Recent Advances In Antibody Drug Conjugates

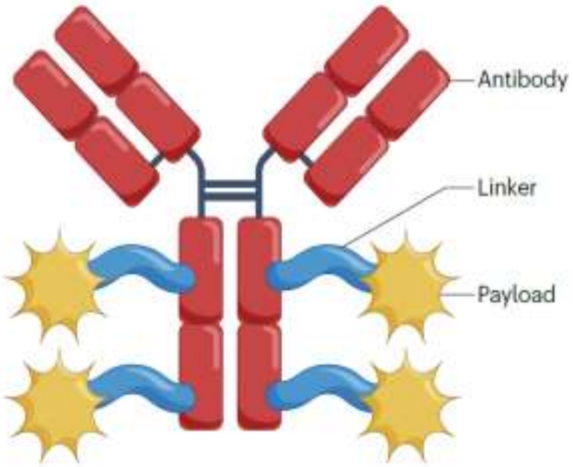
Michael Seganish

CDDF 2025

31 March 2025

Antibody Drug Conjugates and Potential Mechanisms of Action

Principle: targeted payload delivery

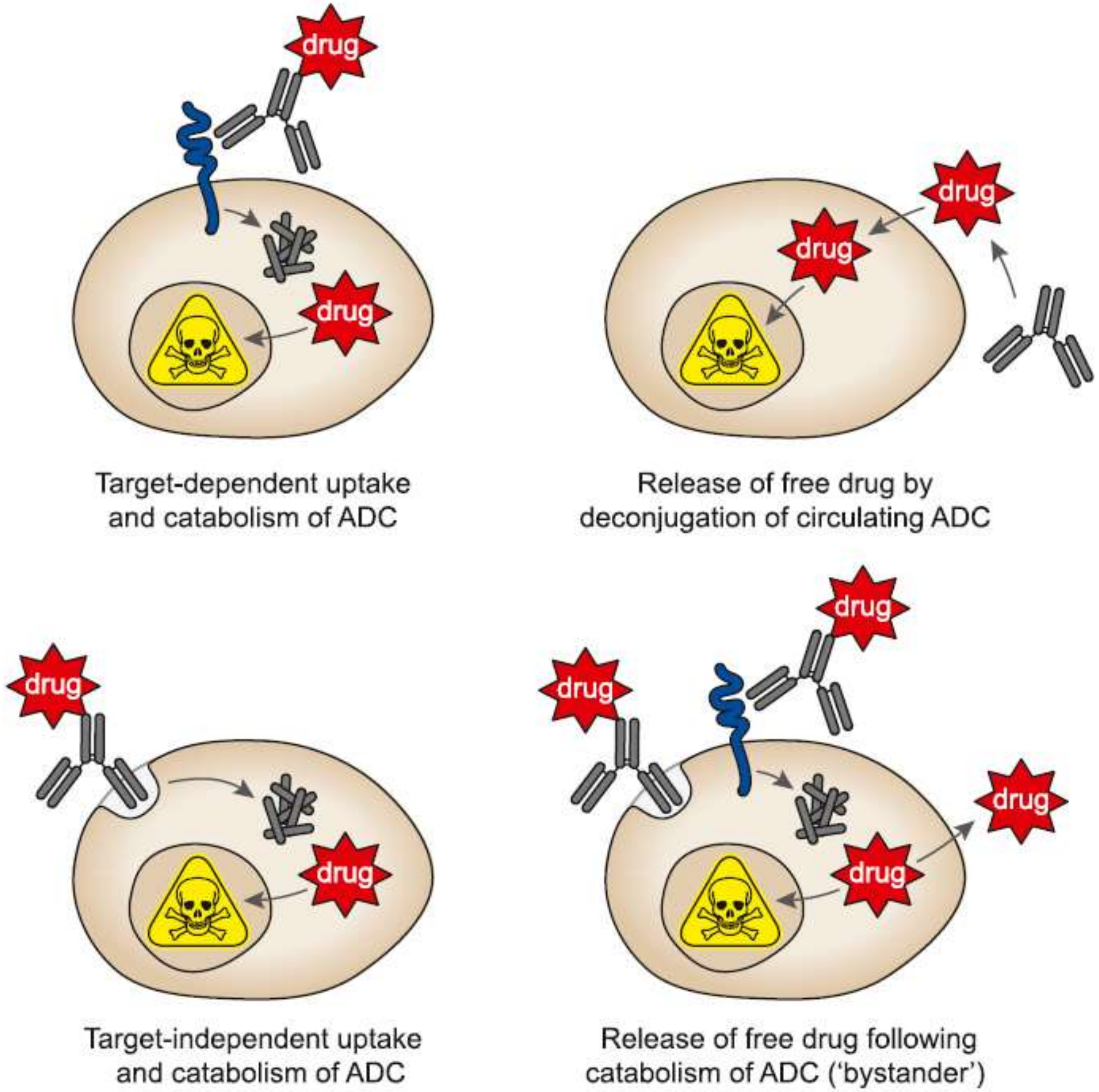


DAR: typically ranges from 0 to 8

<u>2000</u>
First FDA
ADC approval

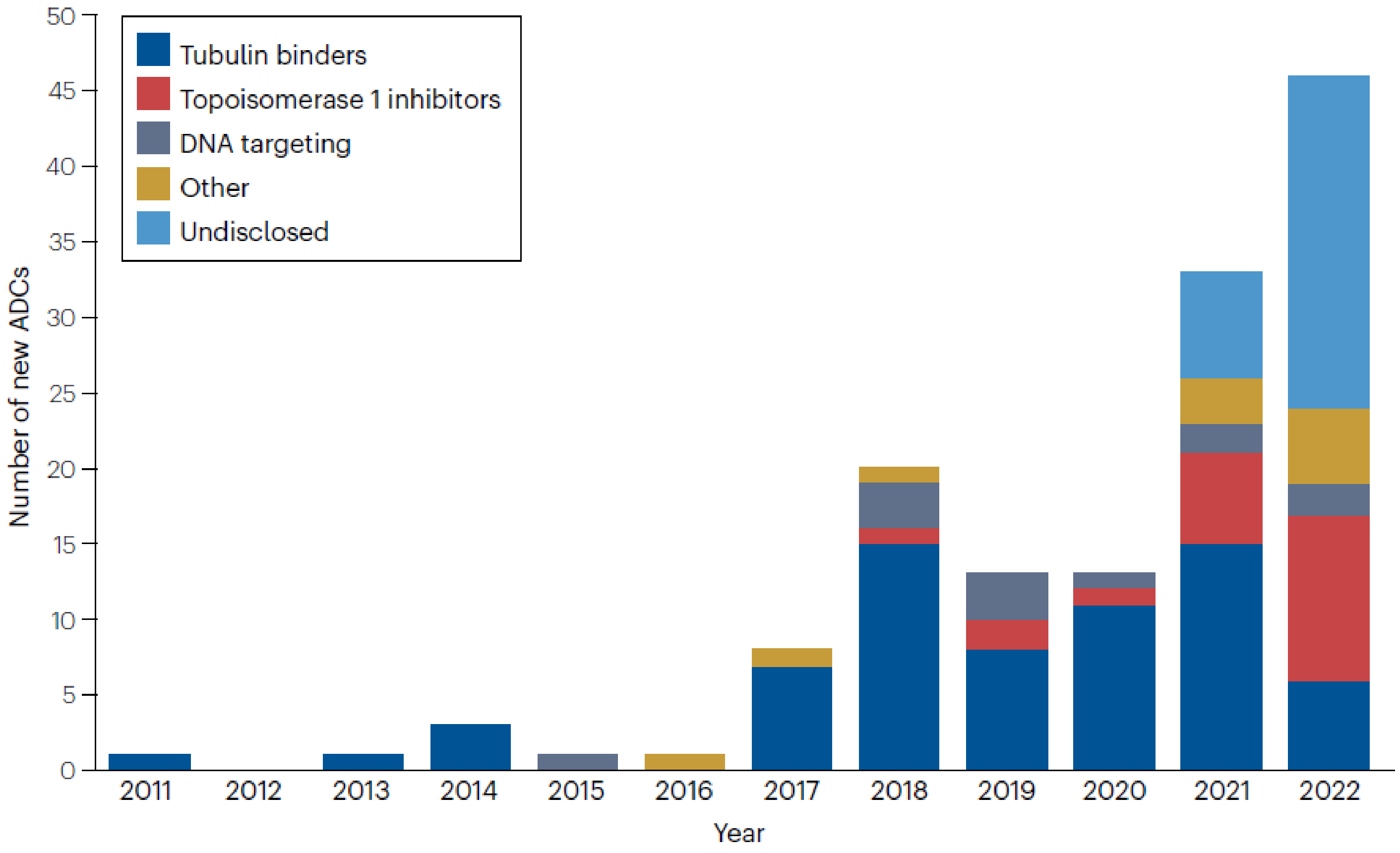
<u>2023</u>
14 approved
worldwide

Possible mechanisms of ADC activity



Dumontet C et al. *Nat Rev Drug Discov.* 2023, 22, 641
Dere R et al. *Bioanalysis.* 2013, 5, 1025
Fu Z et al. *Signal Transduct Target Ther.* 2022, 7, 93
Polakis P. *Pharmacol Rev.* 2016, 68, 3

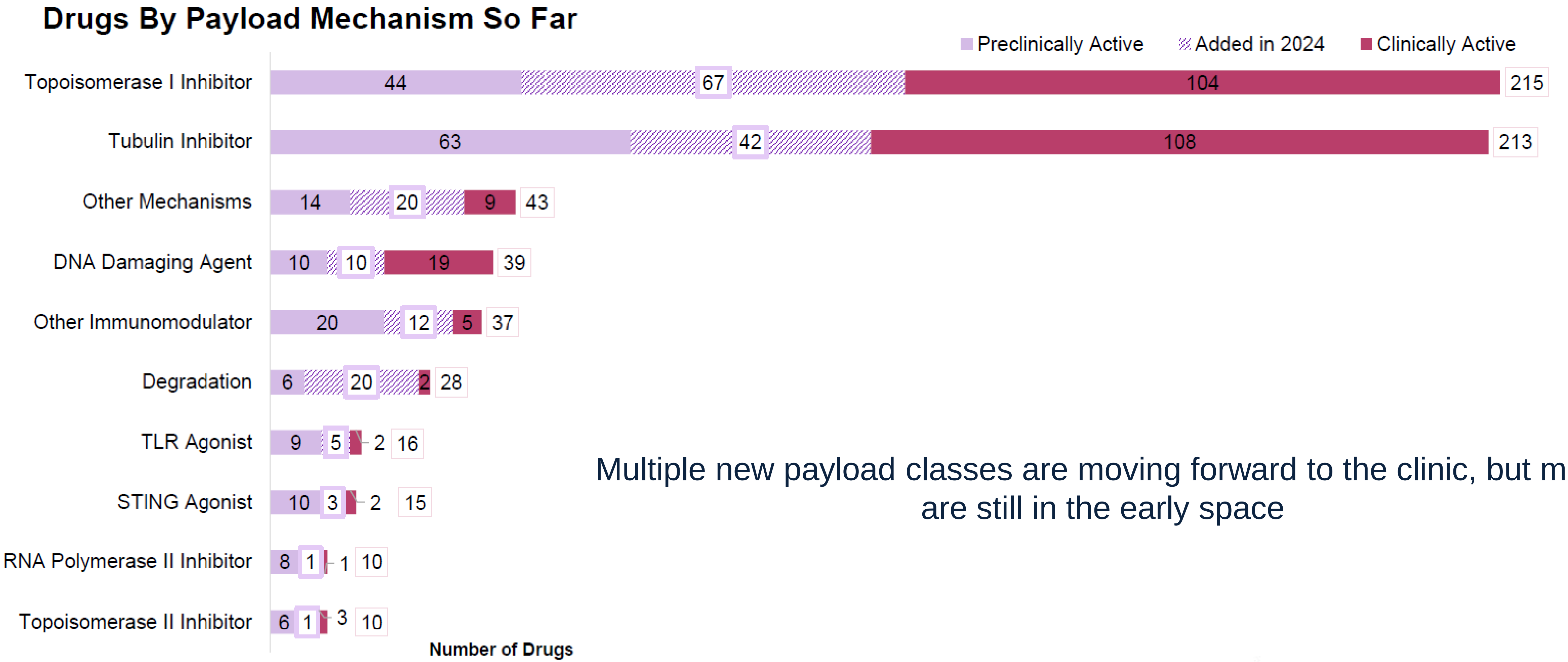
The Number of Clinical Stage ADCs Has Grown Dramatically



- Diversifying payloads is critical to the expansion of ADC indications, given that not all tumor types will be sensitive to a given type of payload.
- Diverse payload options enable options to overcome resistance

Dumontet C et al. *Nat Rev Drug Discov.* 2023, 22, 641

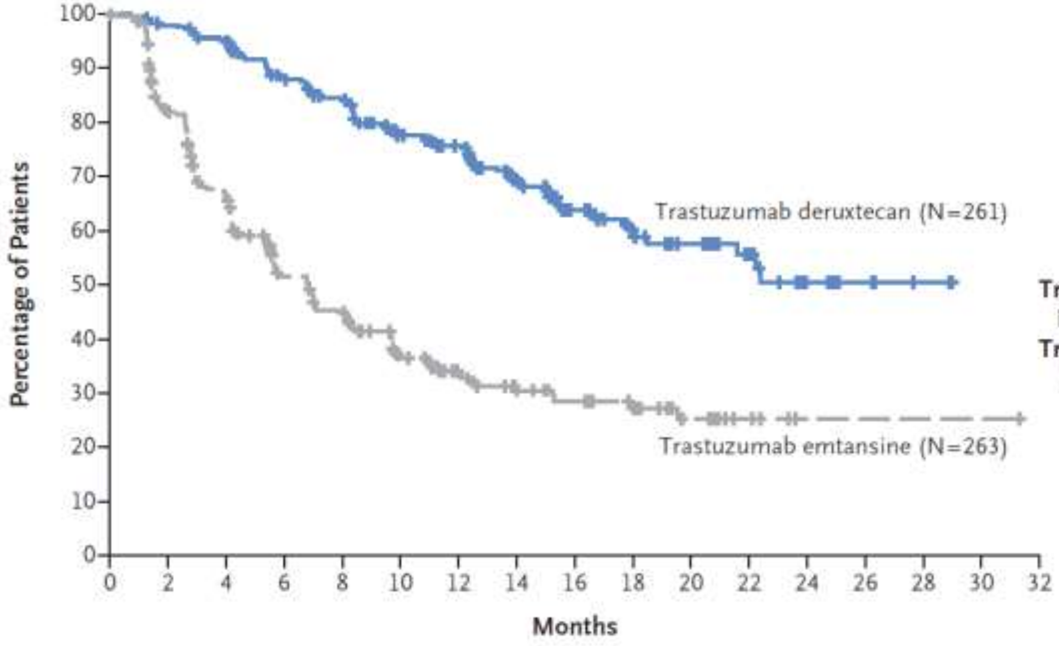
ADCs With Novel Payloads Are on the Horizon



Multiple new payload classes are moving forward to the clinic, but most are still in the early space

Selection of the Right Payload is a Critical Step

DESTINY-Breast03

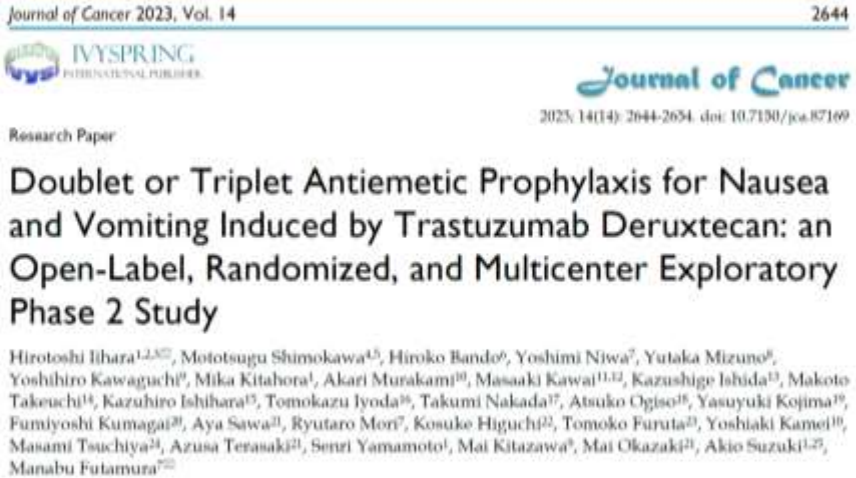


No. at Risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
Trastuzumab deruxtecan	261	250	240	214	200	168	150	112	79	53	36	25	10	5	2		
Trastuzumab emtansine	263	200	155	108	93	65	51	37	29	21	12	6	1	1	1	1	0

	Median Progression-free Survival (95% CI)	12-Mo Progression-free Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NR (18.5–NE)	75.8 (69.8–80.7)
Trastuzumab Emtansine	6.8 (5.6–8.2)	34.1 (27.7–40.5)

Hazard ratio for disease progression or death, 0.28 (95% CI, 0.22–0.37)
P<0.001

- Different payloads can have different effects on patient outcomes
- But issues with toxicity remain


Journal of Cancer 2023, Vol. 14 2644

IVYSPRING INTERNATIONAL PUBLISHER

Journal of Cancer

2023; 14(14): 2644-2654. doi: 10.7150/jca.87169

Research Paper

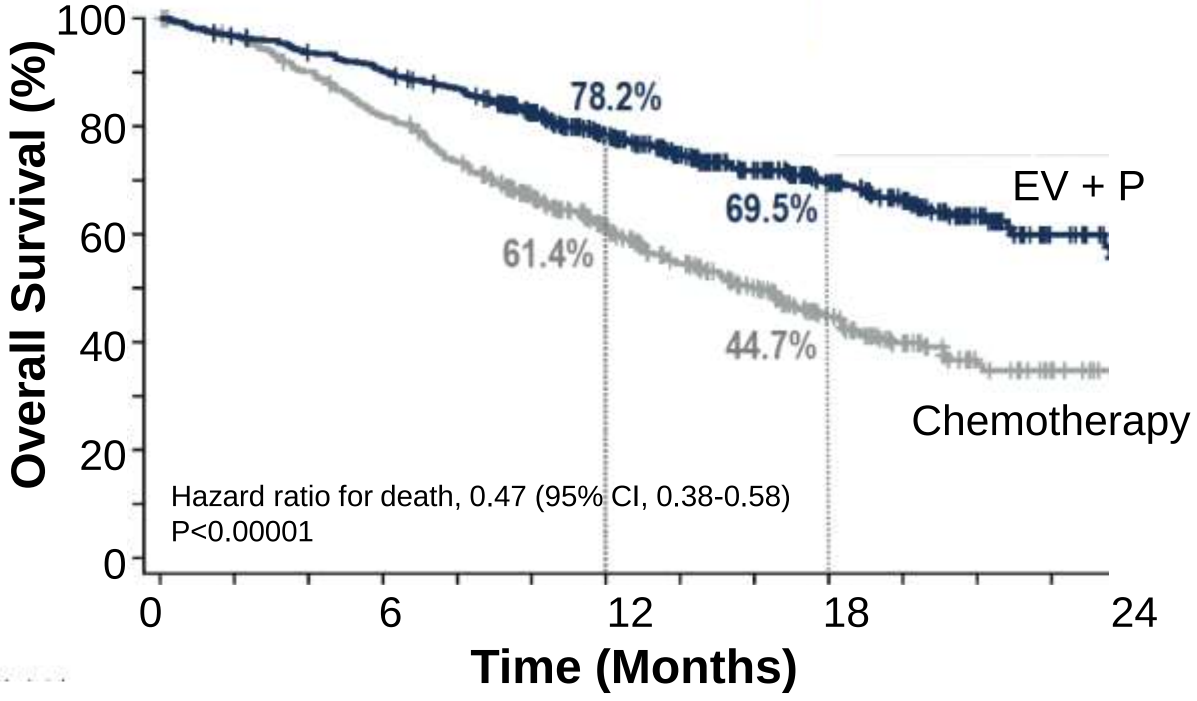
Doublet or Triplet Antiemetic Prophylaxis for Nausea and Vomiting Induced by Trastuzumab Deruxtecan: an Open-Label, Randomized, and Multicenter Exploratory Phase 2 Study

Hirotoshi Iihara[1,2,3✉], Mototsugu Shimokawa[4,5], Hiroko Bando[6], Yoshimi Niwa[7], Yutaka Mizuno[8], Yoshihiro Kawaguchi[9], Mika Kitahora[1], Akari Murakami[10], Masaaki Kawai[11,12], Kazushige Ishida[13], Makoto Takeuchi[14], Kazuhiro Ishihara[15], Tomokazu Iyoda[16], Takumi Nakada[17], Atsuko Ogiso[18], Yasuyuki Kojima[19], Fumiyoshi Kumagai[20], Aya Sawa[21], Ryutaro Mori[7], Kosuke Higuchi[22], Tomoko Furuta[23], Yoshiaki Kamei[10], Masami Tsuchiya[24], Azusa Terasaki[21], Senri Yamamoto[1], Mai Kitazawa[8], Mai Okazaki[21], Akio Suzuki[1,25], Manabu Futamura[7✉]

Cortés J et al. *N Engl J Med.* 2022, 386, 1143

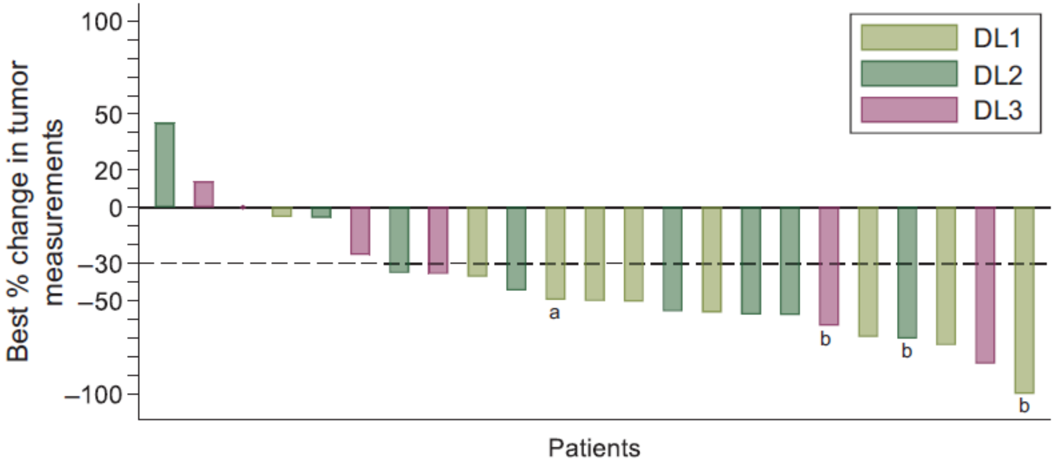
Combination of ADCs With Other Agents Can Improve Response

ADC + IO
Padcev® plus Keytruda®
(Bladder)



US FDA applied a black box warning for peripheral neuropathy for the combination

ADC+ADC
Double Antibody Drug Conjugate (DAD) Trial:
Trodelvy® plus Padcev®
(Bladder)



70% ORR across dose groups
78% of patients experienced grade ≥3 AEs

Powles et al. ESMO 2023: EV-302/KEYNOTE-A39 presentation
McGregor et al. Annals of Oncology 2024, 35, 91

ADC Toxicity: A Major Issue With Two Broad Causes

- In a meta-analysis of 169 ADC clinical trials (N=22,492):
  - Incidence of all-grade TRAEs was 91.2% (N=12,315), with grade ≥3 TRAEs observed in 46.1% of patients (N=11,204)

Off-target, off-tumor

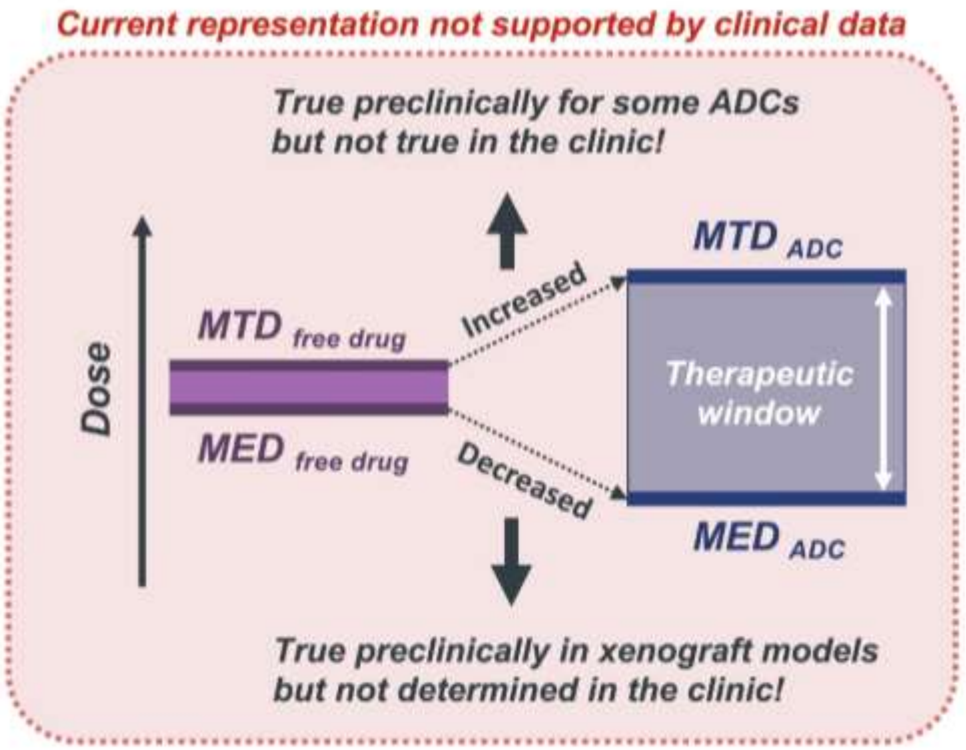
- Predominate toxicity profile of most approved ADCs
- Extent of off-target exposure of non-malignant cells to payload determines tolerability of the ADC
- Key mechanism potentially due to premature deconjugation of payload in systemic circulation and diffusion of free payload into extratumoral compartments

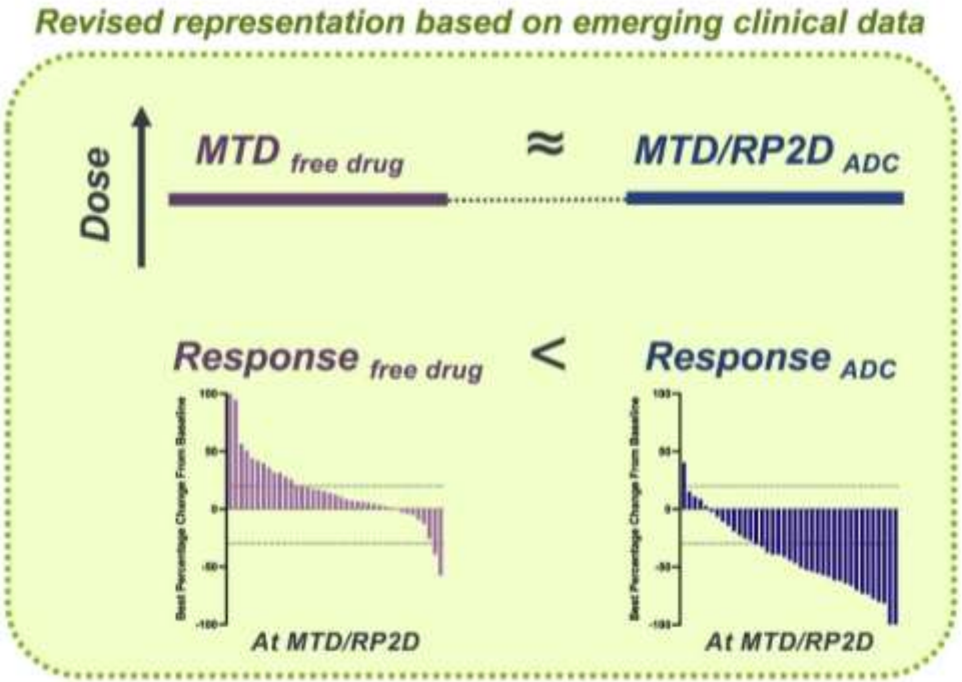
On-target, off-tumor

- Related to engagement of antibody with cognate antigen located in non-malignant tissues, resulting in accumulation of payload in non-malignant tissues expressing the ADC target
- ADCs with same payload and linker can differ in adverse effect profile due to on-target, off-tumor toxicities
- Ideal ADC target: differential antigen expression levels between tumor cell (ideally high expression) and non-malignant cells (ideally low or absent expression) to minimize on target toxicities

Zhu Y et al. *Cancer.* 2023, 129, 283
Tarantino P et al. *Nat Rev Clin Oncol.* 2023, 20, 558

ADCs Improve Efficacy But Generally not MTD in the Clinic





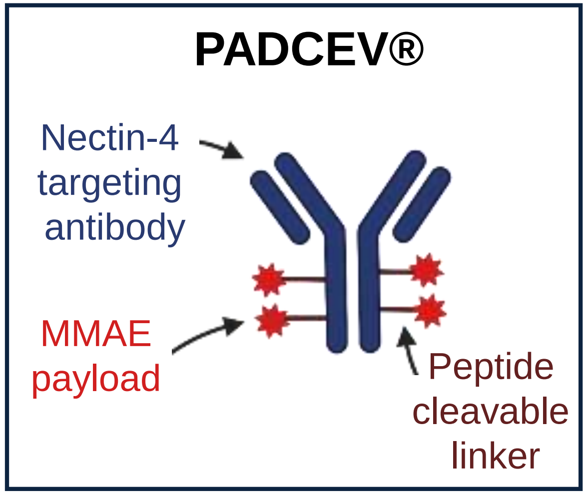
Efficacy of Trodelvy® in TNBC (n=267): ORR of 31%
Efficacy of irinotecan + cetuximab in TNBC (n=11): ORR of 18%

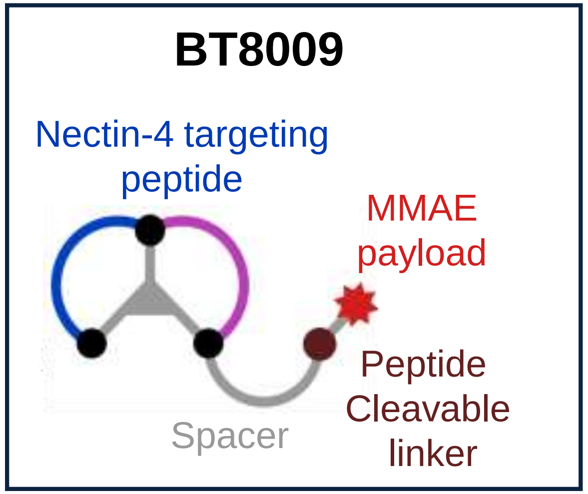
**Not compared head-to-head*

Colombo R, Rich JR. *Cancer Cell.* 2022,40, 1255
Bardia A et al. *N Engl J Med.* 2021, 384, 529
Crozier JA et al. *Clin Breast Cancer.* 2016, 16, 23

Will more stable linker-payloads and ADCs change this paradigm?

Peptide Drug Conjugates May Improve Safety vs. ADCs

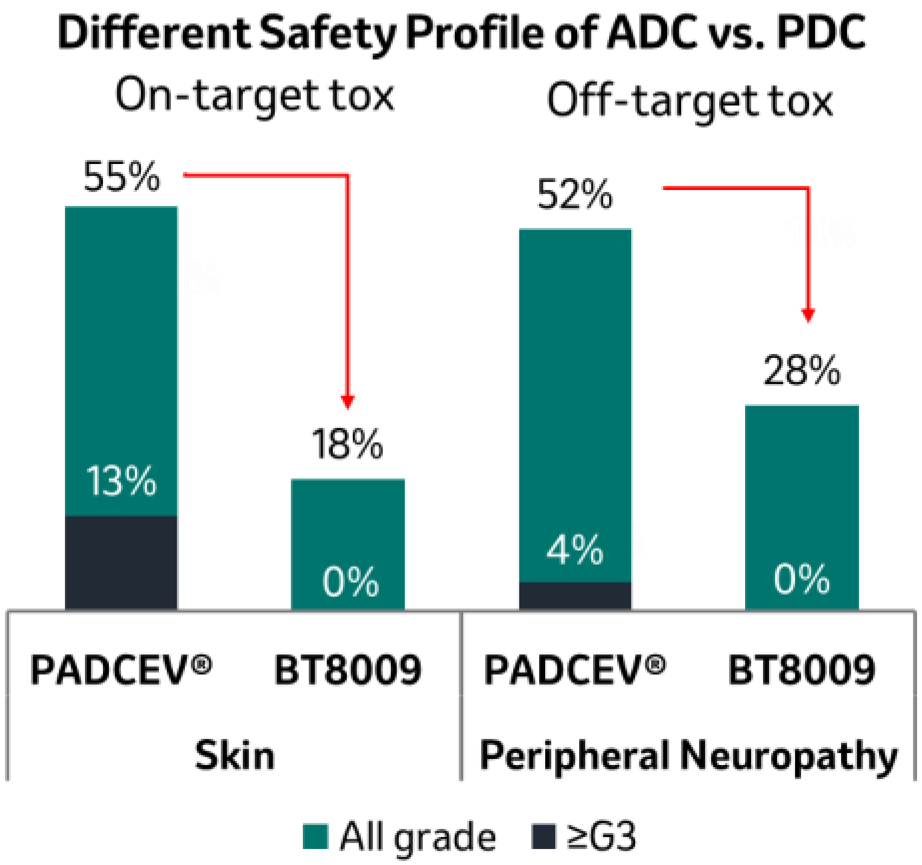




Padcev® vs BT8009

Urothelial Carcinoma Efficacy	PADCEV® 1.25 mg/kg	BT8009 5 mg/m²
N	125	38
ORR	44%	45%
mDOR (months)	7.6	11.1
Half Life	3.6 days	<1hr

Can a "hit and run" approach alleviate toxicity?



PADCEV® Data from *NJEM,* 2021, 384, 1125. PADCEV® data drug label
BT8009 data ASCO 2023 and ESMO 2024, cross-trial comparison

Near Term Outlook

- ADCs have made a dramatic impact in the treatment of many cancer types with the promise of more exciting data to come
- Most clinical stage ADCs leverage the same payload classes and diversification will be a key component of improving patient response
- Combinations of ADCs with other agents is a promising direction but careful attention needs to be paid to overlapping toxicity
- ADCs with more stable linkers and alterative formats (like peptide drug conjugates) for delivering toxic payloads are being explored that can mitigate some of the issues associated with the currently approved ADCs.

Thank you