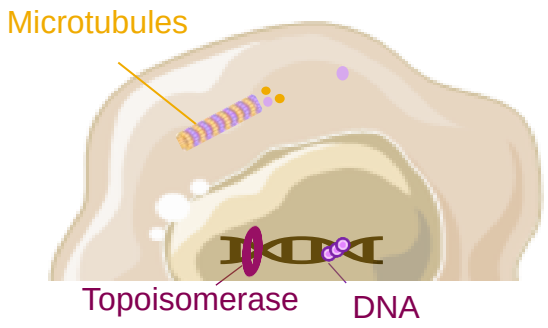
Not all ADCs are created equal- marry the target biology with the right technology

With the right technology we can redefine cancer treatment

Building Next generation ADCs: Learning the right combinations for successful ADCs

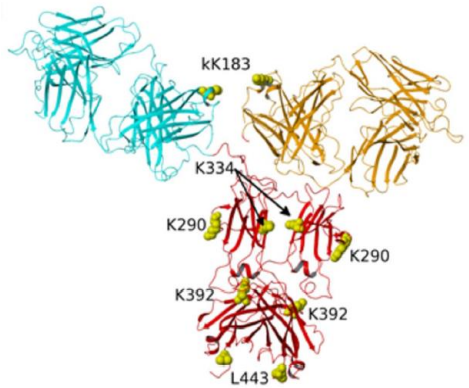
1 WARHEADS

Diverse payloads have been successful



2 LINKERS

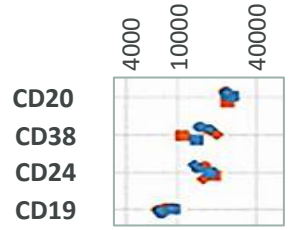
Optimized conjugation chemistry



3 TARGETS

Target properties

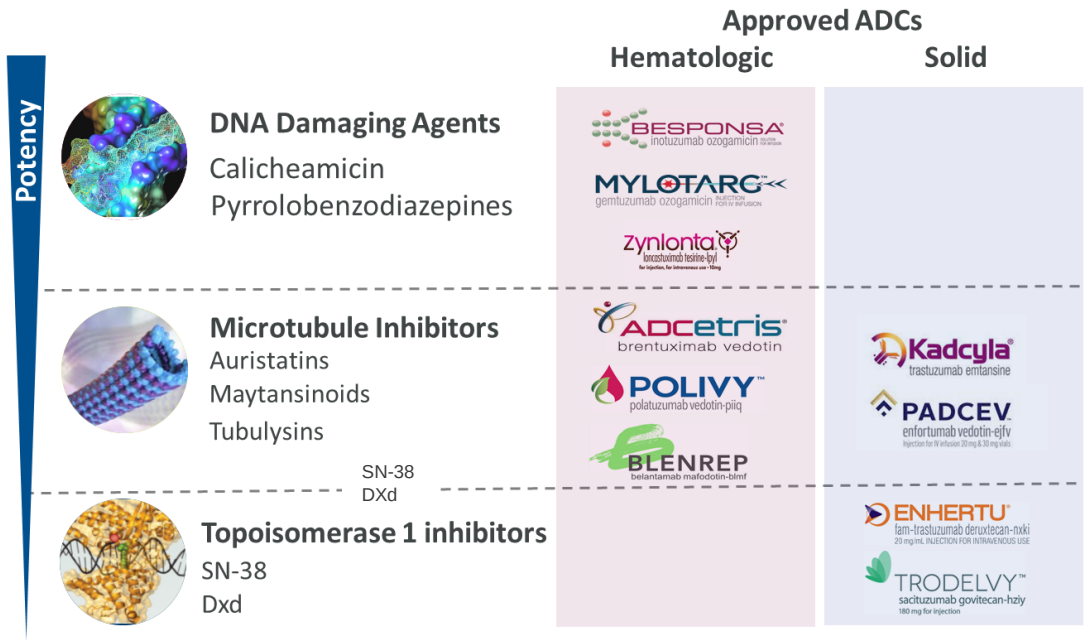
Normal and tumor expression



Target copies / cell

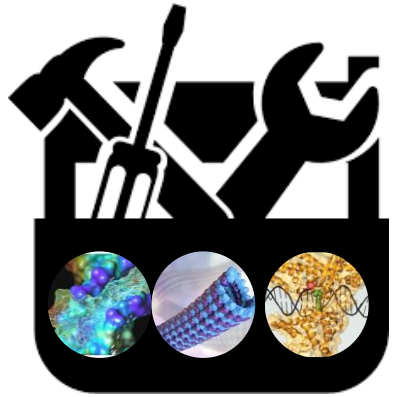
ADCs with diverse linker-payloads may enable novel combinations

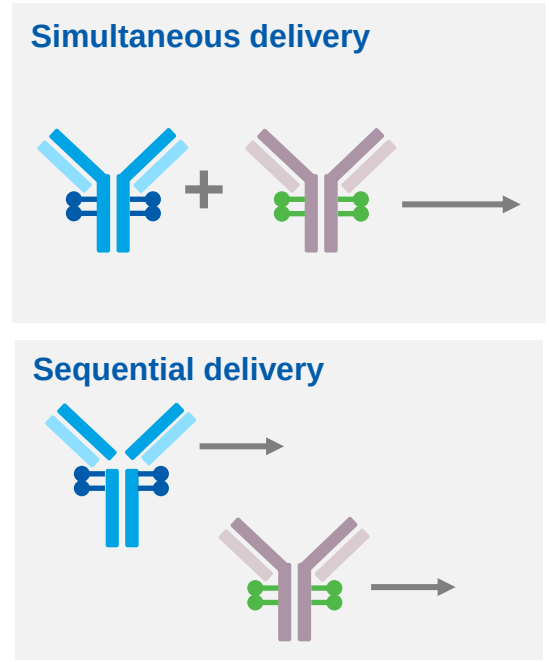
Currently approved ADCs show the promise of diverse linker-payload MoA



Highly potent cytotoxics have more success in heme malignancies than solid tumors

The future: Match disease and target biology with payload mechanism





Combine and sequence ADCs with different payloads and/or targets to maximize response and evade resistance

Widening therapeutic index of ADCs: Site-specific conjugation

Stochastic versus site-specific conjugation

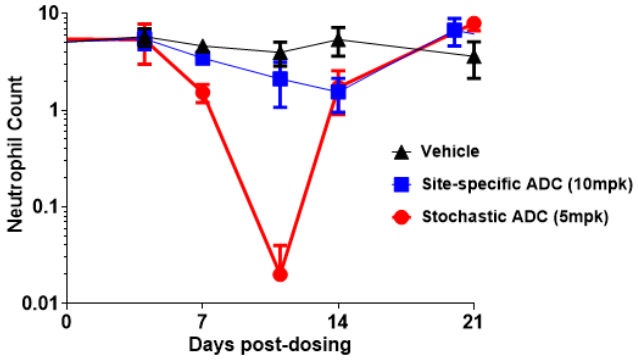
Native lysines

Native cysteines

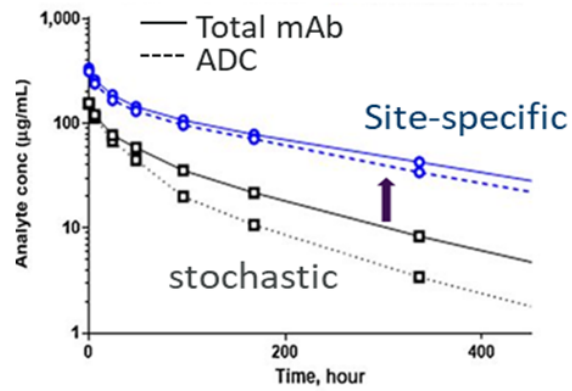
However, limited by toxicity…

Site-Specific Conjugation

ssADCs reduce MTI-mediated neutropenia[1]

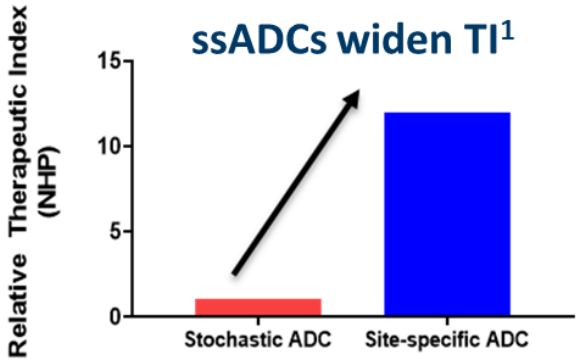


ssADC enhance stability[1]



Site-specific conjugation improves therapeutic index in pre-clinical models

ssADCs widen TI[1]



ssADC = site-specific conjugated ADC

1. Graziani…Sapra et al. Mol Canc Thera. 2020.

Target discovery using surface proteomics

ADC Target ID guided by these principles

Surface Protein density

High for TOP1i – avg surface proteins/cell
- **HER2**: 1.2x10^6-200,000[1]
- **TROP2**: 350,000[2]

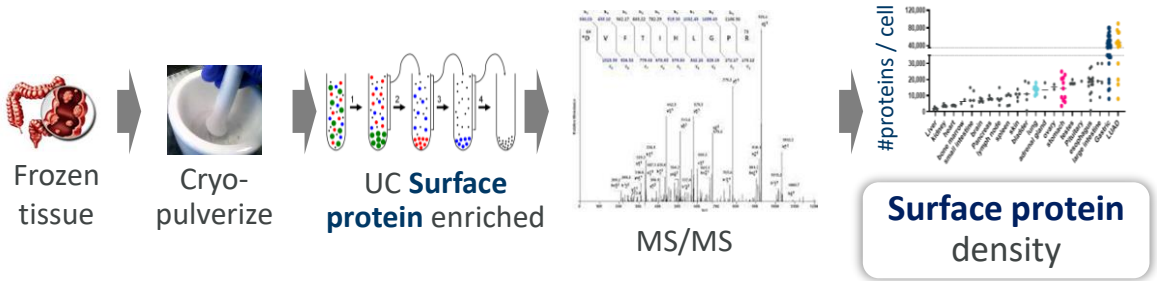
Lower with more potent warheads and/or when target drives biology, e.g., mHER2 in NSCLC

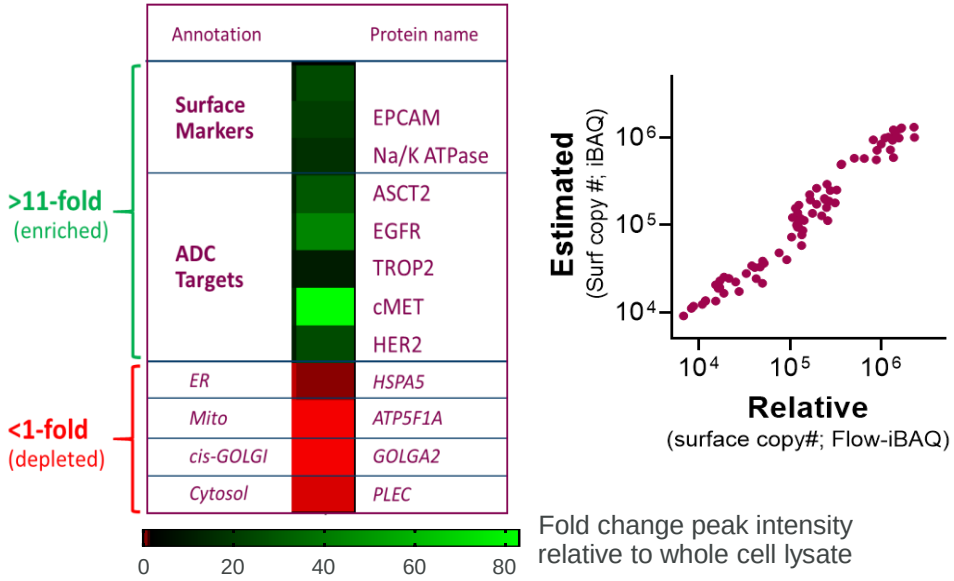
Normal tissue expression

Tolerated with lower-potency warheads
- Avoid sink / vital organs

Shifting away from RNA to protein-based target identification

Robust proteomics approach to fuel target selection





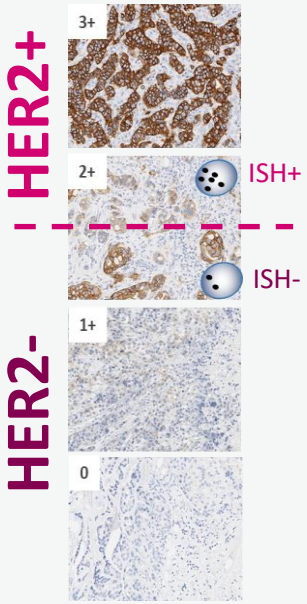
Enabling quantitative approach to better target identification

Revolutionizing patient outcomes with next generation diagnostics

TODAY

Conventional IHC

Manual Scoring



Focused on positivity and intensity or pre-defined rules

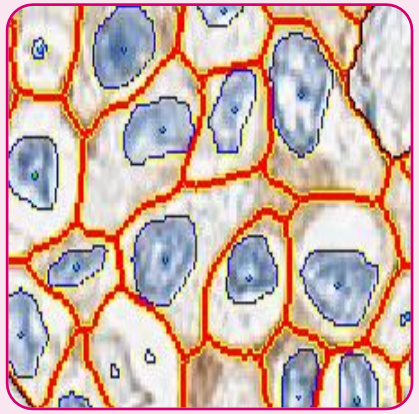
Subjective and semi-quantitative

FUTURE DIRECTION

Computational Pathology

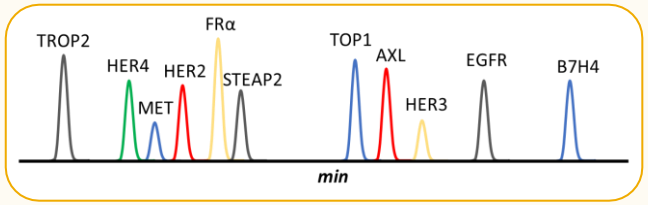
Dx Beyond Human Capability

Quantify target expression on membrane of every tumor cell



Proteomics through MS

Quickly identify which ADC will benefit the patient



Multiplex proteins for single-sample quantification

Directly comparable by absolute quantitation

Conventional pathologist score* (IHC/ISH)

Outcomes with T-DXd treatment	HER2+ (IHC 3+ or 2+/ISH+) (n = 72)	HER2– (IHC 2+/ISH–, 1+ or 0) (n = 65)
ORR, %	56	**42**
mPFS, mo	14.1	**11.0 months**

**14 patients were not included due to missing FISH data.*

HER2 Quantitative Continuous score (IHC/IA)

Outcomes with T-DXd treatment	HER2 QCS+ (OD > 8) (n = 120)	HER2 QCS- (OD > 8)) (n = 31)
ORR, %	56	**26**
mPFS, mo	14.1	**9.0 months**

Cellular OD cutoff must be > 8.04 in ≥ 90% of cells for patients to be "positive"

QCS would enable identification of

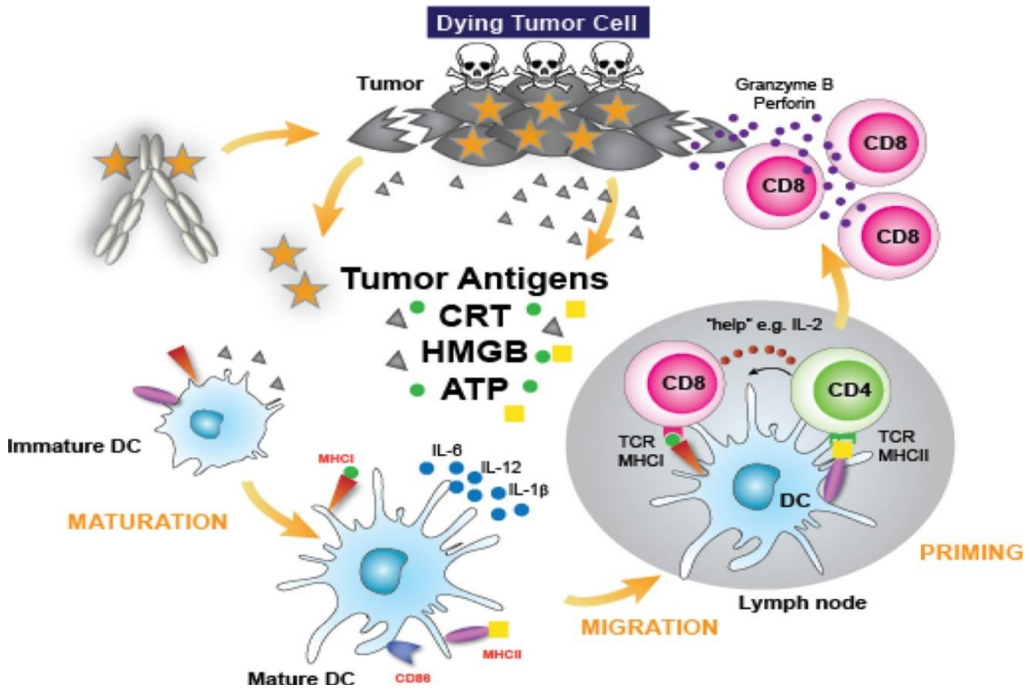
30% more pts

who have greater benefit from T-DXd in this study (J101 Ph1)

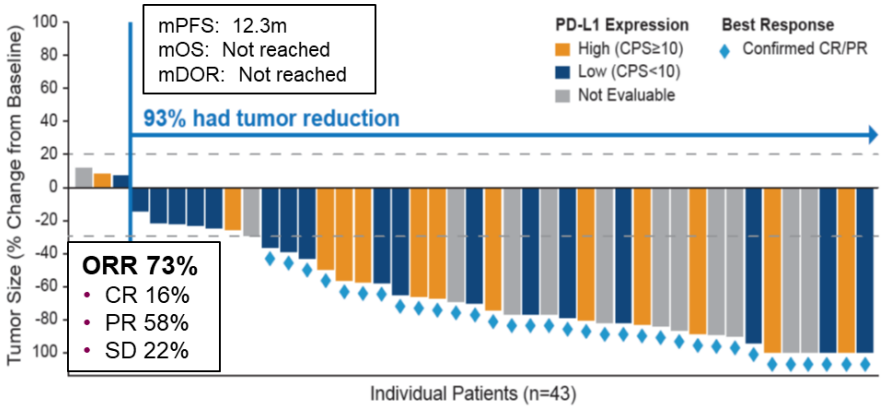
Daiichi-Sankyo | AstraZeneca

Evidence of ADC-IO combination benefit emerging in the clinic

BIOLOGICAL RATIONALE: IMMUNOGENIC CELL DEATH



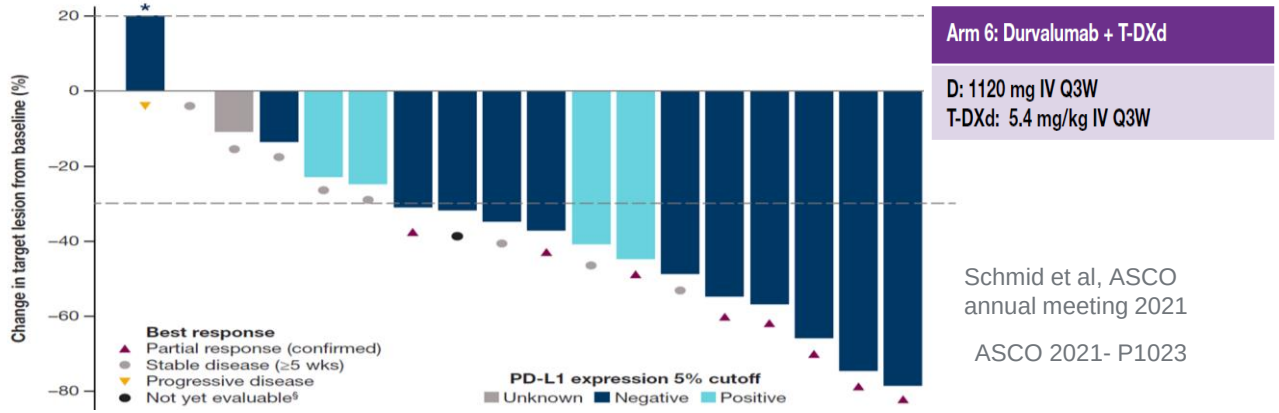
CLINICAL PROOF-OF-CONCEPT WITH MTi ADCS



Nectin 4 ADC + pembrolizumab combo: improved clinical activity vs ADC alone

Rosenberg et al, J Clin Onc, 38 supp, 2020

CLINICAL PROOF-OF-CONCEPT FOR IO COMBINATION WITH TOP1I- ADC (T-DXd) - BEGONIA PHASE 1B/2 TRIAL



Schmid et al, ASCO annual meeting 2021

ASCO 2021- P1023

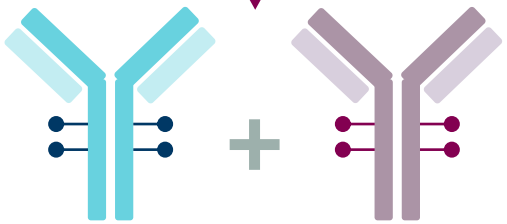
Daiichi-Sankyo | AstraZeneca

Where can the future take us?

ADCs **REPLACE CHEMOTHERAPY**

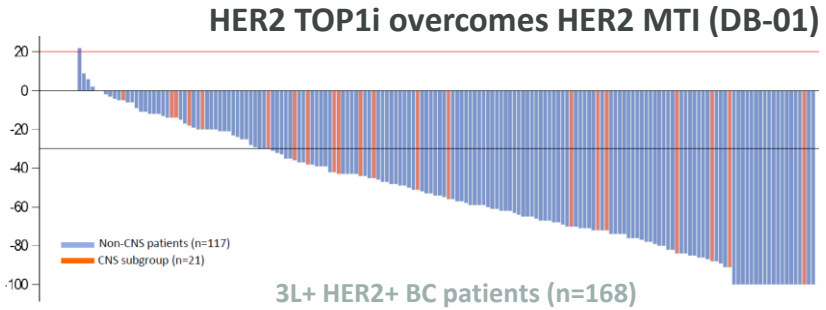
Indication & target **BIOLOGY DRIVES ADC DESIGN**

ADC combinations & sequencing **OVERCOME RESISTANCE**



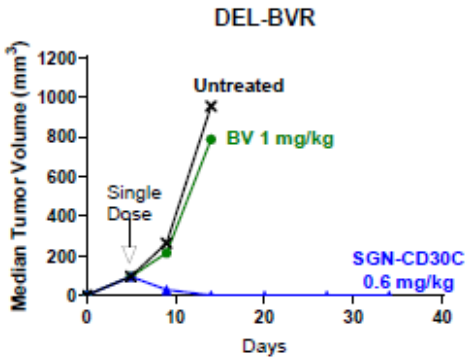
ADC-ADC sequencing/combination

Clinical evidence:



Modi S, et al. N Engl J Med. 2020; 382(7):610-621.

Preclinical evidence:



Ryan et al, Cancer Res 80:16 Supp, 2020

Daiichi-Sankyo | AstraZeneca

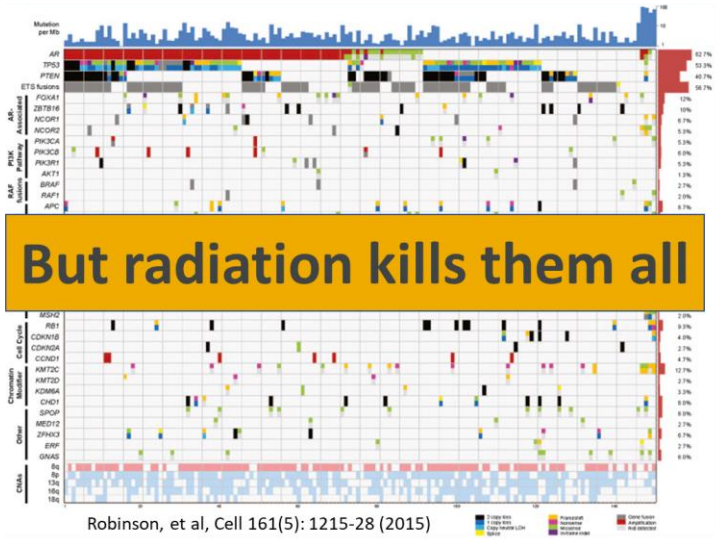
Outline

1. Antibody-based therapies- Vision and History
2. Antibody drug conjugates (ADCs)
3. Radioconjugates
4. T-cell engagers
5. Targeted nanoparticles

Radioconjugates have the promise to expand beyond today's limits of radiotherapy

Radiation is a powerful modality

Challenge: mCRPC is a heterogeneous group of diseases

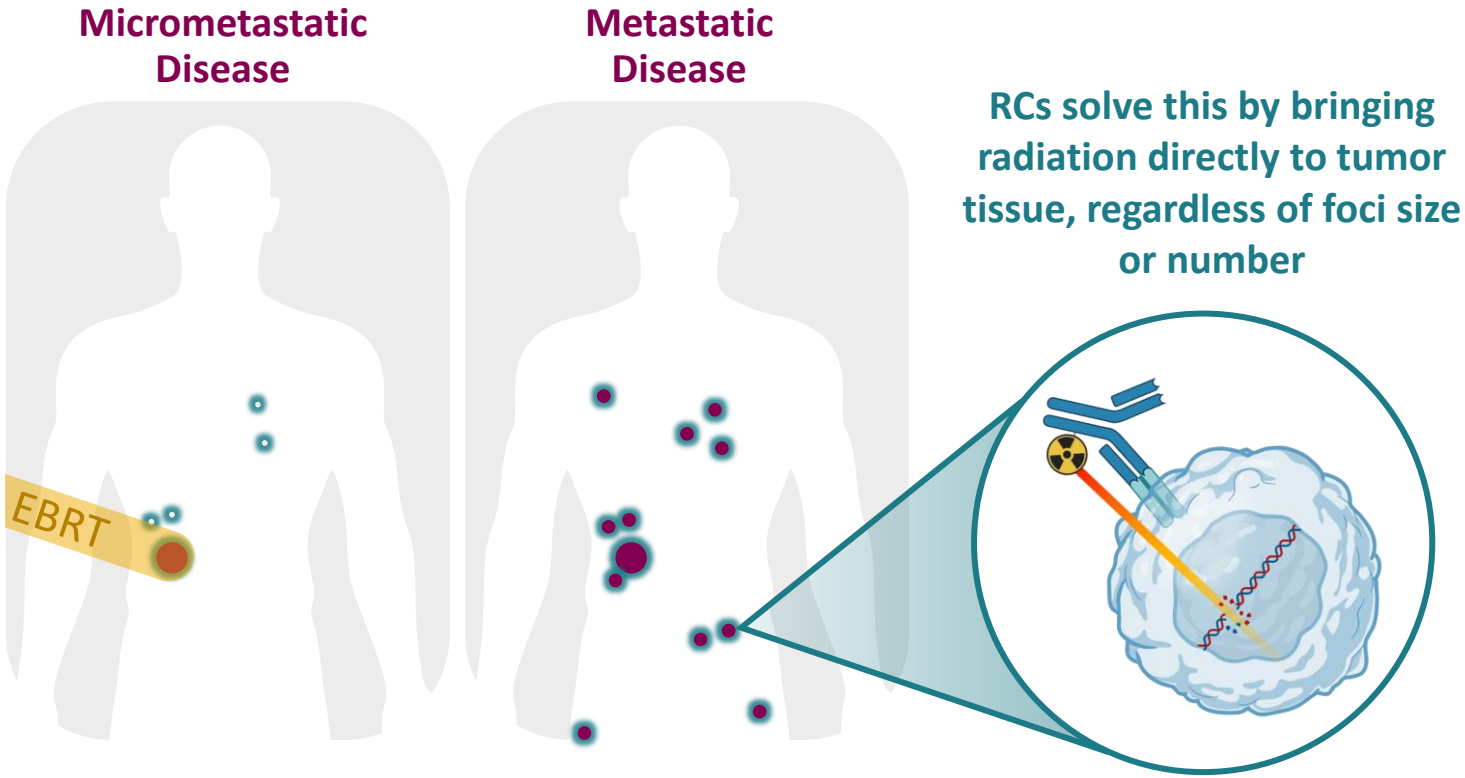


But radiation kills them all

Robinson, et al, Cell 161(5): 1215-28 (2015)

February External Science Panel

The challenge is delivering it to micrometastatic and metastatic disease



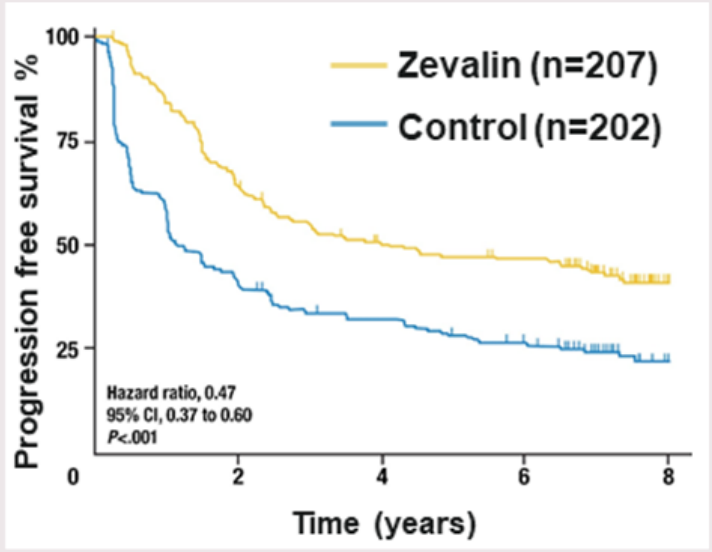
RCs solve this by bringing radiation directly to tumor tissue, regardless of foci size or number

Radioconjugates show clinical promise for both hematological and solid tumors

HEMATOLOGICAL MALIGNANCIES

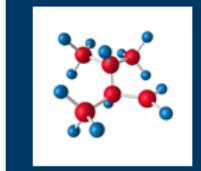
Zevalin (^{90}Y-CD20 mAb)

Bexxar (^{131}I-CD20 mAb)



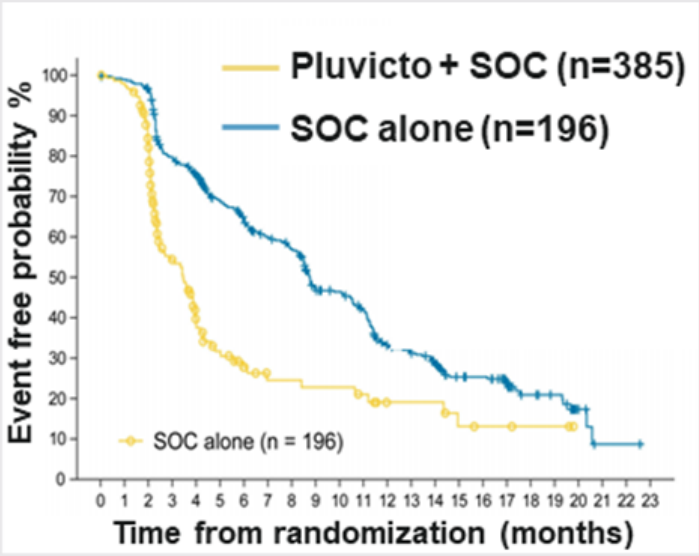
Adapted from Morschhauser, J Clin Oncol 2008

SOLID TUMOR MALIGNANCIES



Lutathera (^{177}Lu-Dotatate)

Pluvicto (^{177}Lu-PSMA-617)



Adapted from Sartor, N Engl J Med 2021

Future of radioconjugates may expand clinical responses

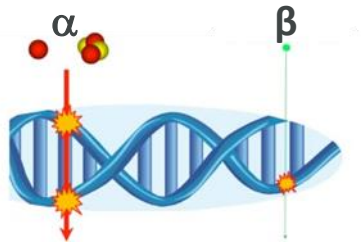
EXPANDING ON THE SUCCESS OF RADIOCONJUGATES

Choice of radionuclide may expand and improve clinical responses

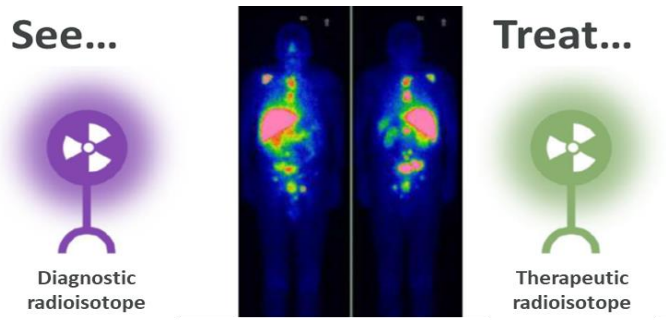
α-emitters vs β-emitters:

HIGH ENERGY + SHORT RANGE = MORE POTENT + LESS TOXIC?

All current approved radioconjugaes are β-emitters



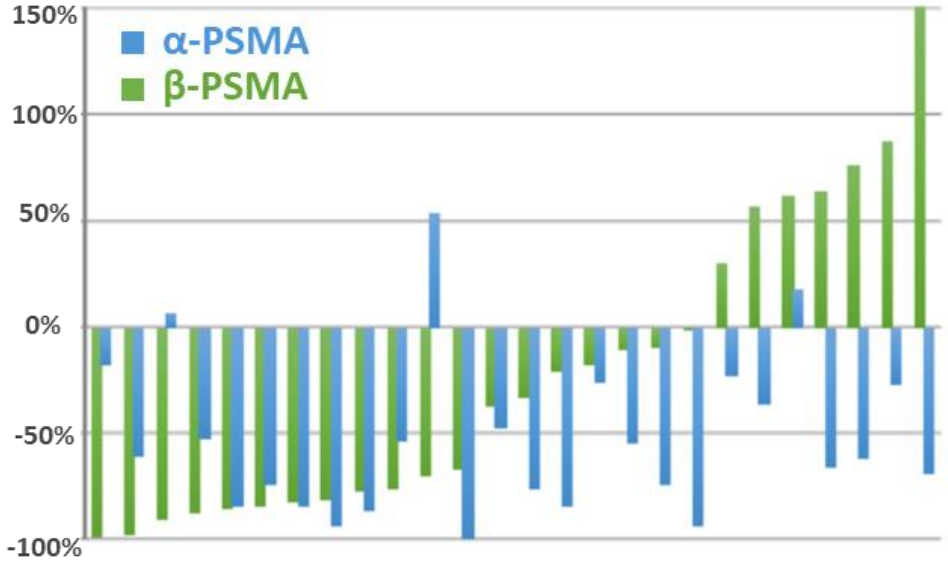
RCs have a built-in imaging biomarker



Adpated from: Targeted Radiopharmaceutical Conference Dec 2020
Chris Behrenbruch, Telix Pharmaceuticals

FUTURE CLINICAL STRATEGIES

Response to α-therapy after β-therapy provides sequencing & combo rationale



European Urology 79:343-350 (2021)

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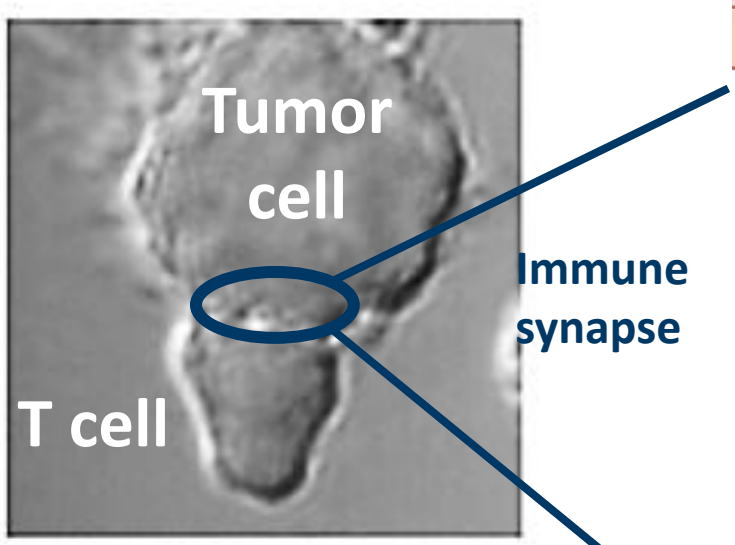
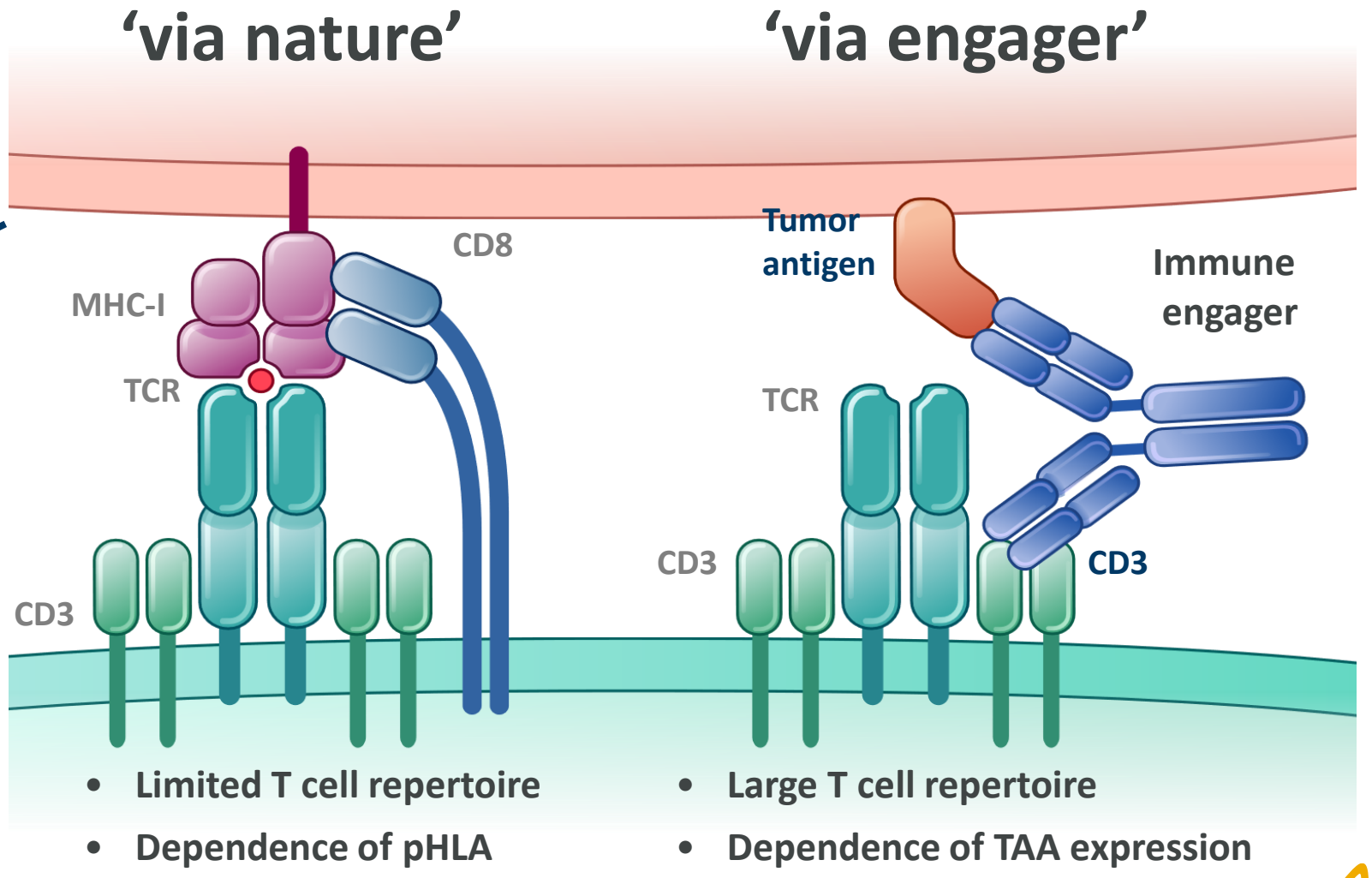
What are Immune Engagers?

T cell bispecifics link the tumor associated antigen to CD3ε of the TCR complex;

T cell activation



Adapted from Cemerski et al, Immunity 2007



T Cell Engagers (TCE) set to transform Heme landscape

Approved TCEs

2

BLINCYTO™
Acute lymphoblastic leukemia

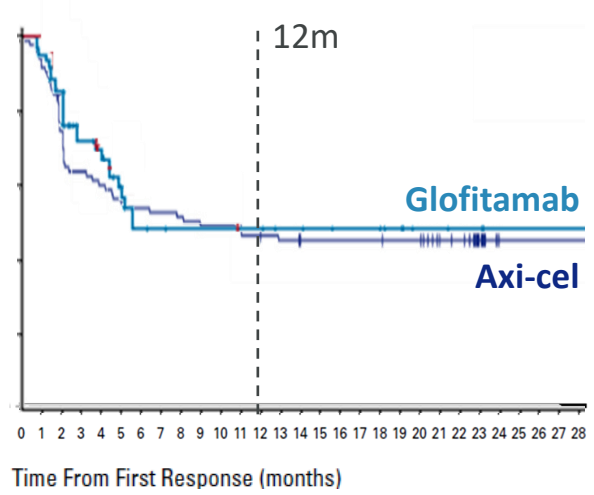
KIMMTRAK
Metastatic uveal melanoma

CD20 TCE shows favorable response and better safety profile

		CD20 TCE (Glofitamab)	CD19 CAR-T (SOC – Axi-cel)
	Population	2L+ R/R aNHL	3L+ R/R DLBCL
Efficacy	CR	33% (**64%** @RP2D)	53%
Efficacy	**DOR @12m**	**49%**	**~47%**
Safety	CRS AG	**50%**	**92%**
Safety	CRS G3+	4% (**6%** @RP2D)	**11%**

ASH2021

Duration of response



Promising solid tumor efficacy is beginning to emerge but are limited by significant toxicities

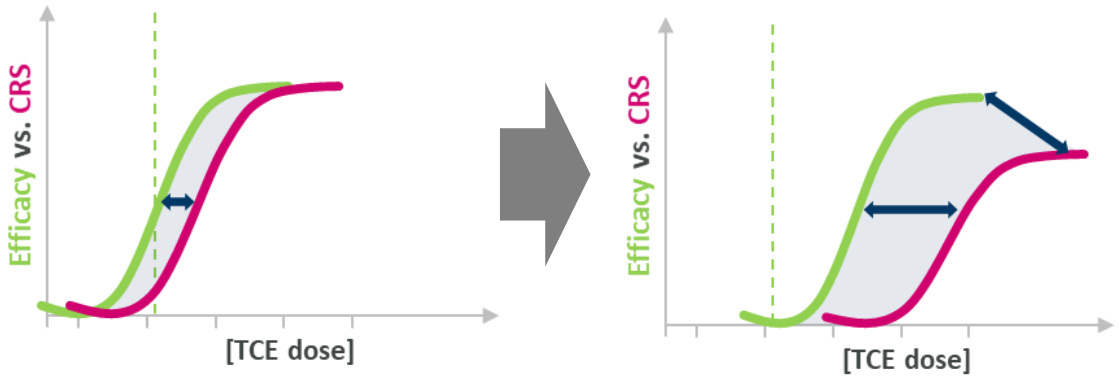
Glofitimab used as example TCE as has most expansion mDOR data available. Pivotal P1b as monotherapy in 3L+ DLBCL w/ filing due 2022. P3 ongoing in 2L+ DLBCL in combo + CTx w/ filing due 2024+.
*n=14 aNHL with 2.5/10/30mg IV (step-up doses). Duration of response rate provided for all responders (total) and those with complete response (CR)

Future: Substantial investment in the field in optimizing TCEs

Field evolving to decrease CRS and increase TI

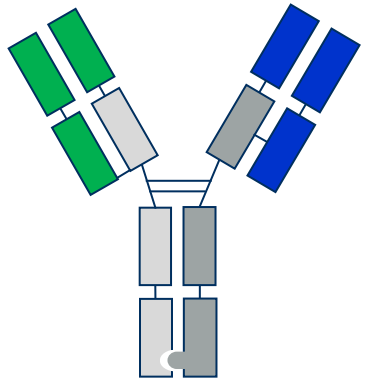
Cytokine release storm (CRS) results from **excessive** and supraphysiological **activation of T cells**

Field is actively looking to expand TI index by reducing CRS



Antibody engineering for decreasing CRS

1. *Identification of TAAs*
2. *'Tuned' CD3 domains*
3. *Half-life extension*
4. *Novel formats*



Outline

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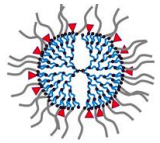
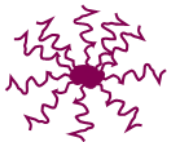
Targeting nanoparticles for greater therapeutic index

Untargeted nanoparticles



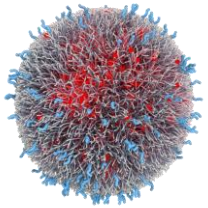
Dendrimers/
Star polymers

~10- 20 nm

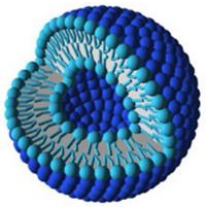


Polymeric
micelles

20-50 nm



Polymeric
nanoparticles



Liposomes

70-150 nm

Untargeted liposomes have been successful

6

Approved liposomes

DOXIL (doxorubicin HCl liposome injection)

Myocet (liposomal doxorubicin)

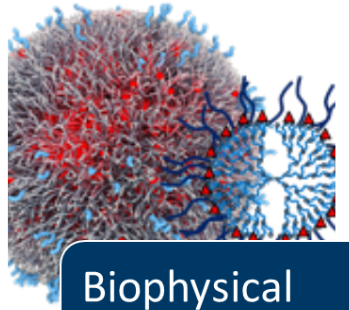
DaunoXome

Marqibo (vinCRIStine sulfate LIPOSOME injection) 5 mg per 31 mL for intravenous infusion

onivyde® (irinotecan liposome injection)

Vyxeos Liposomal daunorubicin / cytarabine

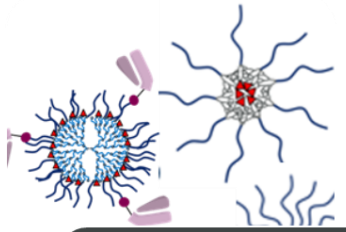
Use of mAb fragments to target nanoparticles



Biophysical

Pharmacokinetics

Controlled release



Active

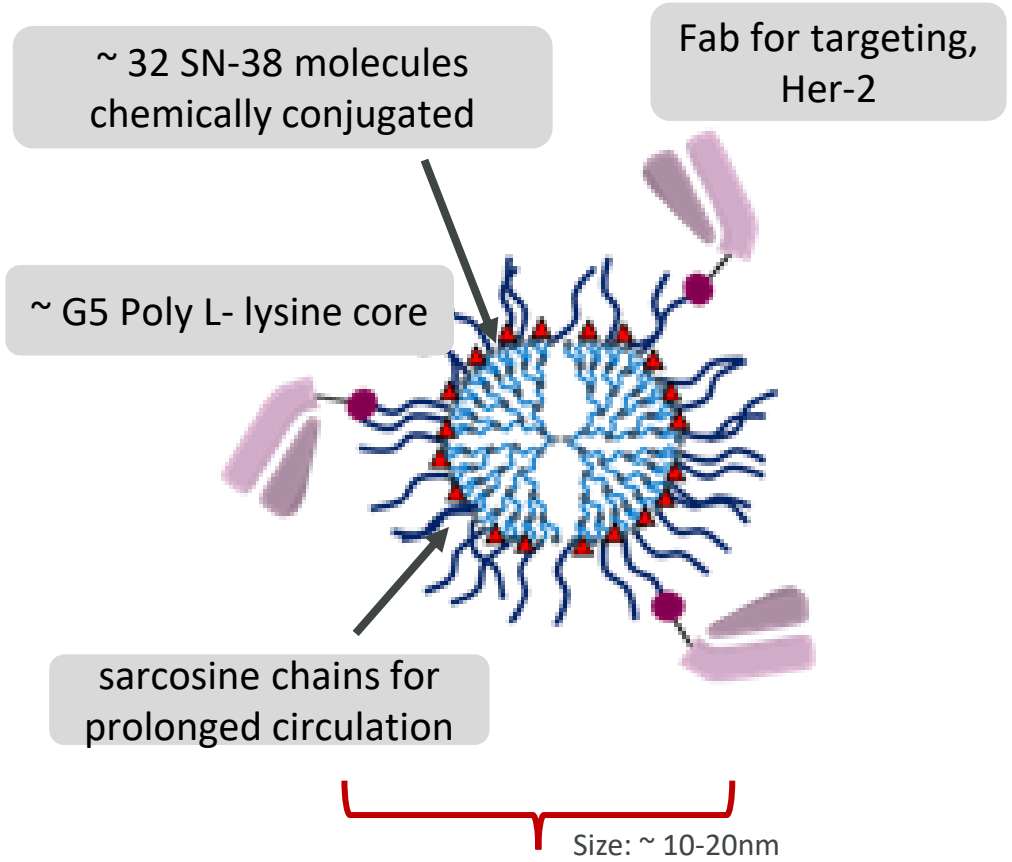
Ligand targeted

Tumour specific

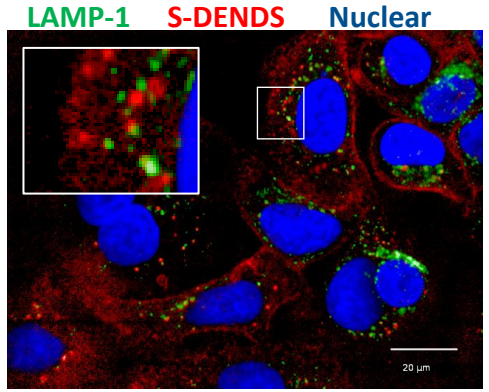
- Improved therapeutic index
- Solid and haematological tumours
- Range of drugs/drug properties
- High drug load per particle vs ADC

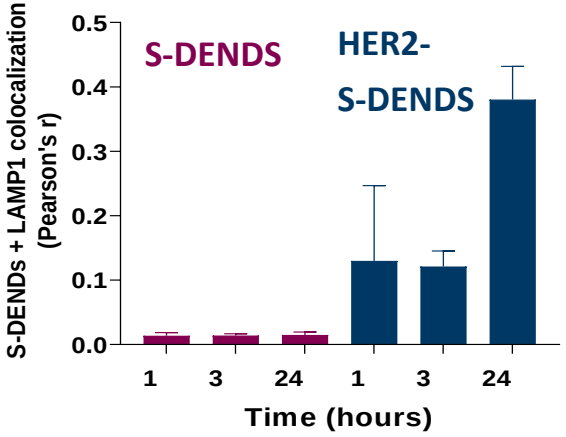
HER2-targeted S-DENDS shows improved cell uptake and killing

HER2-Fab targeted SN38 S-DENDS

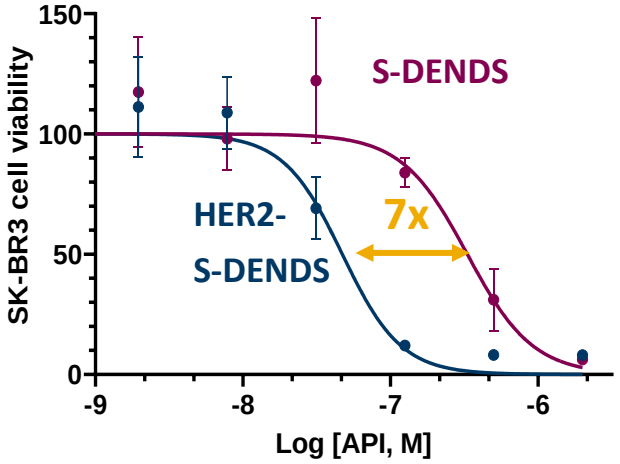


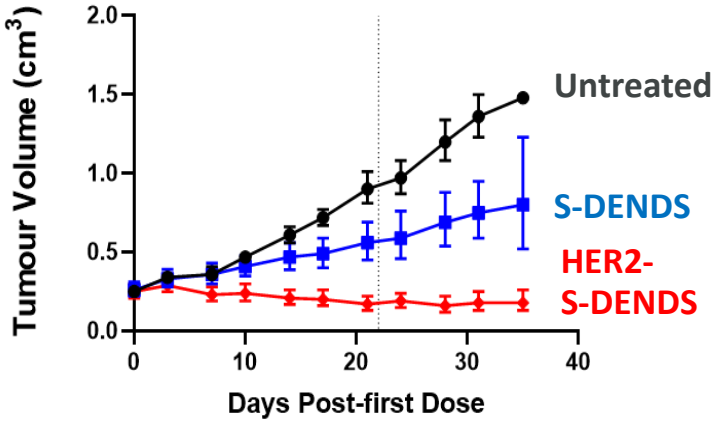
Increased cellular uptake





Increased cellular toxicity and in vivo efficacy

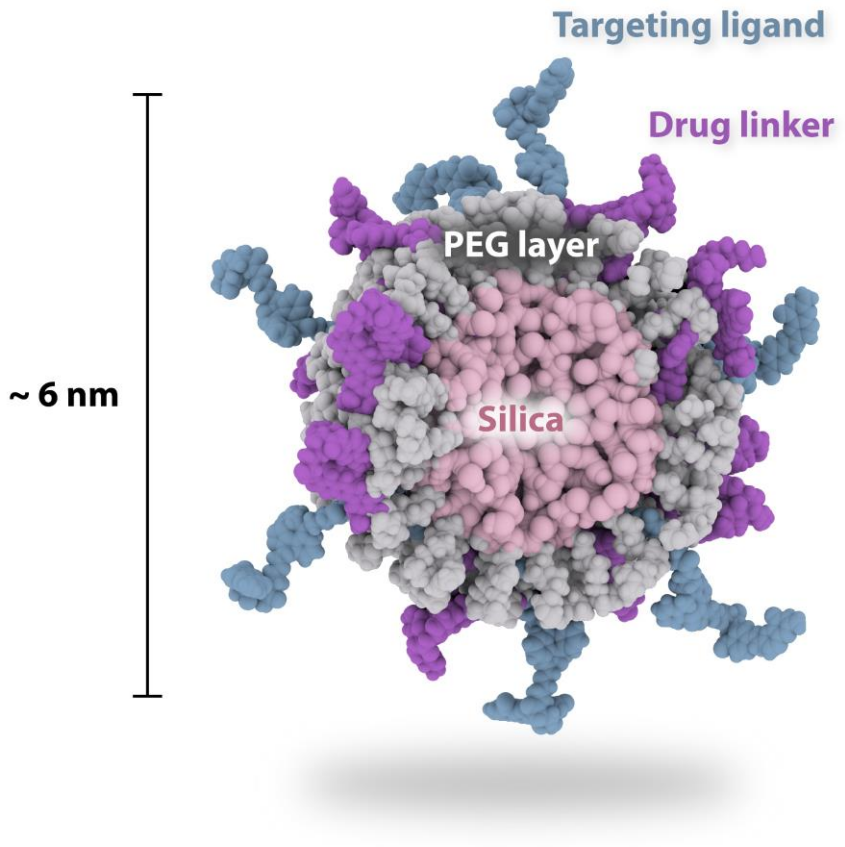




England et al 2020 Biomacromolecules ; Sonzini, England et al unpublished data

CDC: Next Frontier in Precision Cancer Therapy

C'Dot-Drug-Conjugate (CDC)



Novel Technology

- Ultra-small platform - can be loaded with multiple targeting moieties, linkers and payloads
- Short oligo-PEGs reduce platform immunogenicity
- Unique surface chemistry avoids off-target interactions
- Unique renal elimination due to the small size different than dendrimers or other polymeric NPs

Flexibility of Target and Payload

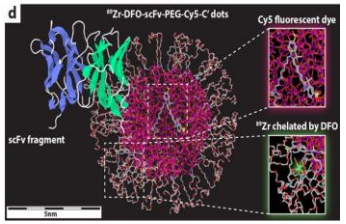
- Target using peptides, antibody fragments, aptamers, etc.
- Potential to incorporate more than one targeting moiety and payload

Novel Target-or-Clear® Paradigm

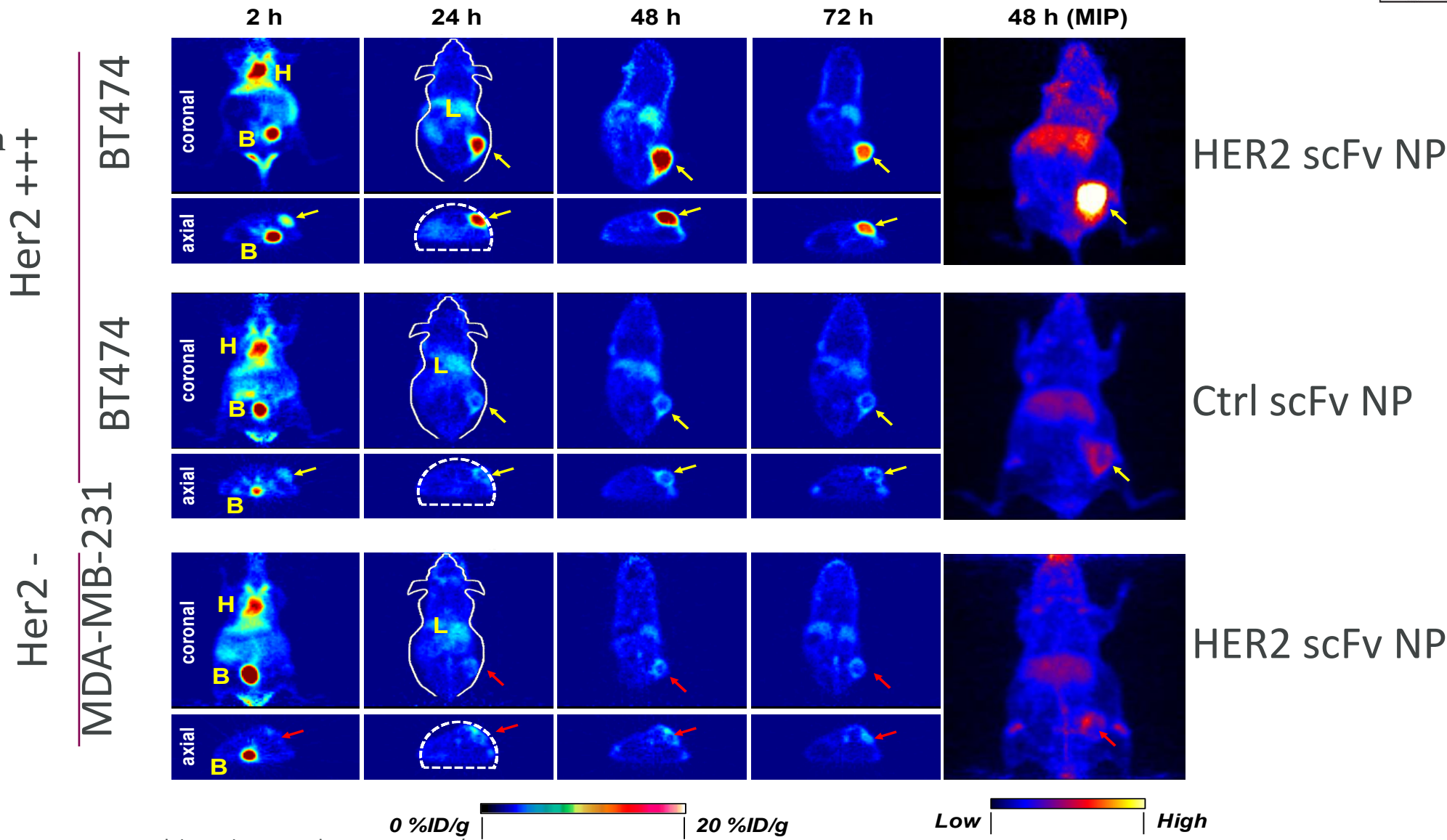
- High solid tumor penetration and distribution
- Low off-target exposure and efficient renal clearance

www.ScienceTranslationalMedicine.org 29 October 2014 Vol 6 Issue 260 260ra149

CDCs w/ engineered scFvs to enhance tumor targeting

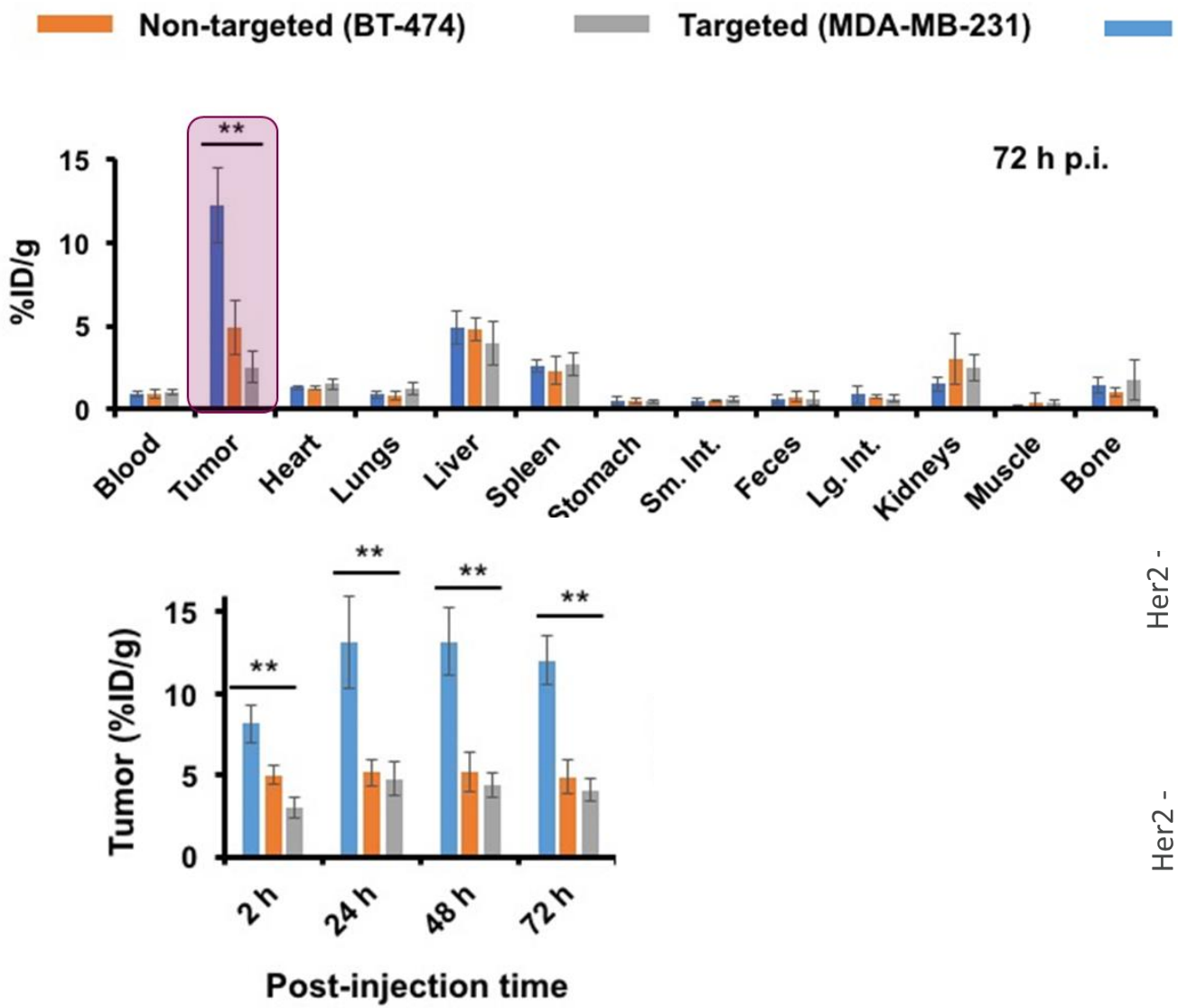


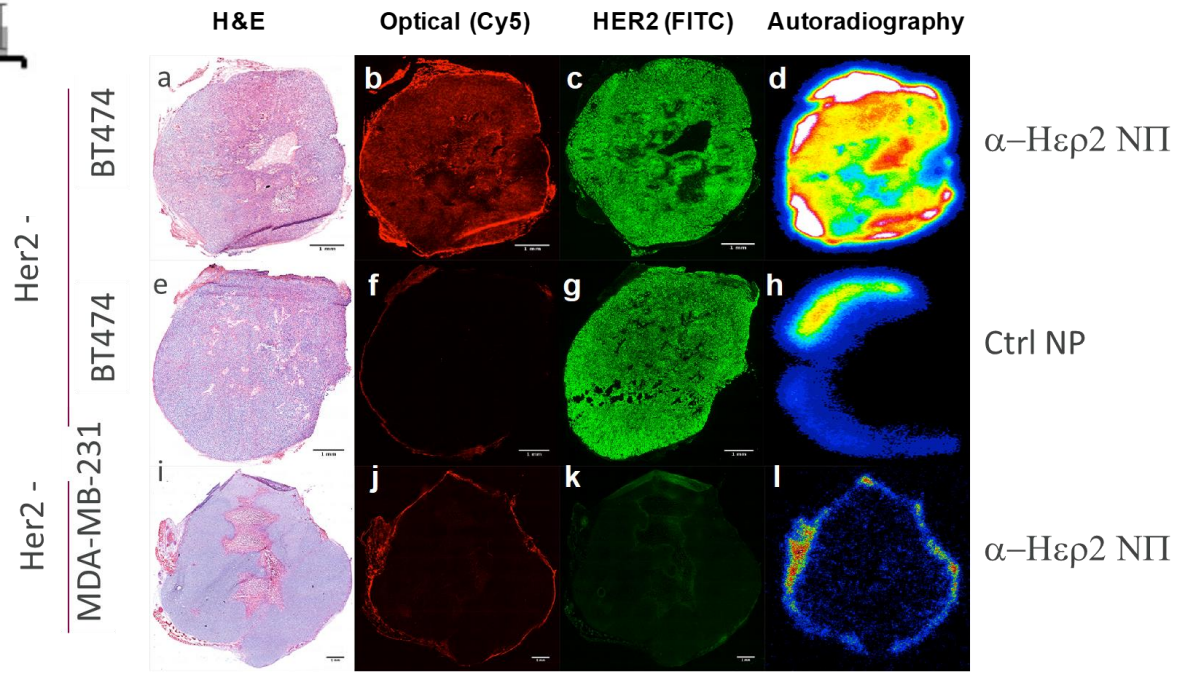
Rapid and specific localization of NPs to tumor sites



NATURE COMMUNICATIONS | (2018) 9:4141 | DOI: 10.1038/s41467-018-06271-5

Targeted CDC NPs rapidly accumulate in tumors





Nat Commun 2018 Oct 8;9(1):4141. doi: 10.1038/s41467-018-06271-5.
Ultrasmall targeted nanoparticles with engineered antibody fragments for imaging detection of HER2-overexpressing breast cancer

Conclusions

- Antibodies have been shown to successfully deliver chemotherapy, radiation, direct T cells to tumors and have potential to deliver nanoparticulate systems
- With 11 approved ADCs, this modality continues to influence cancer treatment and in future we will see a plethora of ADCs with various payloads and linkers that will be combined and sequenced
- The field of Radioimmunoconjugates is at inflection point and more future will see various radioisotopes, targets and infrastructure to enable success
- T cell bispecifics and immune-engagers is a growing field and with advancements in Ab engineering tools and understanding of safety aspects, this field will provide applications in solid tumors
- Ab- mediated nanoparticles will have to prove in clinical oncology and this will be possible with the right choice of payload, target and disease biology
- Drug delivery modalities will continue to influence pharmaceutical development in oncology and all therapeutic areas