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MOLECULAR TARGETS AND CANCER THERAPEUTICS
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Refining our understanding of ADCs: Drug development insights from 40 years of data

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AACR American Association for Cancer Research
NIH NATIONAL CANCER INSTITUTE
EORTC European Organisation for Research and Treatment of Cancer

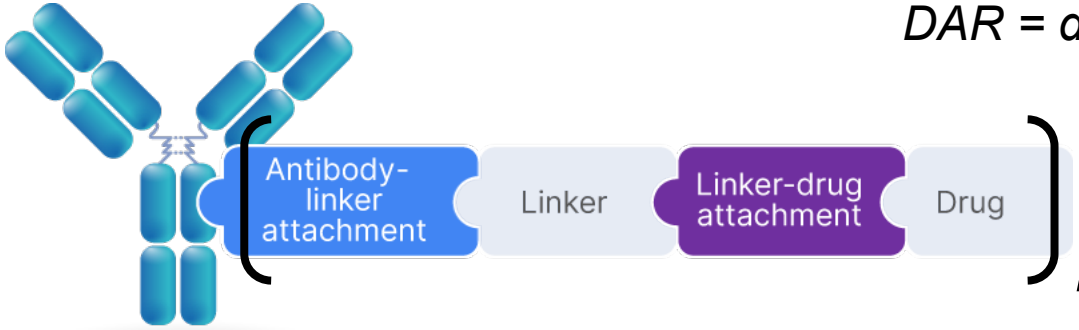
Raffaele Colombo

I have the following relevant financial relationships to disclose:

Employee of: Zymeworks Inc.

Stockholder in: Zymeworks Inc., AstraZeneca

40 years of (clinical) ADC data



DAR = drug-to-antibody ratio

305 ADCs have entered the clinic:

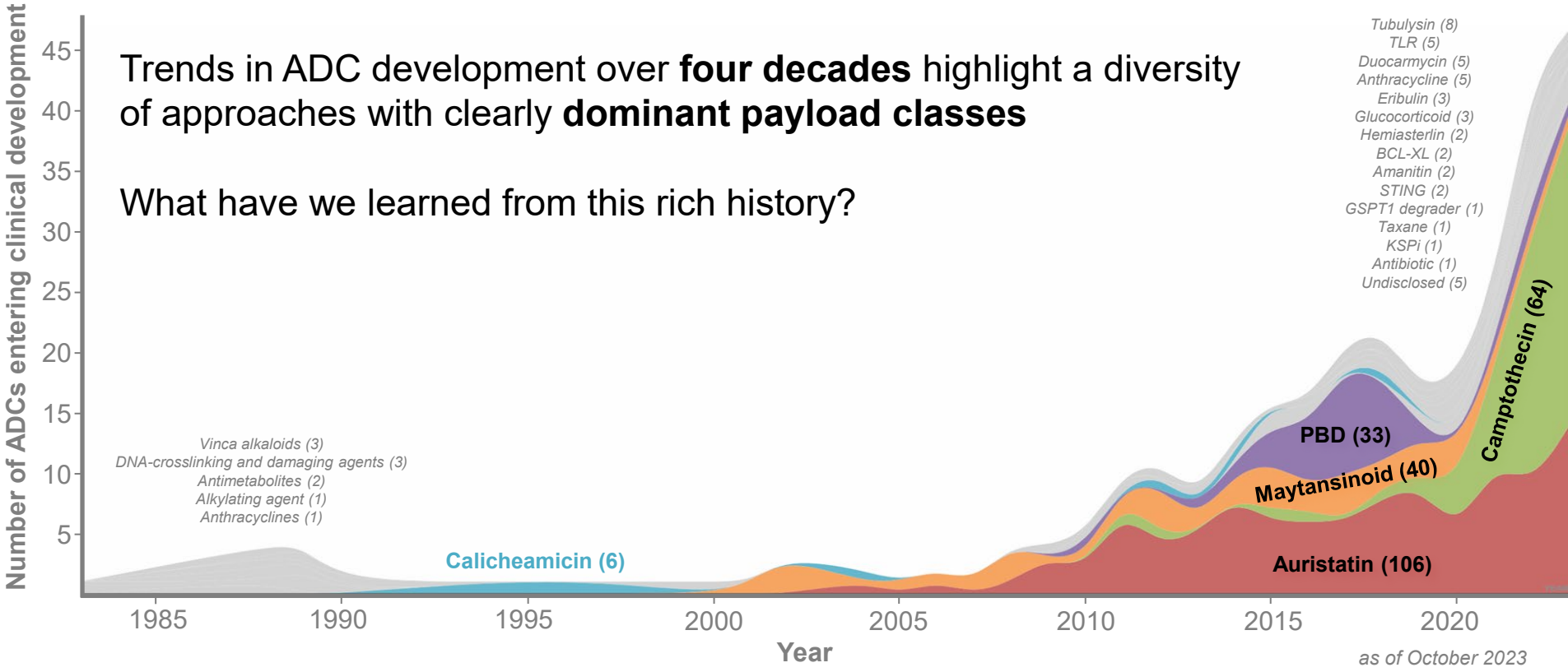
- **13 approved (11 by FDA)**
- **175 in active clinical development**
- **117 discontinued**

Data from ~170 ADCs to drive correlations

~130 new ADCs in the clinic with no data (yet)

as of October 2023

Clinical ADC landscape has evolved over time



Classic ADC dogma

1. **The therapeutic window dogma:**
   - ADCs widen the therapeutic window of the conjugated drug by both *increasing the maximum tolerated dose* (MTD) and *reducing the minimum efficacious dose* (MED) of the drug

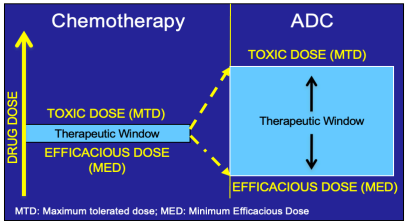


Figure from: M. M. Schutten, NorCal Society of Toxicology Meeting, September 27, 2012

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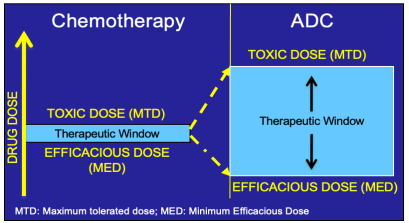

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   - A *highly stable linker* is paramount to the clinical success of the ADC

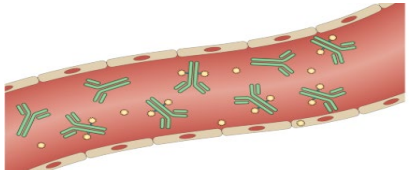

Figure from: J. Z. Drago et al. *Nat. Rev. Clin. Oncol.* **2021**, *18*, 327-344

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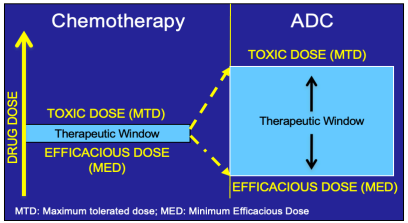

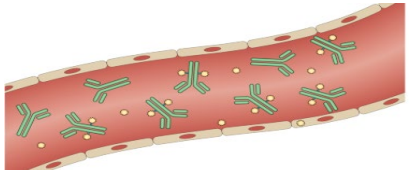

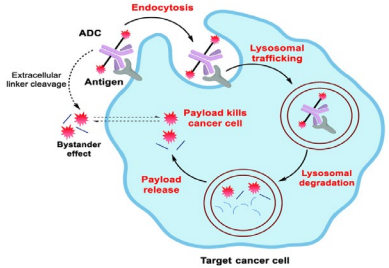

Figure from: I. Cheng-Sánchez et al. *Mar. Drugs.* **2022**, *20*, 494

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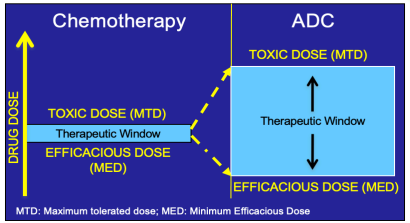

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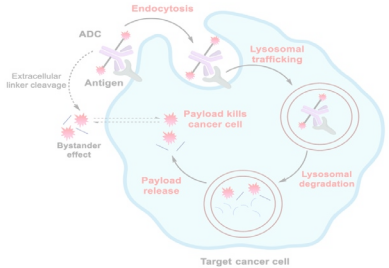
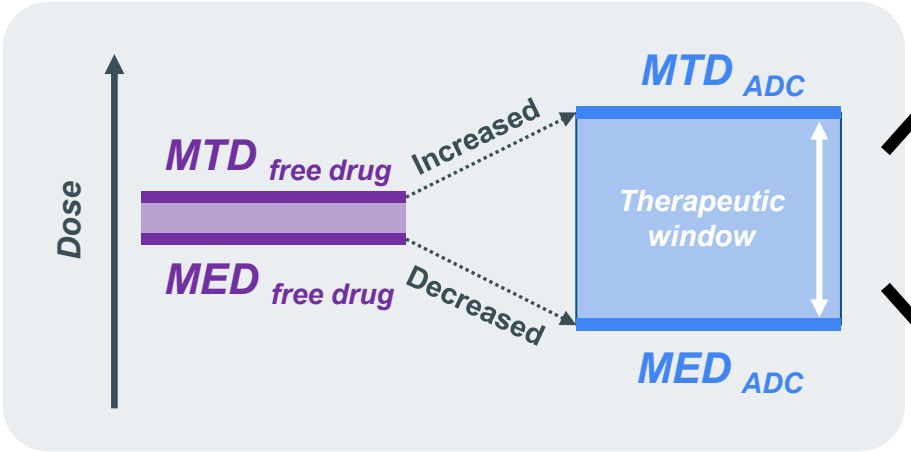


The ADC therapeutic window dogma was established in preclinical models



Animals can tolerate ADCs better than free drugs

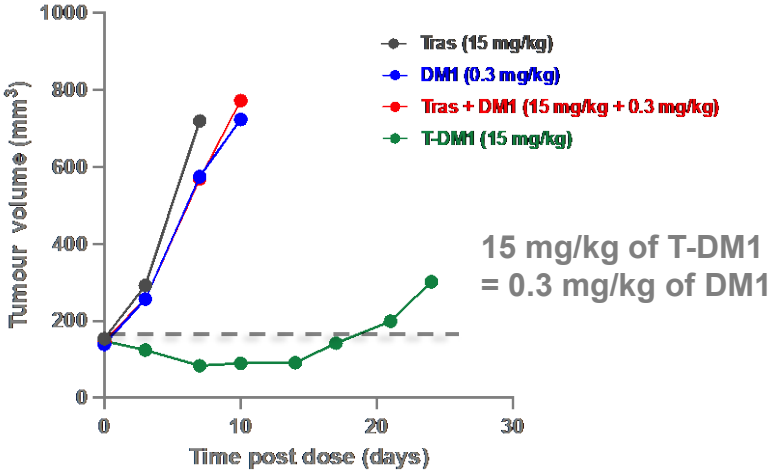
ADCs can shrink tumors in animals at a lower dose than free drugs

MTD = maximum tolerated dose
MED = minimum efficacious dose

Example: T-DM1 showed better efficacy and tolerability than free DM1 preclinically

T-DM1 is significantly more efficacious than free DM1 in mouse models

Efficacy in a HER2+ breast cancer model

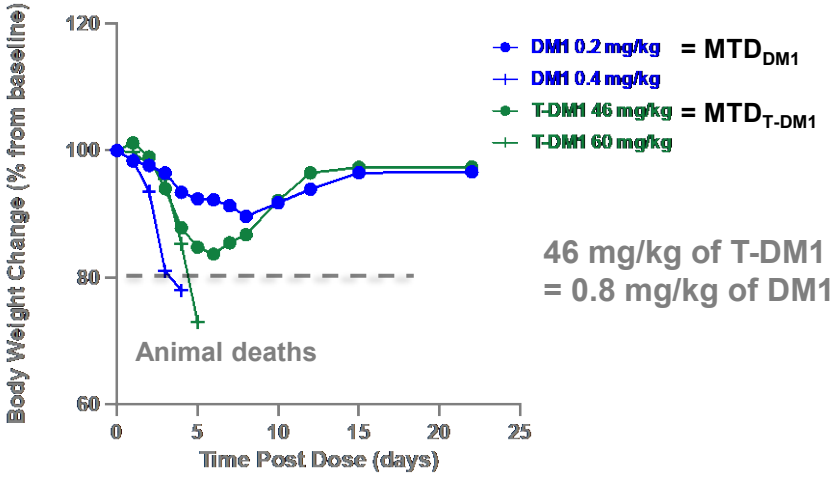


15 mg/kg of T-DM1 = 0.3 mg/kg of DM1

Similar trends observed for numerous other ADCs

Conjugated DM1 is better tolerated than free DM1 in rats

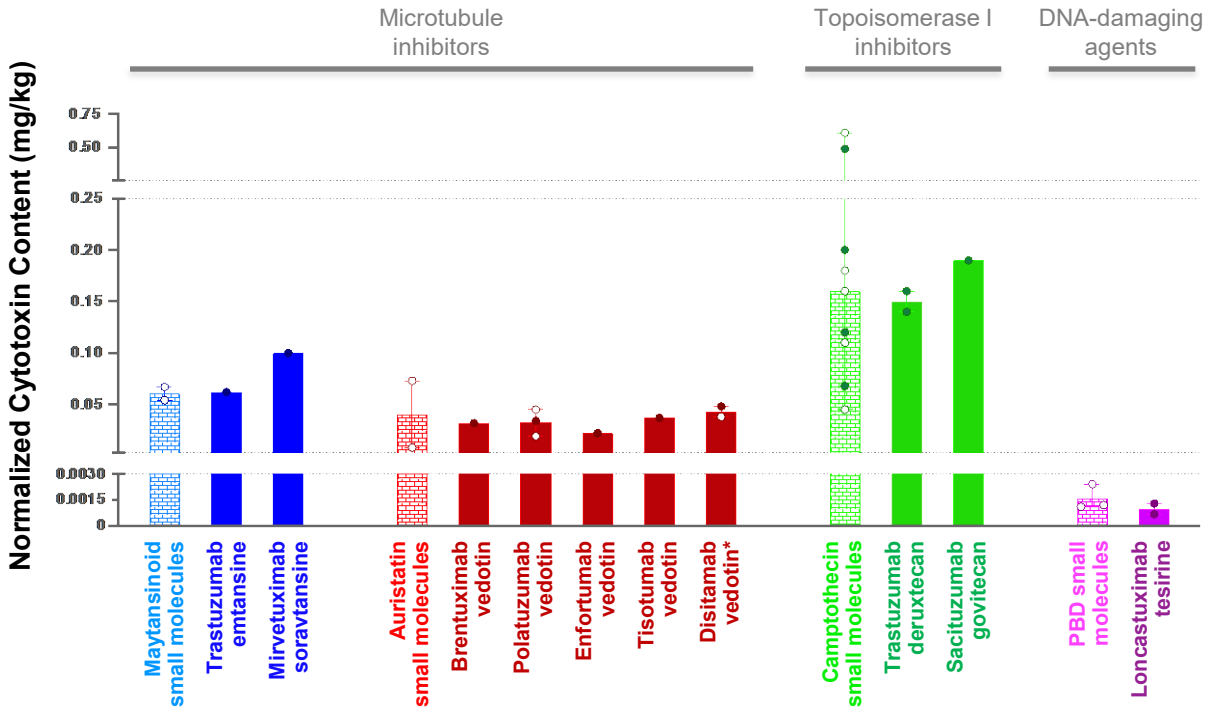
Tolerability in healthy rats



46 mg/kg of T-DM1 = 0.8 mg/kg of DM1

T. T. Junttila et al. *Breast Cancer Res. Treat.* **2011**, *128*, 347-356
K. A. Poon et al. *Toxicology and Applied Pharmacology* **2013**, *273*, 298-313

Human MTD of approved ADCs is comparable to human MTD of related small molecules



*approved by the NMPA of China

Small molecules

- Maytansinoid
- Auristatin
- Camptothecin
- PBD

Approved ADCs

- Maytansinoid
- Auristatin
- Camptothecin
- PBD

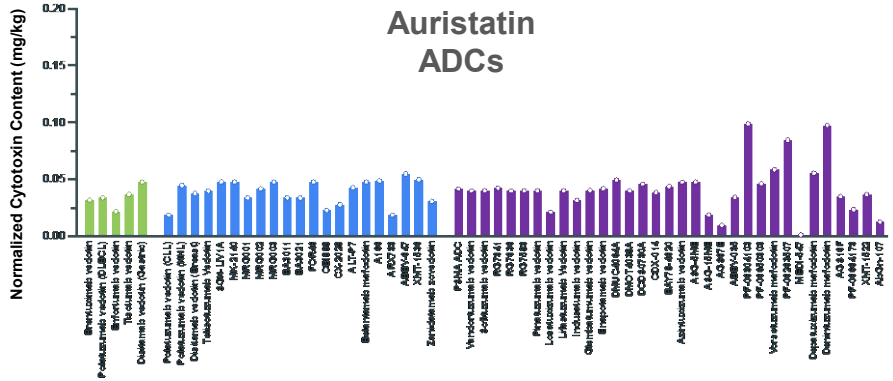
- ● *MTD for approved drug*
- ○ *MTD for experimental drugs*

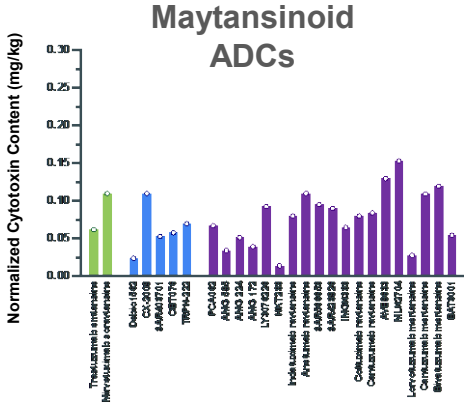
Normalized cytotoxin content

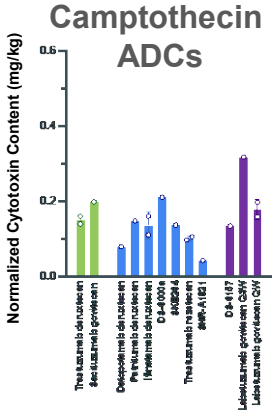
$$= \frac{Dose_{ADC} \cdot DAR \cdot MW_{payload}}{MW_{ADC}}$$

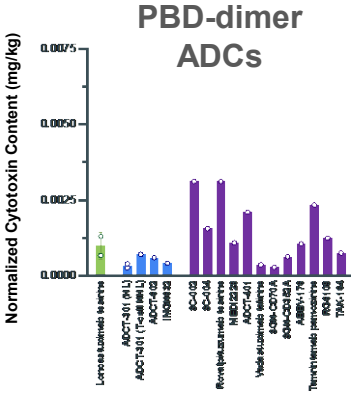
R. Colombo, J. R. Rich. *Cancer Cell*, **2022**, *40*, 1255-1263

Approved ADCs don't have higher MTD than discontinued ADCs









MTDs/RP2Ds:

- ADC approved
- ADC in clinical development
- ADC discontinued

Normalized Cytotoxin Content

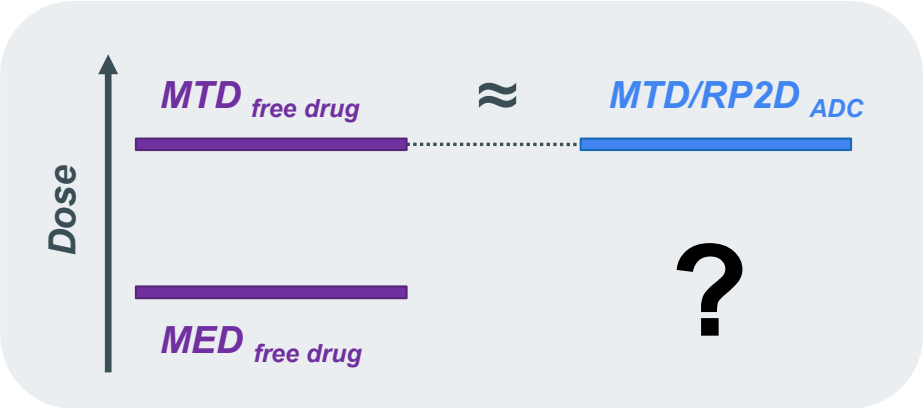
$$= \frac{Dose_{ADC} \cdot DAR \cdot MW_{payload}}{MW_{ADC}}$$

MTD = maximum tolerated dose
RP2D = recommended phase 2 dose

R. Colombo, S. D. Barnscher, J. R. Rich. *Cancer Research*, **2023**, *83(7_Supplement)*, 1538

Revised representation of ADC therapeutic window (in humans)

Revised representation based on emerging clinical data



ADCs do not significantly increase the maximum tolerated dose (MTD) of the payload

- **Minimum efficacious dose (MED) is not established in the clinic**
- **Comparison of clinical efficacy at their MTD/RP2D**

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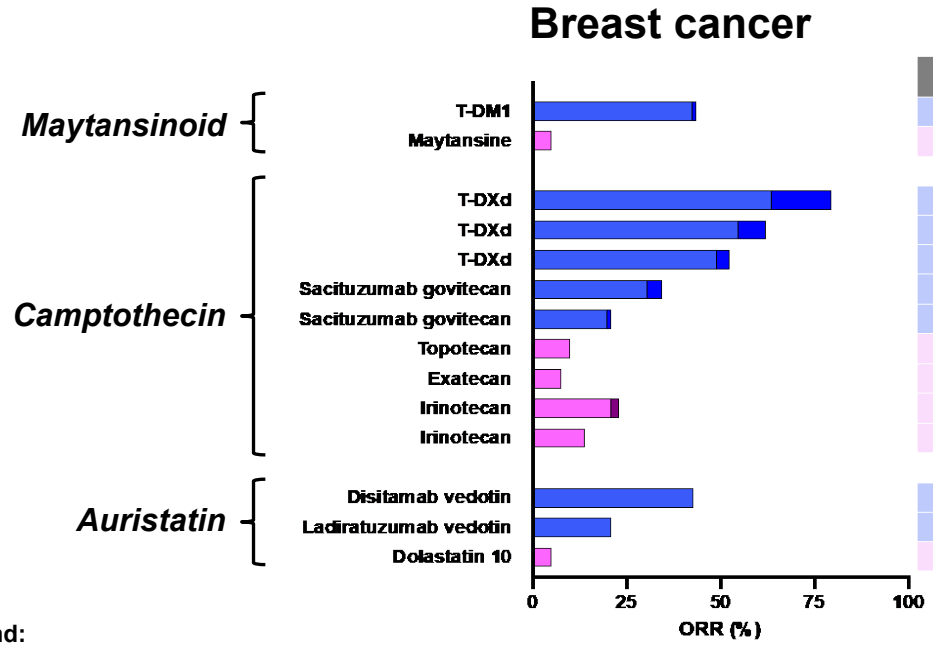
ADCs improve ORR over related small molecules when dosed at MTD/RP2D

Selected cross-trial comparisons



Target	Phase	Prior lines of therapy	Patients	Publication	Note
HER2	3	1	495	2012	*EMILIA (HER2-high)*
-	2	1+	31	1979	
HER2	3	1	261	2021	*DESTINY-Breast03 (HER2-high)*
HER2	2	2+	184	2021	*DESTINY-Breast01 (HER2-high)*
HER2	2	1-9 (median 3)	373	2022	*DESTINY-Breast04 (HER2-low)*
TROP2	3	2+	235	2020	*ASCENT (TNBC)*
TROP2	3	0-8 (median 3)	272	2022	*TROPiCS-02 (HR+/HER2–)*
-	2	1	40	1999	
-	2	1+	39	2003	
-	2	1+	52	2004	*QW regimen*
-	2	1+	51	2004	*Q3W regimen*
HER2	1b	2+	21	2021	*C003 CANCER (HER2-high)*
LIV1	1b	2+	44	2018	*SGNLVA-001 trial (TNBC)*
-	2	0	39	2003	

Legend:

- Blue = ADC ORR (%)
- Pink = Small molecule ORR (%)
- Darker bars = CR (%)
- Lighter bars = PR (%)

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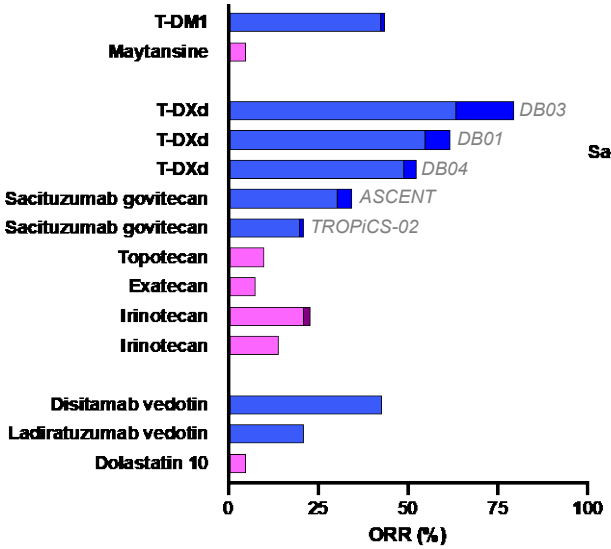
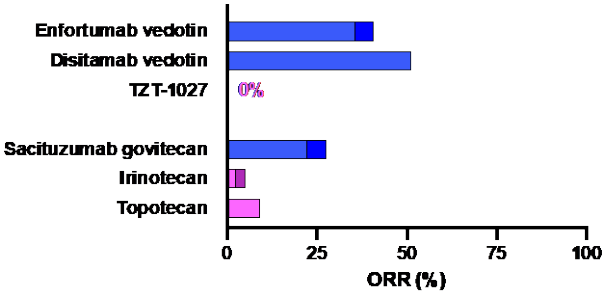
Efficacy of ADCs is improved over related small molecules in multiple indications

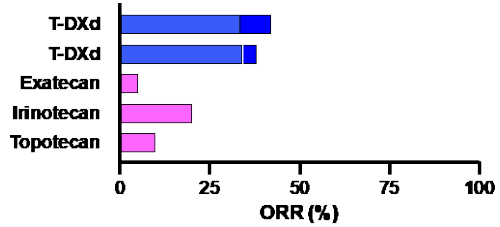
Breast cancer



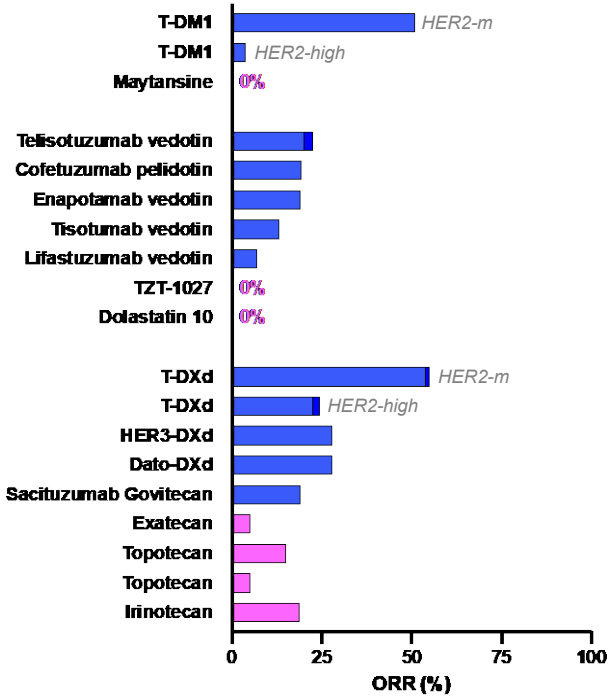
Urothelial cancer



Gastric cancer



Non-small cell lung cancer



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R. Colombo, J. R. Rich. *Cancer Cell*, **2022,** *40*, 1255-1263

Revised representation of ADC therapeutic window (in humans)

Revised representation based on emerging clinical data

- **ADCs do not significantly increase the maximum tolerated dose (MTD)** of their conjugated payloads

- **Minimum efficacious dose (MED) not established** in clinical studies
- When dosed at their MTD/RP2D, **ADCs can offer improved efficacy over related unconjugated small molecules** (and, in certain cases, standard of care)

R. Colombo, J. R. Rich. *Cancer Cell,* **2022,** *40*, 1255-1263

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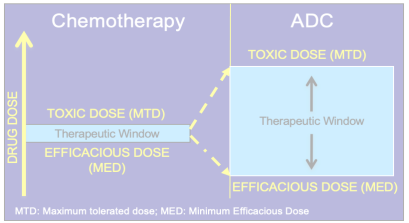

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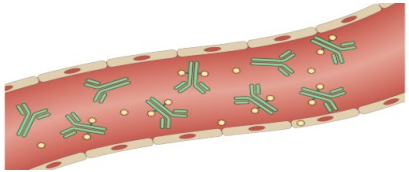

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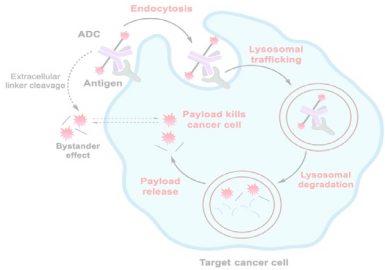
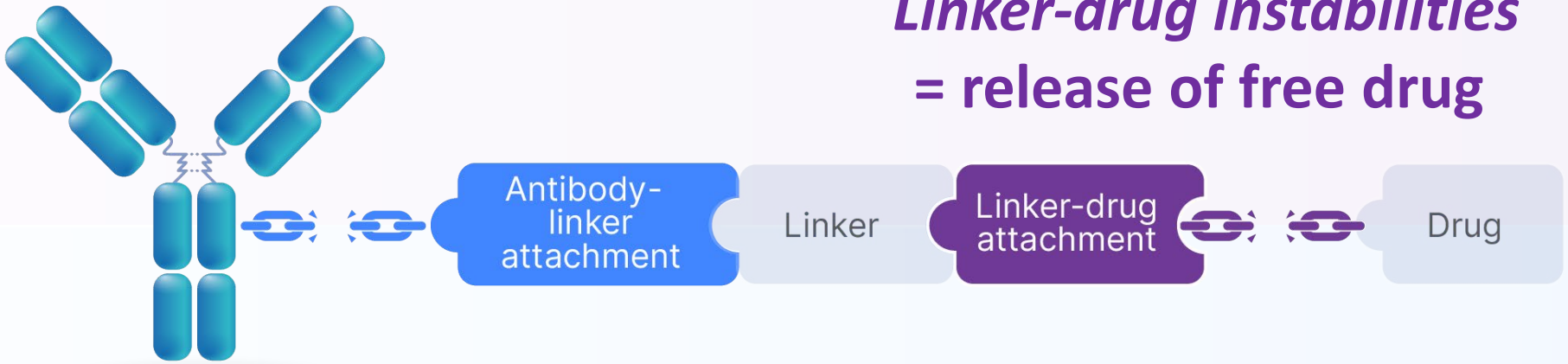


There are two types of ADC drug-linker instability in circulation



Linker-drug instabilities

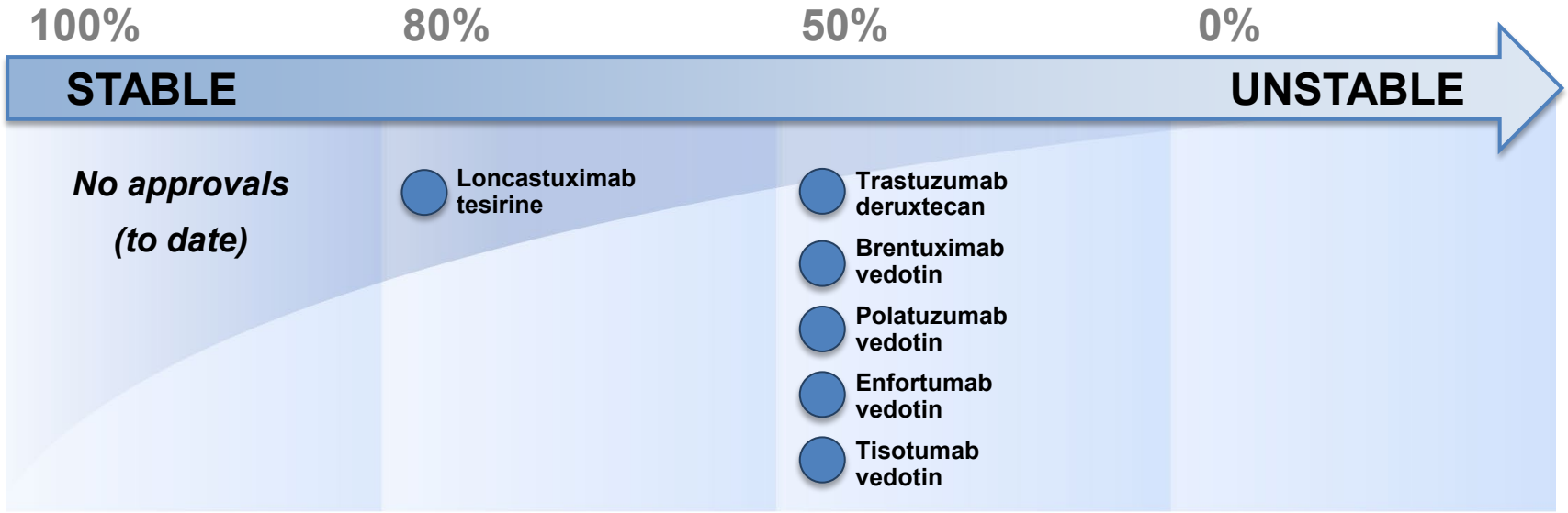
= release of free drug

Antibody-linker instabilities

= release of the whole drug-linker

R. Colombo et al. *Cancer Research*, **2023**, *83(7_Supplement)*, 1538

Approved ADCs with antibody-linker instabilities



Percentage of drug remaining conjugated to the antibody after 7 days in plasma

= release of the whole drug-linker

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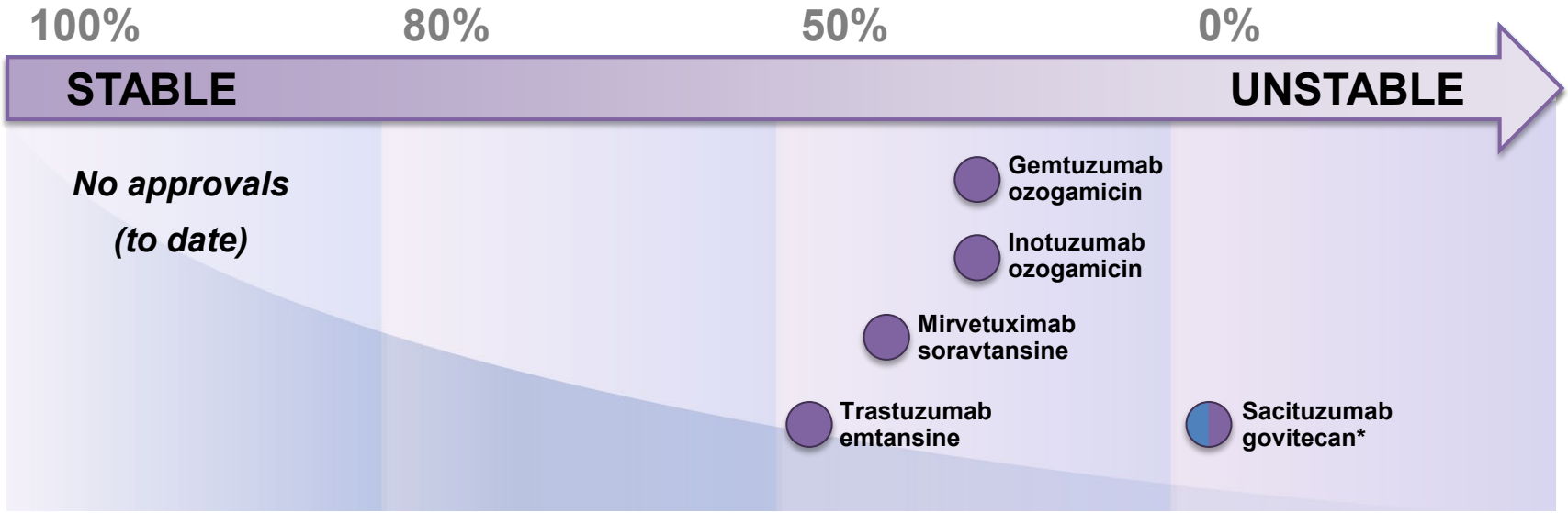
Approved ADCs with linker-drug instabilities



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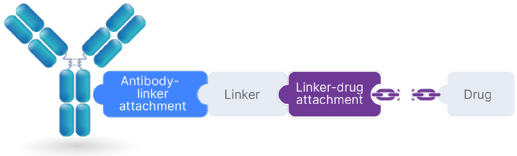

= release of free drug

*sacituzumab govitecan has both linker-drug instability and antibody-linker instability, with the former more rapid

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None of the approved ADCs are stable in circulation

Linker-drug instabilities

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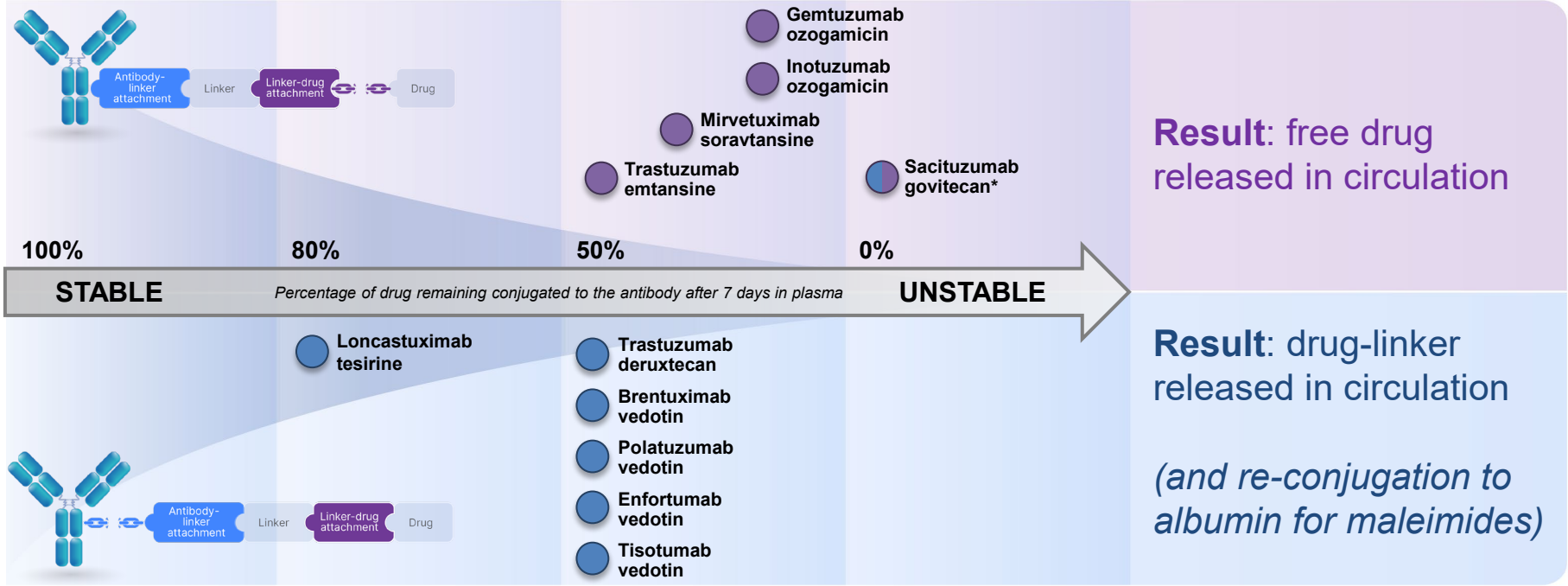

Result: free drug released in circulation

Result: drug-linker released in circulation

(and re-conjugation to albumin for maleimides)

Antibody-linker instabilities

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Approved ADCs with thiol-maleimide conjugation

Linker-drug instabilities

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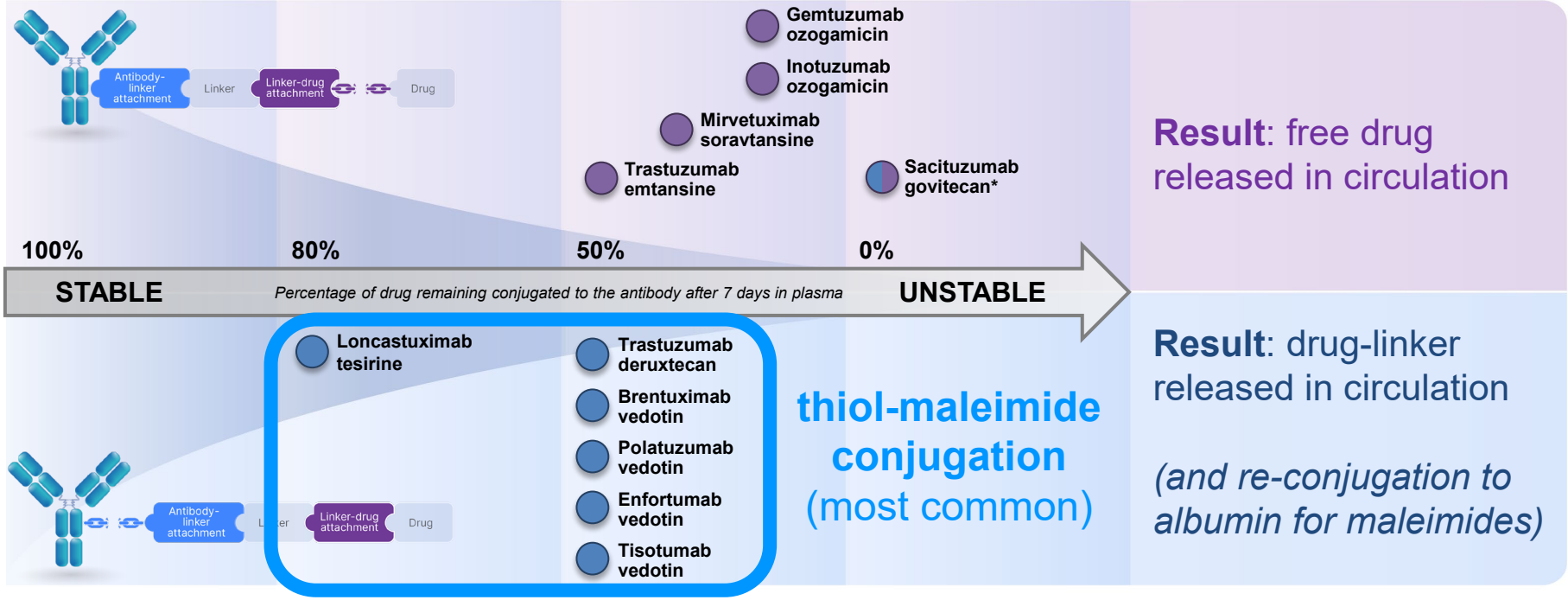

Result: free drug released in circulation

thiol-maleimide conjugation (most common)

Result: drug-linker released in circulation

(and re-conjugation to albumin for maleimides)

Antibody-linker instabilities

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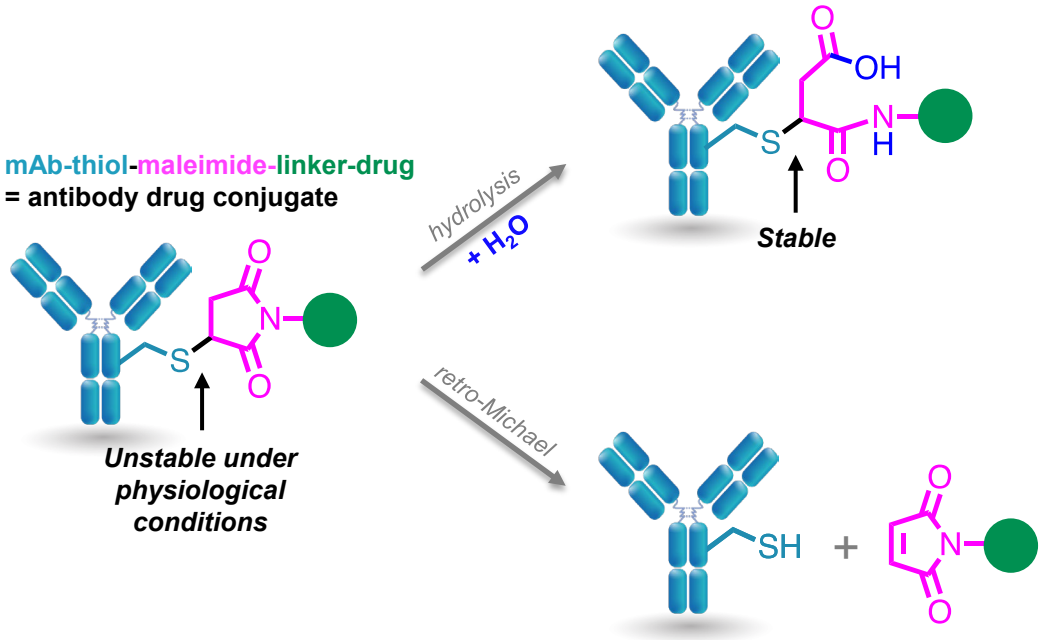
ADCs with thiol-maleimide conjugation are susceptible to deconjugation

mAb-thiol-maleimide-linker-drug
= antibody drug conjugate

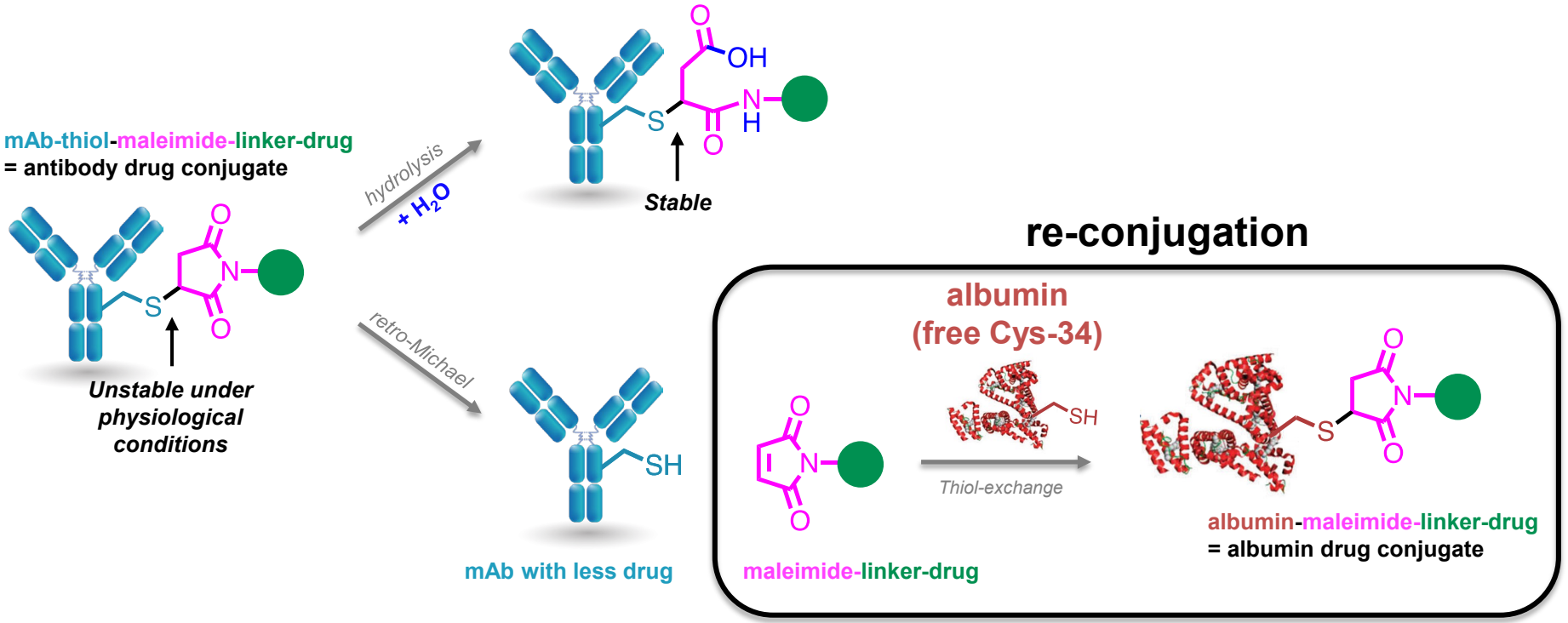


deconjugation

Hydrolysis and retro-Michael are **competing transformations**

Thiol-maleimide **stability** is *tunable* based on linker-drug!

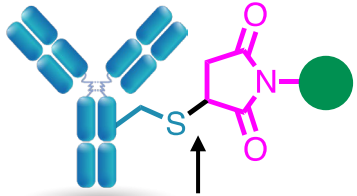
Deconjugated drug-linker re-conjugates to albumin (thiol-exchange)



Deconjugated drug-linker re-conjugates to albumin (thiol-exchange)

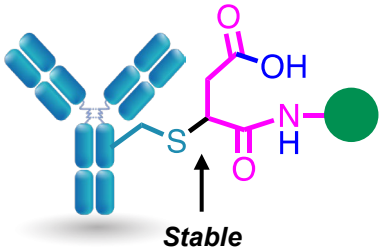
Despite the vast majority of ADCs relying on thiol-maleimide conjugation, albumin drug conjugate is not quantified in clinical trials

mAb-thiol-maleimide-linker-drug
= antibody drug conjugate



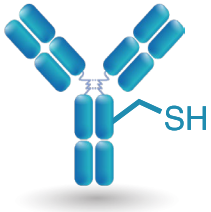
Unstable under physiological conditions

hydrolysis
+ H_2O



Stable

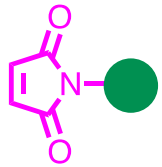
retro-Michael



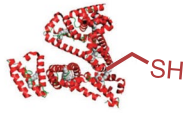
mAb with less drug

re-conjugation

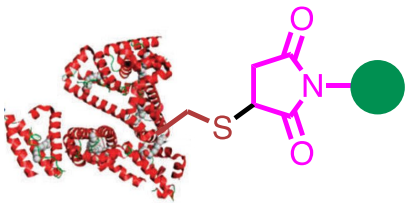
albumin
(free Cys-34)



maleimide-linker-drug



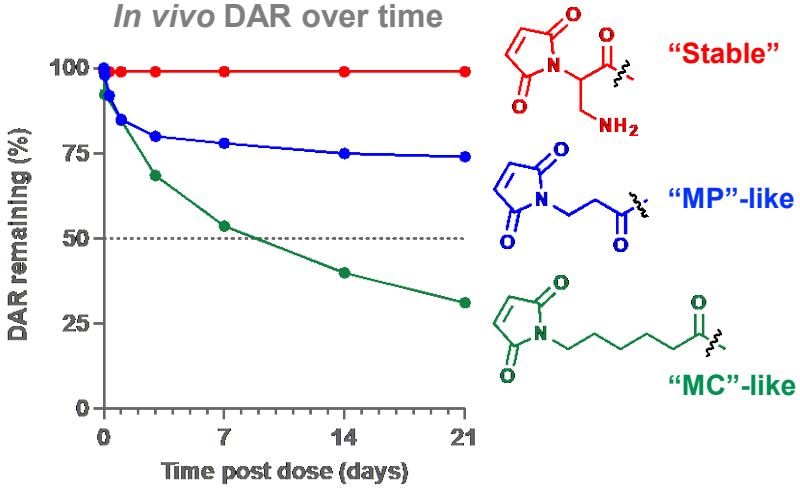
Thiol-exchange



albumin-maleimide-linker-drug
= albumin drug conjugate

Approved ADCs with thiol-maleimide conjugation undergo deconjugation

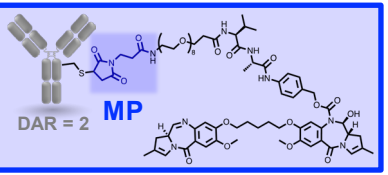
Under physiological conditions, unhydrolyzed thiol-maleimide linkers undergo deconjugation



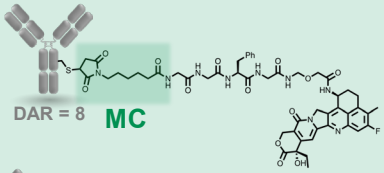
Approved ADCs

NONE!

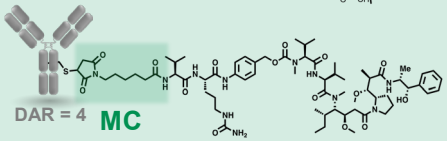
Loncastuximab tesirine (Lonca-T)



Trastuzumab deruxtecan (T-DXd)



Brentuximab vedotin (BV)
Polatuzumab vedotin (PV)
Enfortumab vedotin (EV)
Tisotumab vedotin (TV)



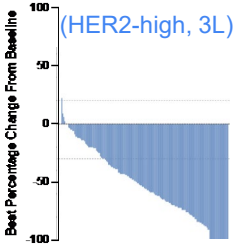
C. Wei et al. Anal. Chem. **2016**, *88*, 4979−4986
B. Rago et al. *Bioanalysis*, **2016**, *8*, 2205–2217
R. J. Christie et al. *J Control Release*. **2015**, 220(Pt B), 660–670
H. Habara et al. *Biopharm. Drug Dispos.* **2023** Aug 3. doi:10.1002/bdd.2371. Online ahead of print

Antibody-linker stability is not required for successful ADCs

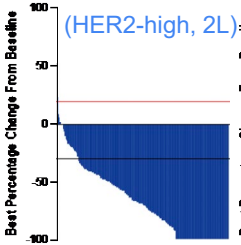
Selected data for approved ADCs

Trastuzumab deruxtecan (T-DXd)

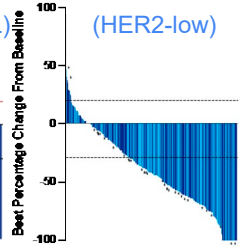
DESTINY-Breast01 (HER2-high, 3L)



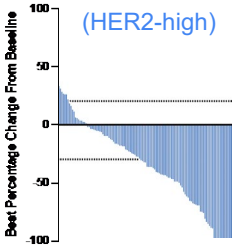
DESTINY-Breast03 (HER2-high, 2L)



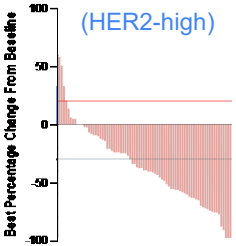
DESTINY-Breast04 (HER2-low)



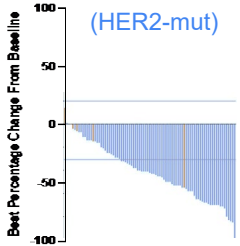
DESTINY-Gastric01 (HER2-high)



DESTINY-Gastric02 (HER2-high)

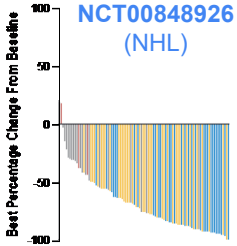


DESTINY-Lung01 (HER2-mut)



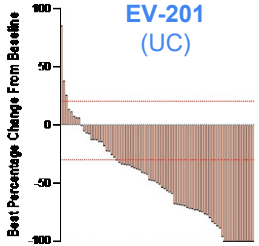
Brentuximab vedotin (BV)

NCT00848926 (NHL)



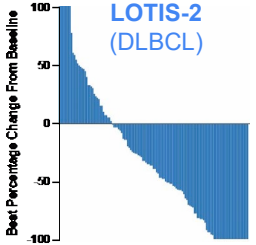
Enfortumab vedotin (EV)

EV-201 (UC)



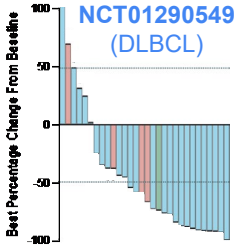
Loncastuximab tesirine (Lonca-T)

LOTIS-2 (DLBCL)



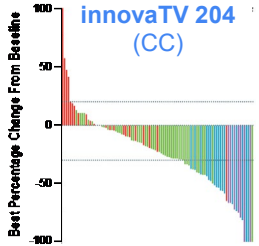
Polatuzumab vedotin (PV)

NCT01290549 (DLBCL)



Tisotumab vedotin (TV)

innovaTV 204 (CC)

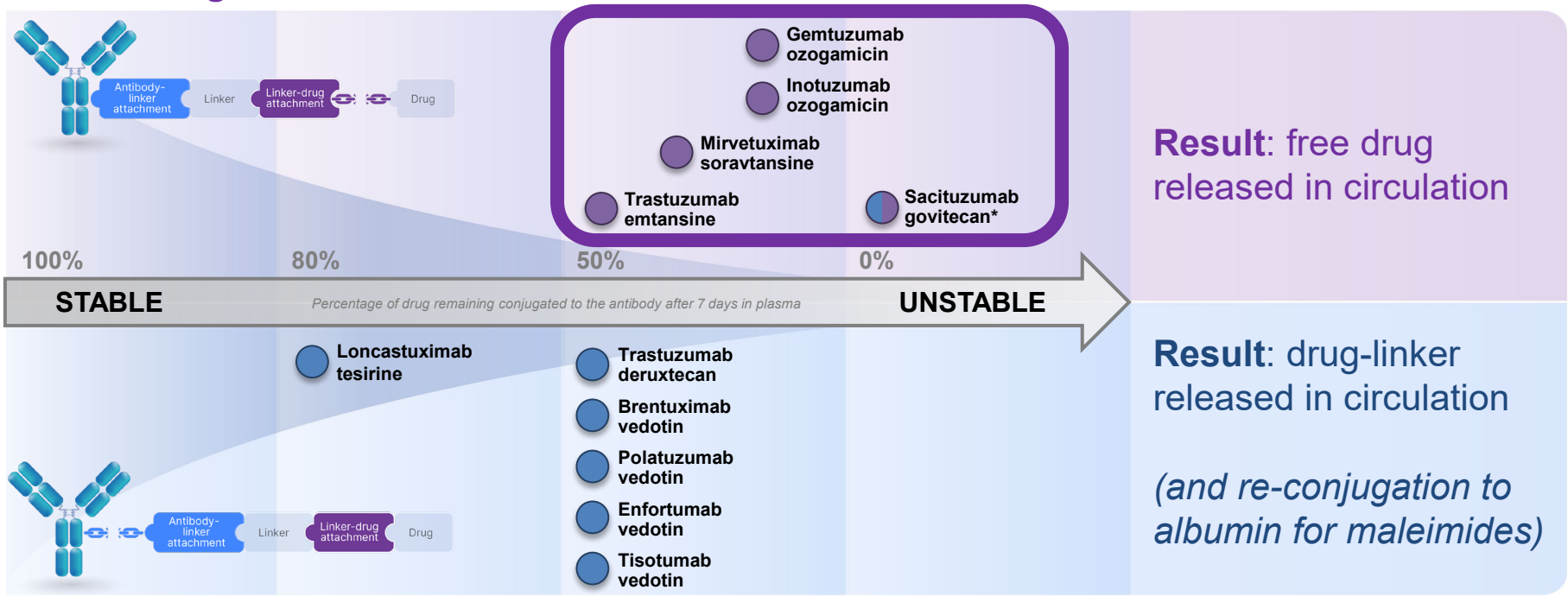


T-DXd: DESTINY-Breast01: *N. Engl. J. Med.* **2020**, *382*, 610-621; DESTINY-Breast03: *N. Engl. J. Med.* **2022**, *386*, 1143-1154; DESTINY-Breast04: *N. Engl. J. Med.* **2022**, *387*, 9-20; DESTINY-Gastric01: *N. Engl. J. Med.* **2020**, *382*, 2419-2430; DESTINY-Gastric02: *Lancet Oncology.* **2023**, *24*, 744-756; DESTINY-Lung01: *N. Engl. J. Med.* **2022**, *386*, 241-251; **BV:** *J. Clin. Oncol.* **2012**, *30*, 2183-2189; **EV:** *Lancet Oncol.* **2021**, *22*, 872-882; **PV:** *Lancet Oncol.* **2015**, *16*, 704–715; **TV:** *Lancet Oncol.* **2021**, *22*, 609-619; **Lonca-T:** *Lancet Oncol.* **2021**, *22*, 790-800

Approved ADCs with linker-drug instabilities

Linker-drug instabilities

*sacituzumab govitecan has both linker-drug instability and antibody-linker instability, with the former more rapid



Result: free drug released in circulation

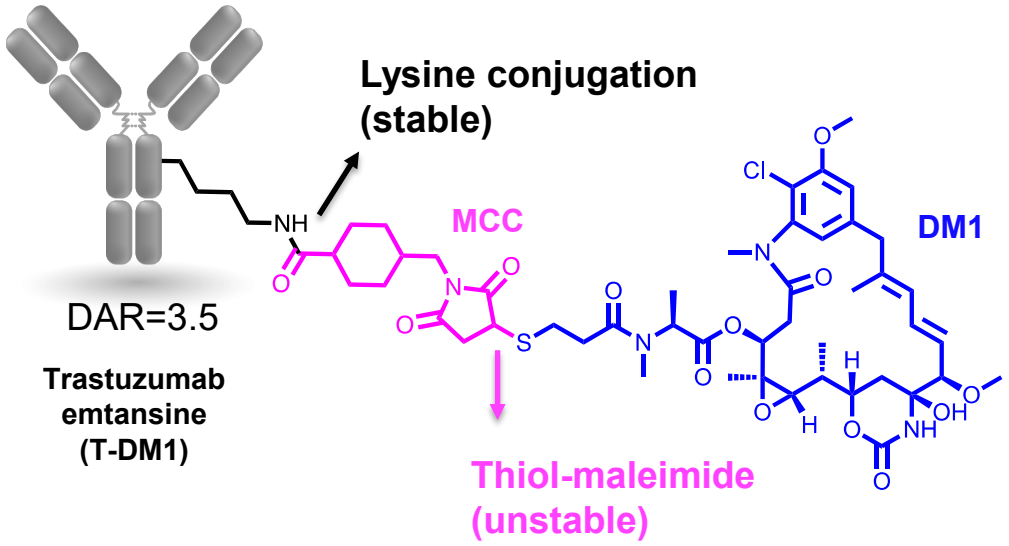
Result: drug-linker released in circulation

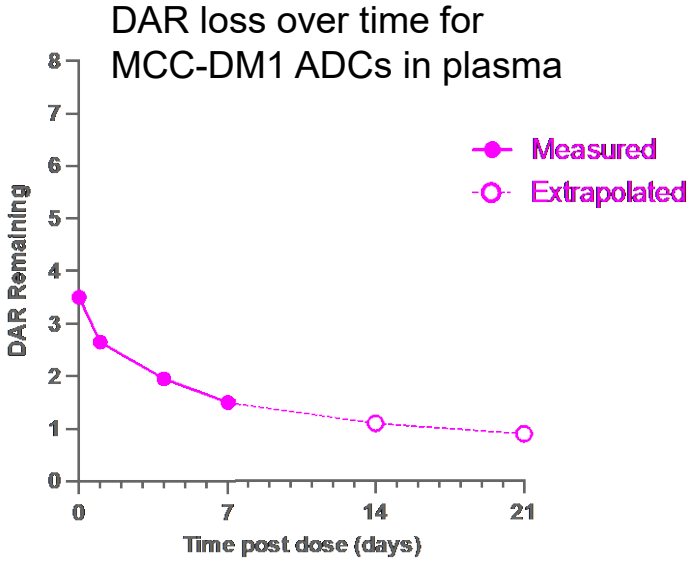
(and re-conjugation to albumin for maleimides)

Antibody-linker instabilities

R. Colombo et al. *Cancer Research,* **2023**, *83(7_Supplement),* 1538

MCC-DM1 linker is unstable resulting in spontaneous payload release





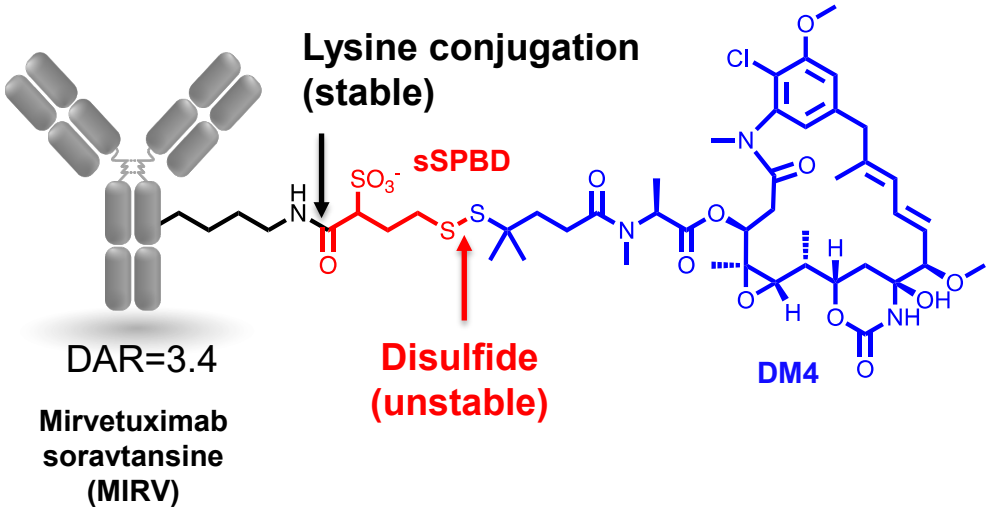
MCC deconjugation rate is similar to MC

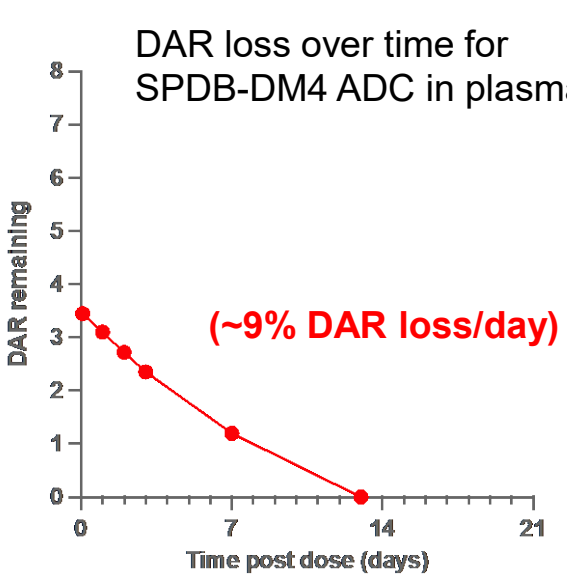
Primary catabolites formed from mAb-MCC-DM1:

- **DM1** from linker instabilities (potent and permeable)
- **Lys-MCC-DM1** from antibody catabolism (potent and less permeable)

J. He et al. *MAbs* **2018**, *10*, 960-967
J. F. Ponte et al. *Bioconjugate Chem.* **2016**, *27*, 1588-1598
S. Park et al. *Appl. Sci.* **2021**, *11*, 9437

SPDB-DM4 linker is unstable resulting in spontaneous payload release



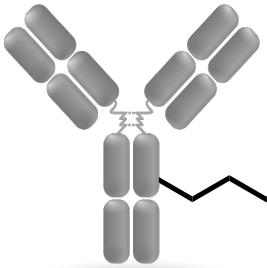


Active metabolites formed from mAb-sSPDB-DM4:

- **DM4** (permeable)
- **Me-DM4** (permeable)
- **Oxidized derivatives of DM4 and Me-DM4** (less permeable)

C. Pouzin et al. *J. Pharmacokinet. Pharmacodyn.* ***2022***, *49*, 381–394

Calicheamicin ADC linker is unstable resulting in spontaneous payload release



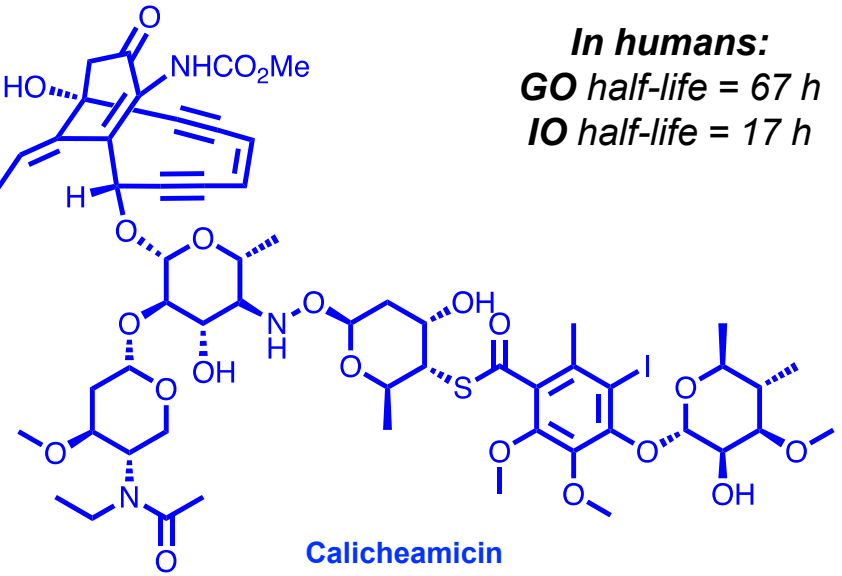
DAR = 2-3 (GO)
DAR = 6 (IO)

Lysine conjugation (stable)

Disulfide *(~9% DAR loss/day)*

Hydrazone (pH sensitive)

~7% DAR loss/day at pH = 7.4
~97% DAR loss/day at pH = 5.0



Calicheamicin

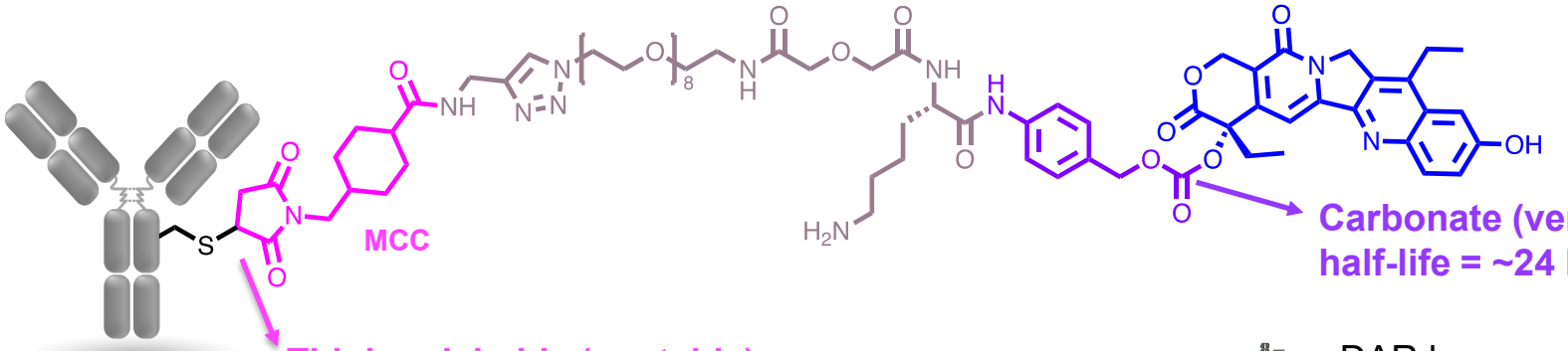
In humans:
GO *half-life = 67 h*
IO *half-life = 17 h*

Gemtuzumab ozogamicin (GO)

Inotuzumab ozogamicin (IO)

B.S. Vollmar et al. *Mol. Cancer Ther.* ***2021***, *20*, 1112-1120

Sacituzumab govitecan linker is unstable resulting in spontaneous payload release



Sacituzumab govitecan

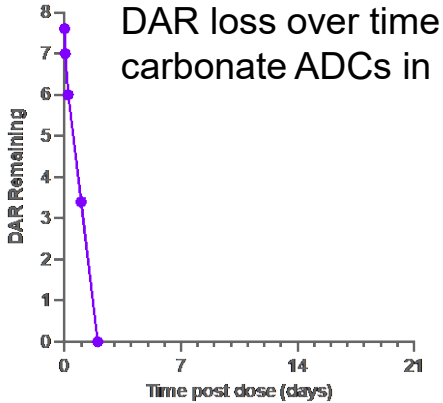
Editorial Commentary

Page 1 of 3

Does sacituzumab-govitecan act as a conventional antibody drug conjugate (ADC), a prodrug of SN-38 or both?

Daniel V. Santi[1], Luc Cabel[2], François-Clément Bidard[2,3]

Ann. Transl. Med. **2021**, *9*, 1113.



DAR loss over time for carbonate ADCs in plasma

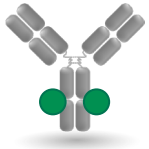
Y. Cheng et al. *Front. Oncol.* **2022**, *12*, 951589

Improving antibody-linker stability has been a major research focus: thiomab example

CD79b ADCs:
- Pola-V *(less stable)*
- Ila-V *(more stable)*

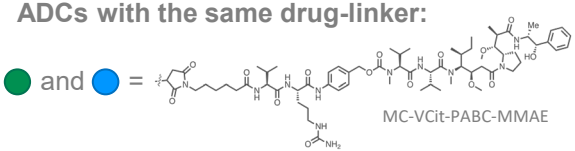
MUC16 ADCs:
- Sofi-V *(less stable)*
- DMUC4064A *(more stable)*

Native Cys stochastic *(less stable)*



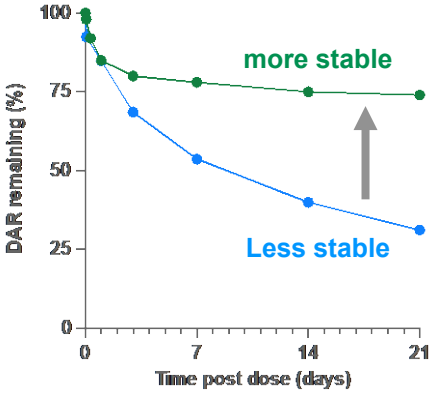
Thiomab site-specific *(more stable)*

ADCs with the same drug-linker:

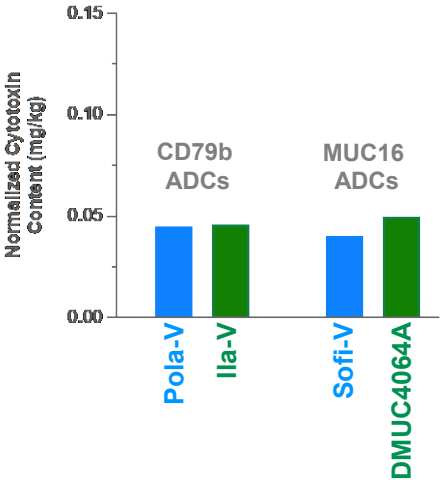


Increased antibody-linker stability didn't translate into better MTDs

ADC stability



ADC MTDs



Polatuzumab vedotin (Pola-V): *Lancet Oncol.* **2015**, *16*, 704-715; **Iladatuzumab vedotin (Ila-V):** *Clin. Cancer Res.* **2022**, *28*, 1294-1301; **Sofituzumab vedotin (Sofi-V):** *Ann. Oncol.* **2016**, *27*, 2124-2130; **DMUC4064A**: *Gynecol Oncol.* **2021**, *163*, 473-480

Improving antibody-linker stability may result in emergence of unexpected toxicities

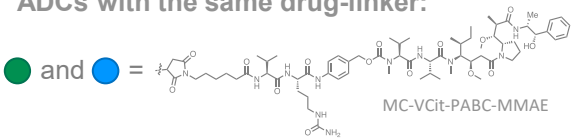
CD79b ADCs:
- Pola-V *(less stable)*
- Ila-V *(more stable)*

MUC16 ADCs:
- Sofi-V *(less stable)*
- DMUC4064A *(more stable)*

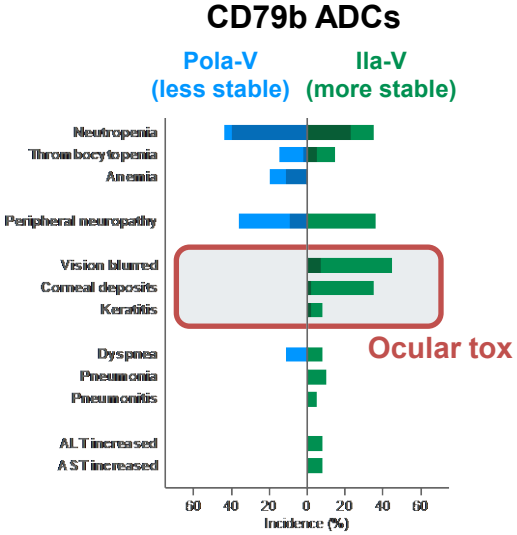
Native Cys stochastic *(less stable)*

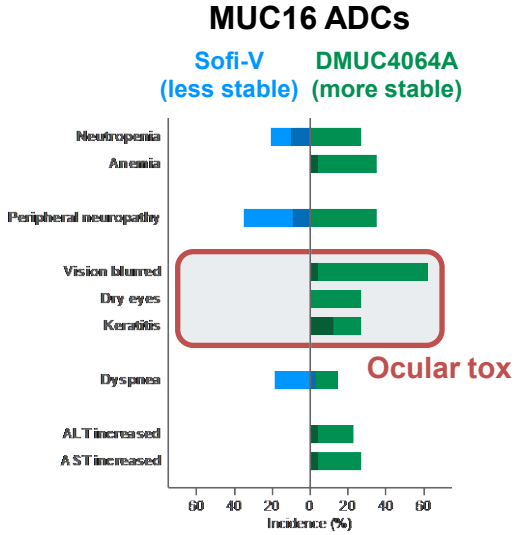
Thiomab site-specific *(more stable)*

ADCs with the same drug-linker:



Distinct clinical toxicities: reduced hematological toxicities and neuropathy but increased incidence of ocular toxicities



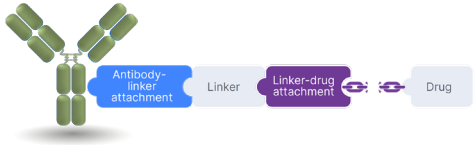


Selected adverse events (lighter shade, G<3; darker shade, G≥3)
Pola-V and Sofi-V (stochastic DAR4); Ila-V and DMUC4064A (thiomab site-specific DAR2)

Polatuzumab vedotin (Pola-V): *Lancet Oncol.* **2015**, *16*, 704-715; **Iladatuzumab vedotin (Ila-V):** *Clin. Cancer Res.* **2022**, *28*, 1294-1301; **Sofituzumab vedotin (Sofi-V):** *Ann. Oncol.* **2016**, *27*, 2124-2130; **DMUC4064A**: *Gynecol Oncol.* **2021**, *163*, 473-480

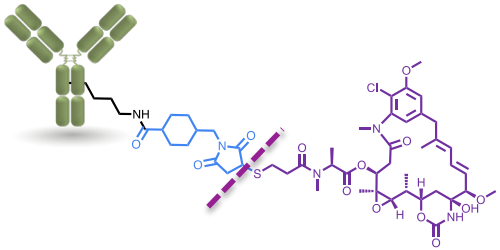
Maytansinoid ADCs with identical antibody, DAR, and dose showed distinct toxicities

Linker-drug instability



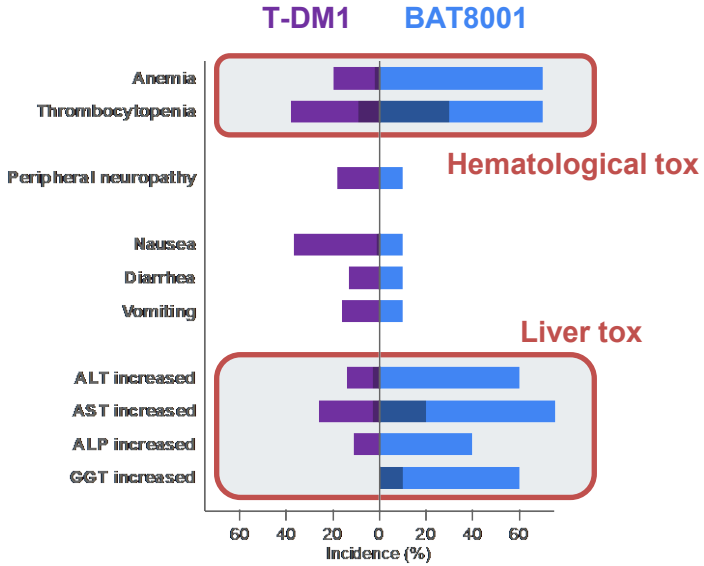
T-DM1

- trastuzumab
- stochastic lysine, DAR = 3.5
- MTD = 3.6 mg/kg



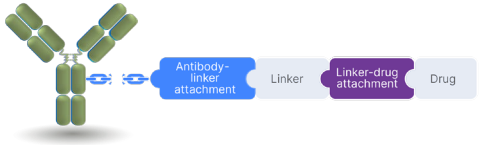
T-DM1 releases free payload

Pronounced hematological and liver toxicities for BAT8001 (discontinued) compared to T-DM1 (approved)



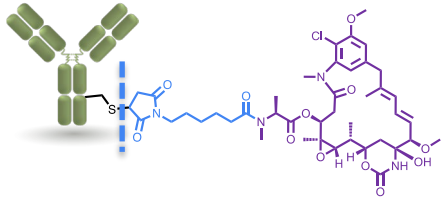
Selected adverse events (lighter shade, G<3; darker shade, G≥3)

Antibody-linker instability



BAT8001

- trastuzumab
- stochastic cysteine, DAR = 3.5
- MTD = 3.6 mg/kg

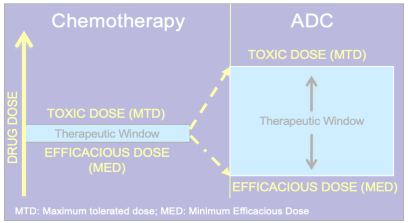


BAT8001 releases linker-payload

T-DM1: *J. Clin. Oncol.* **2012**, *30*, 3234-3241; **BAT8001**: *Cancer Commun. (Lond.)* **2021**, *41*, 171-182.

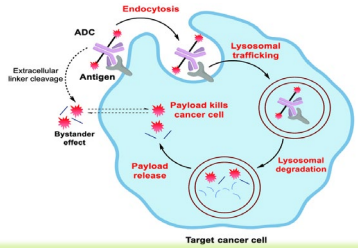
Classic ADC dogma

1. **The therapeutic window dogma:**
   - ADCs widen the therapeutic window of the conjugated drug by both *increasing the maximum tolerated dose* (MTD) and *reducing the minimum efficacious dose* (MED) of the drug



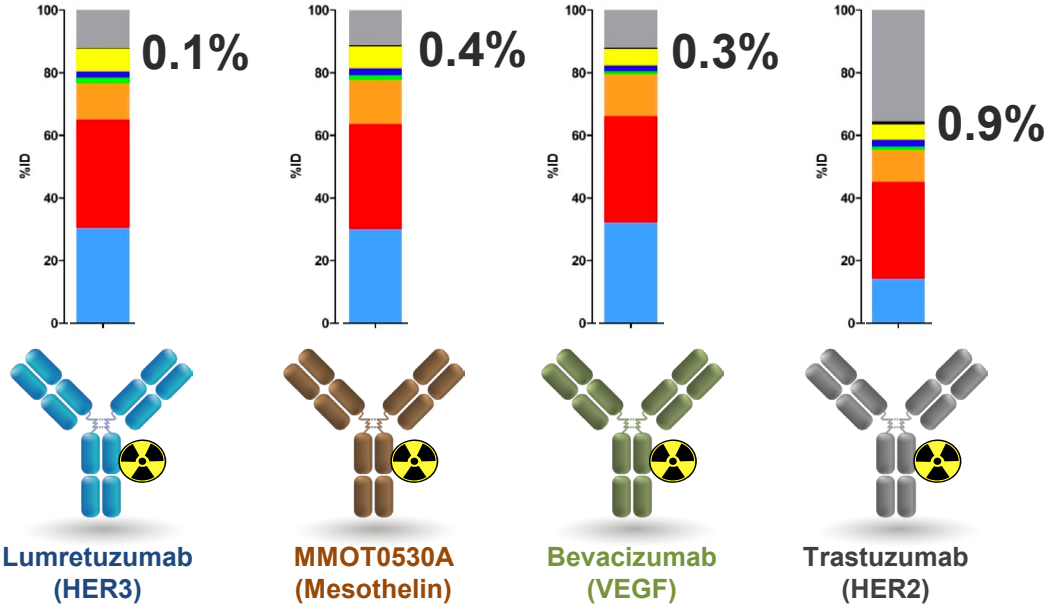
2. **The stability dogma:**
   - A highly stable linker is paramount to the clinical success of the ADC

3. **The magic bullet dogma:**
   - ADCs deliver conjugated drugs *selectively to cancer cells while sparing normal cells*. If the payload is bystander active, it can then kill neighboring cancer cells.



Radiolabeled antibodies can reveal the fate of antibody-based therapeutics

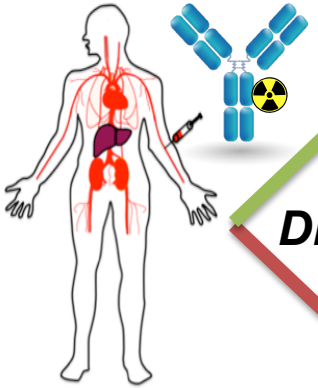
Irrespective of the target, radiolabeled antibodies show high normal tissue distribution and <1% tumor uptake in humans



Absolute **uptake in healthy tissues and tumor 4 days after dosing**

F. Bensch et al. *Theranostics* **2018**, *8*, 4295-4304

Less than 1% of antibody (and ADC) injected dose reaches the tumor sites



Distribution

On-target on-tumor (<1%)

Typical range 0.001-0.1 %ID

Off-target (>99%)

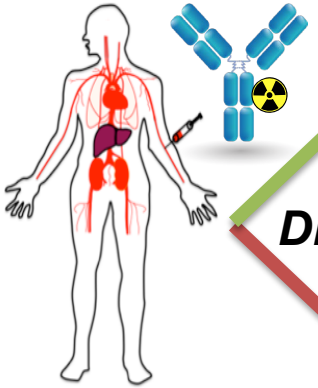
(+ on-target off-tumor)

References:

- J. P. Mach et al. *N. Engl. J. Med.* **1980**, *303*, 5-10
- A.A. Epenetos et al. *Cancer Res.* **1986**, *46*, 3183-3191
- A. M Scott et al. *Clin. Cancer Res.* **2005**, *11*, 4810–4817
- E. C. Dijkers et al. *Clin. Pharmacol. Ther.* **2010**, *87*, 586–592
- J. A. *Carrasquillo* et al. *J. Nucl. Med.* **2011**, *52*, 1173–1180
- F. Bensch et al. *Theranostics* **2018**, *8*, 4295-4304
- A. N. Niemeijer et al. *Nat. Commun.* **2018,** *9*, 4664
- G. Lu et al. *Nat. Commun.* **2020**, *11*, 5667
- H. K. Gan et al. *J. Nucl. Med*. **2021**, *62*, 787–794
- J. Smit et al. *J. Nucl. Med.* **2022**, *63*, 686-693
- S. R. Verhoeff et al. *J. Nucl. Med.* **2022**, *63*, 1523-1530

…and others

Antibody catabolism happens mainly in normal tissues and not in the tumor



On-target on-tumor (<1%)

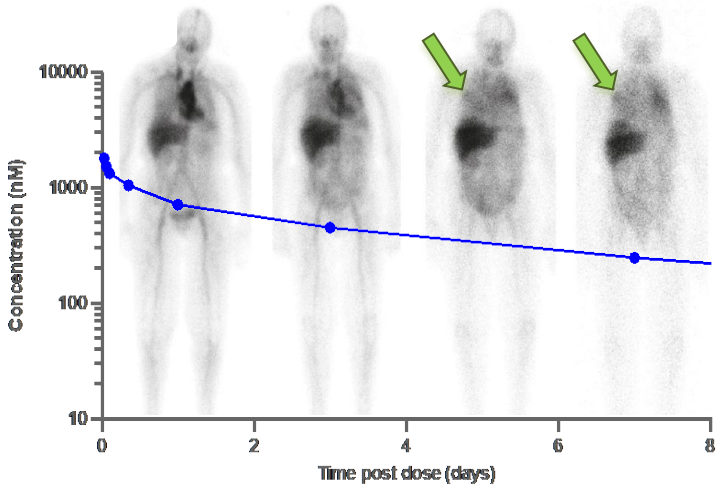
Typical range 0.001-0.1 %ID

Distribution

Off-target (>99%)

(+ on-target off-tumor)

Imaging time series of a patient with a HER2+ lung tumor post ^{111}In-Trastuzumab dose



- Tumor to background ratio increases over time
- Whole-body antibody concentration decreases from normal organ catabolism

Adapted from: Sietske B.M. Gaykema et al. *Molecular Imaging.* **2014**,*13*, 5

Platform toxicities and target independent MTD highlight normal tissue ADC disposition

Payload-dependent toxicities* ('Platform Tox')

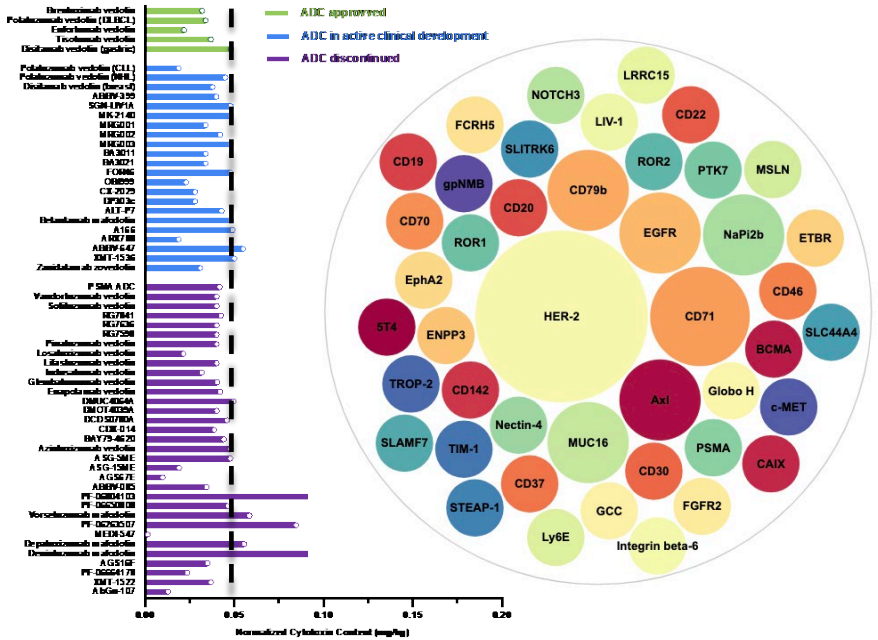
DM1: thrombocytopenia, neuropathy, elevated liver enzymes
DM4: ocular toxicity, neuropathy, elevated liver enzymes

MMAE: neutropenia, neuropathy
MMAF: thrombocytopenia, ocular toxicity

DXd: nausea, neutropenia, anemia, ILD
SN38: diarrhea, neutropenia, anemia

PBDs: edema, pleural effusion, elevated liver enzymes, neutropenia, thrombocytopenia

Target-independent MTDs*

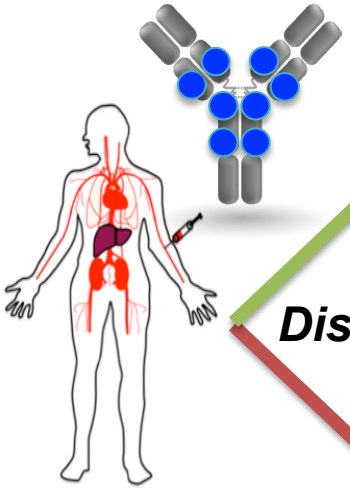


Selected common platform toxicities across multiple ADCs

*On-target off-tumor exceptions exist

Selected MTDs and targets of auristatin ADCs

ADC clearance generates payload in circulation: ADC is a source of payload



Distribution

On-target on-tumor (<1%)

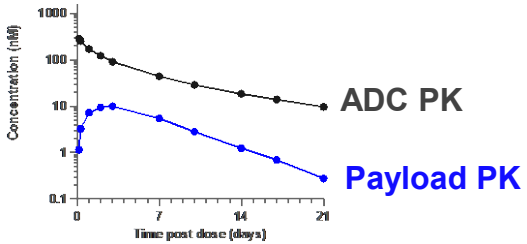
Off-target (>99%)

(+ on-target off-tumor)

Clearance

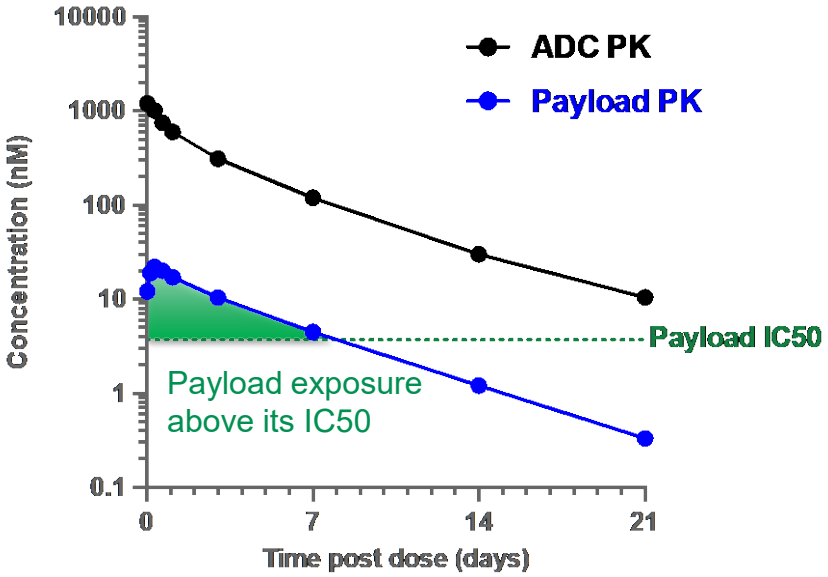
ADC metabolism

Payload in circulation



Circulating payload concentrations achieve pharmacologically active levels in humans

ADC and payload PKs in humans



Payload exposure likely to contribute to ADC clinical efficacy:

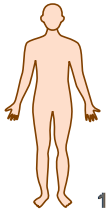
- Activity in tumors with low antigen expression or no antigen expression

ADC significantly alters payload PK:

- Payload half-life extended from hours (typical small molecule PK) to days
- Elimination of payload is limited by its formation

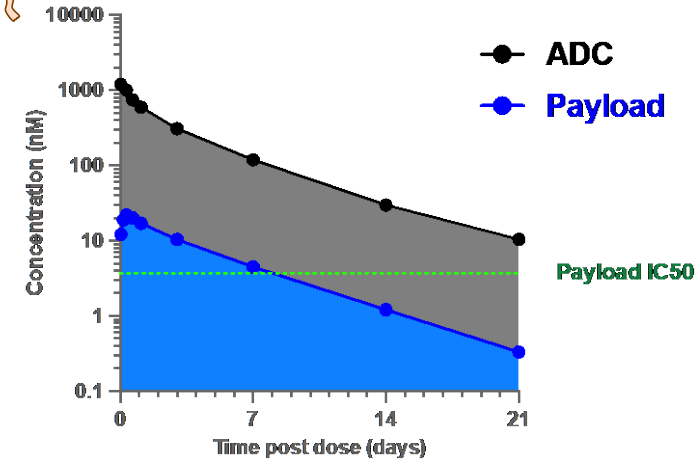
E. Tarcsa et al. *Drug Discov. Today Technol.* **2020,** *37*, 13-22

…but not in preclinical species (even non-human primates!)



ADC and payload PKs in humans

(example: T-DXd, 6.4 mg/kg dose)

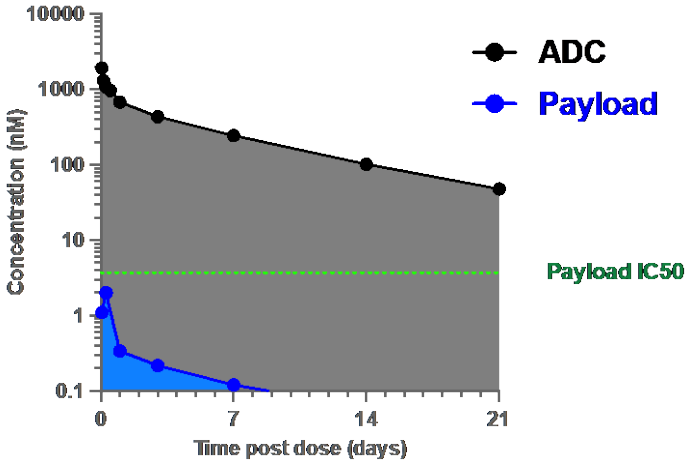


Payload/ADC AUC ratio = 1.8%

>>

ADC and payload PKs in non-human primates

(example: T-DXd, 8 mg/kg dose)

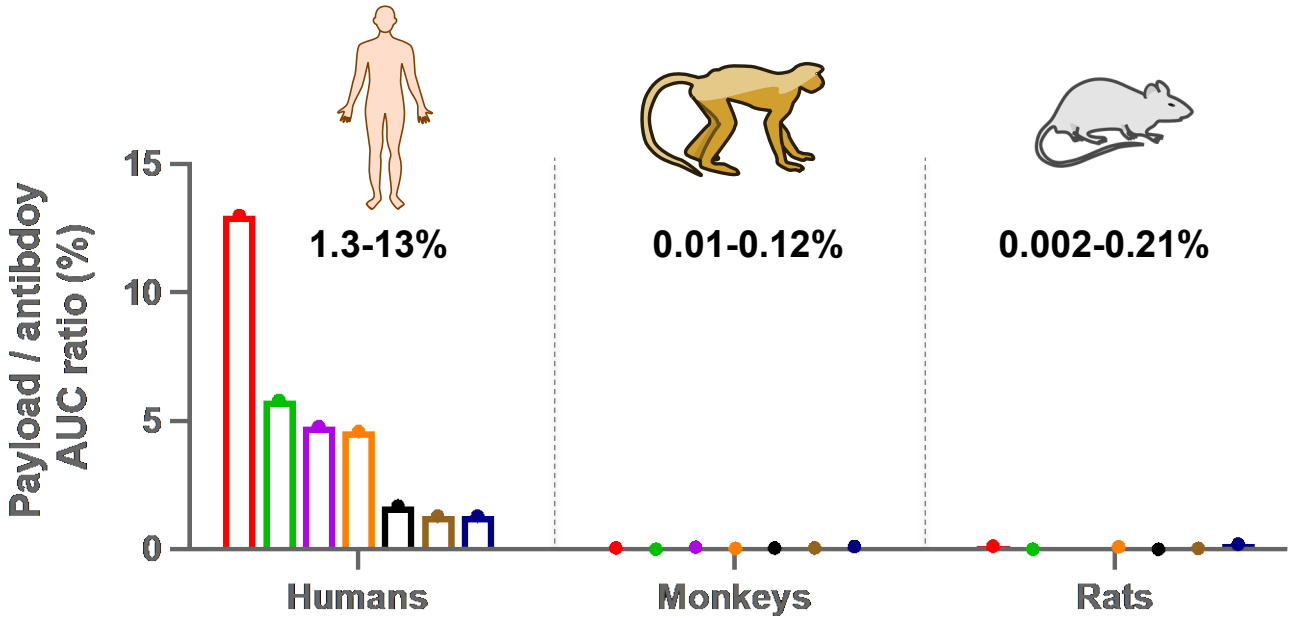


Payload/ADC AUC ratio = 0.06%

Data adapted from: D. Toi et al. *Lancet Oncol.* **2017**, *18*, 1512-1522 and H. Habara et al. *Biopharm. Drug. Dispos.* **2023**, *44*, 380-384

Contribution of circulating payload is underestimated in all the preclinical models

Exposure of payloads in humans is significantly higher than non-human species

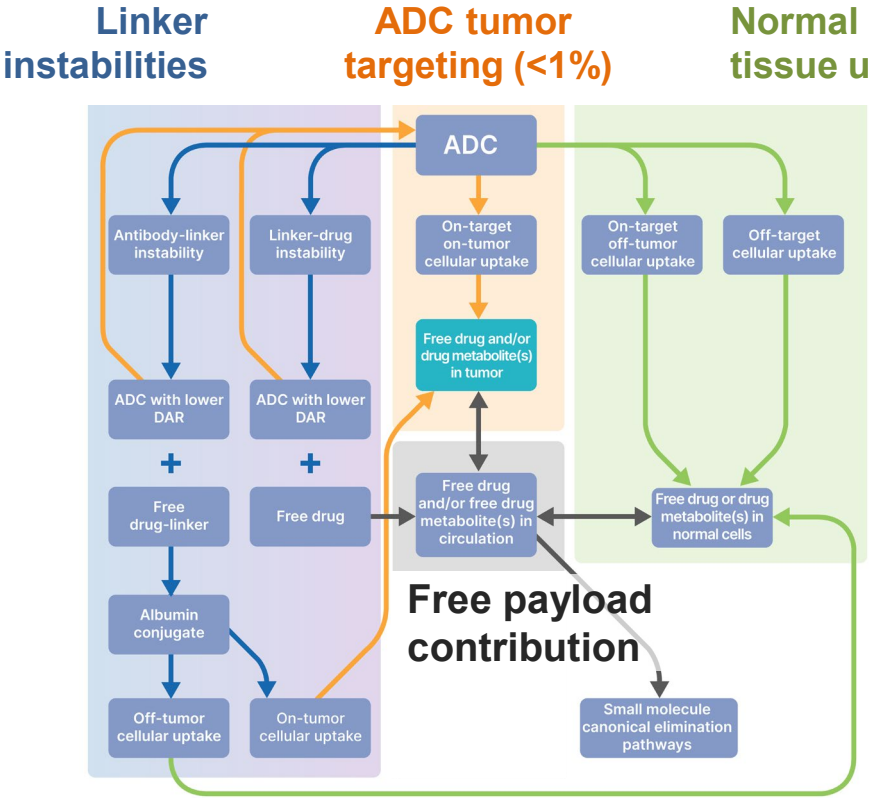


- Enfortumab vedotin
- Polatuzumab vedotin
- Tisotumab vedotin
- Brentuximab vedotin
- Mirvetuximab soravtansine
- Trastuzumab deruxtecan
- Trastuzumab emtansine

Similar results for Cmax ratios

R. Colombo et al. *Cancer Research,* **2023,** *83(7_Supplement),* 1538

How do ADCs work?



- **Efficacy is driven by a complex combination** of targeted payload delivery, free payload exposure, and tumor subtype sensitivity.
- **Target expression and ADC properties** (including linker instabilities) **influence sites and rates of ADC disposition**, and in turn payload tumor, tissue, and systemic exposures
- **ADC linker and payload properties** (including linker stability, cleavability, and payload permeability) can **influence the bystander effect** of ADCs

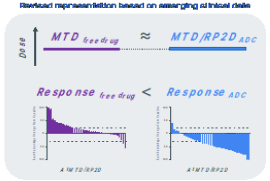
R. Colombo et al. *Cancer Research,* **2023,** *83(7_Supplement),* 1538

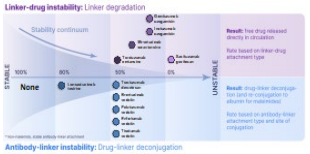
Refining the ADC dogma: understanding ADCs to maximize their clinical success

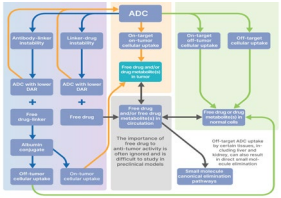
1. **The therapeutic window dogma:**
   - *ADCs don't increase the MTD but are more efficacious* than small molecules when dosed at or near their MTDs

2. **The stability dogma:**
   - *Right stability is critical to balance efficacy and toxicity*. Unexpected toxicities have emerged when trying to overly stabilize ADCs

3. **The magic bullet dogma:**
   - *ADC targeted and non-targeted uptake and linker instabilities contribute to sustained payload concentration* at the tumor site







Nuances of ADC properties have a large impact on efficacy and tolerability in patients

Therefore, it is important to refine our understanding of ADCs in light of clinical data!