Revisiting the dogma of antibody drug conjugates (ADCs): Emerging data challenge the benefit of linker stability and the primacy of payload delivery

Raffaele Colombo, Stuart D. Barnscher, Jamie R. Rich
ADC Therapeutic Development, Zymeworks Inc., Vancouver, BC, Canada

AACR Annual Meeting 2023
Abstract #1538

Introduction: revisiting the ADC dogma

ADCs are an important class of targeted therapeutics hailed for their ability to selectively deliver potent drugs directly to cancer cells (thus often referred to as “magic bullets” or “biological missiles”) and to significantly improve the therapeutic window of their conjugated drug. These widespread beliefs are not supported by clinical evidence.[1]

Nonetheless, ADCs have shown improved efficacy compared to related unconjugated drugs and unrelated standard of care treatments, transforming the way cancer patients are treated.

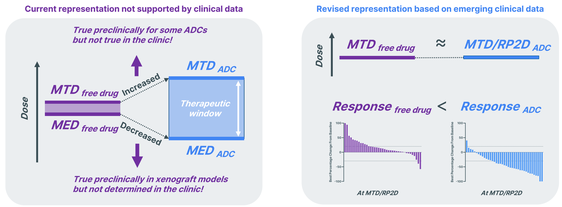


Figure 1. ADCs do not significantly increase the maximum tolerated dose of their conjugated payloads but, when dosed at their MTD or RP2D, they can offer improved efficacy over related unconjugated small molecules.

Herein, we challenge broadly accepted elements of ADC dogma, including the inherent and absolute benefit of linker stability, and the primacy of payload delivery. Although preclinical models generally support these concepts, translation to the clinic is less obvious.

The clinical benefit of approved ADCs is not derived from increased payload dose

Approved ADCs do not achieve a higher MTD or RP2D than other related ADCs or chemotherapies.

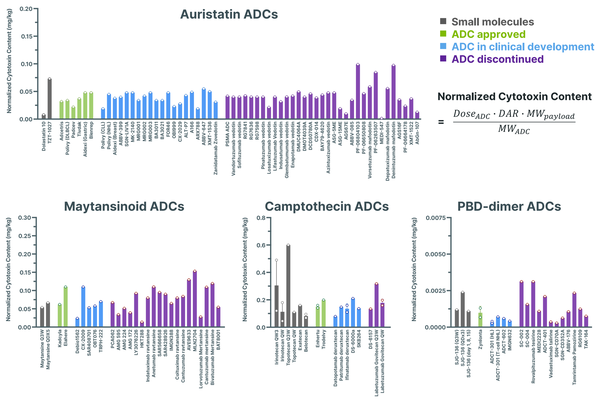


Figure 2. MTD/RP2D doses of small molecules and ADCs (normalized by cytotoxin content). Cut-off: March 2023.

Unresolved questions impact ADC design and development

- Why is the ratio of free payload to ADC exposure substantially higher in humans than in preclinical animal species?
- Why do stable ADCs lead to new toxicities in the clinic and is there a mitigation strategy?
- How do linker instabilities (including albumin exchange) contribute to ADC efficacy and tolerability?

Successful ADCs feature both linker-drug and antibody-linker instability

- None of the approved ADCs are completely stable in circulation.
- ADC instability driven by linker degradation and drug-linker deconjugation influence exposure of both unconjugated (free payload) and conjugated payload (antibody drug conjugate and albumin drug conjugate).

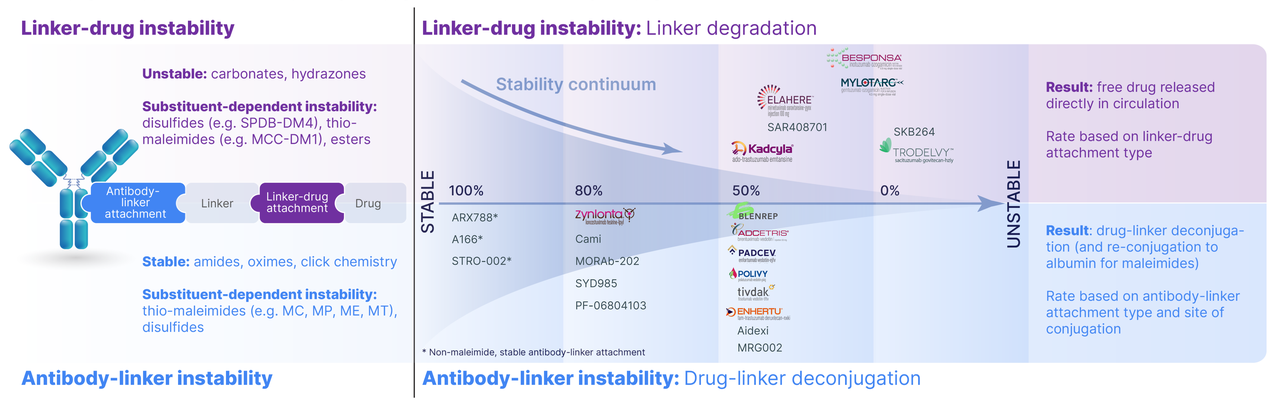


Figure 3. Continuum of ADC stability. Linker degradation and drug-linker deconjugation depend on the type of chemistry used to conjugate the drug to the antibody and the site of conjugation. Percentages shown in the figure represent the amount of conjugated payload remaining on the antibody in circulation after 7 days compared to the initial conjugated payload, estimated from a combination of internal and literature data.

Enhancing ADC stability is an area of intense focus, but does it really improve clinical outcomes?

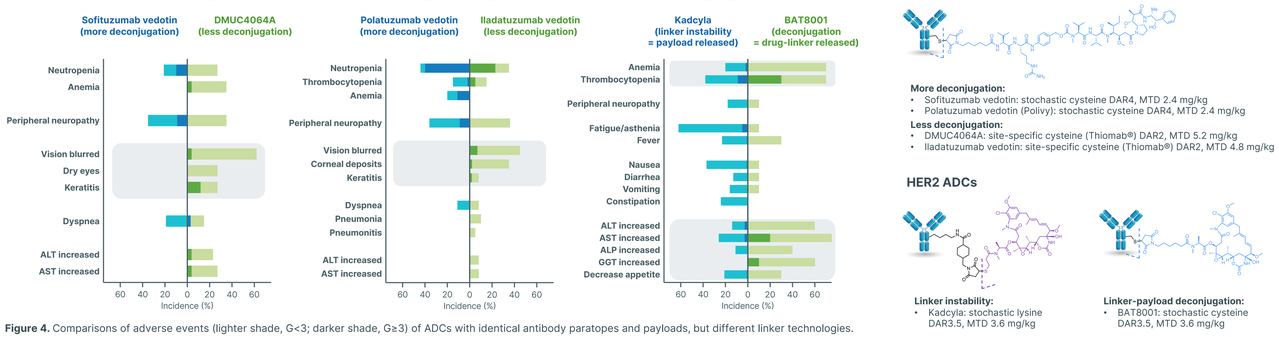


Figure 4. Comparisons of adverse events (lighter shade, G<3; darker shade, G≥3) of ADCs with identical antibody paratopes and payloads, but different linker technologies.

- Several HER2-targeting auristatin ADCs with limited deconjugation (e.g. ARX788, A166, PF-06804103) feature new toxicities compared to ADCs with higher deconjugation (Aidexi, MRG002), although direct comparisons are complicated by linker and payload differences.

ADC targeted-delivery paradigm overlooks additional anti-tumor mechanisms

ADC	Enhertu	Enhertu	Enhertu	Enhertu	Aidexi	SYD985	Trodelvy	Trodelvy	Tivdak
Trial #	NCT00679341	NCT04132960	NCT02564400	NCT03734029	NCT03881138 NCT03529734	NCT02277717	NCT02574455	NCT03901339	NCT03438396
Tumor	BC	BC	BC	BC	BC	BC	TNBC	TNBC	CC
Target	HER2	HER2	HER2	HER2	HER2	HER2	TROP2	TROP2	TF
High expression ORR (%) (# of patients) [criteria]	34% (25/74) [IHC 3+]	71% (48/68) [IHC 3+ or ISH+]	63% (97/154) [IHC 3+]	NA	43% (9/21) [IHC 3+]	33% (16/48) [IHC 3+]	44% (37/85) [H-score >200]	23% (33/142) [H-score >300]	29% (11/38) [H-score >120]
Medium expression ORR (%) (# of patients) [criteria]	5% (1/21) [IHC 2+ or 1+ or 0]	38% (27/72) [IHC 2+ or 1+]	46% (13/28) [IHC 2+ and ISH+]	57% (60/158) [IHC 2+]	43% (15/35) [IHC 2+]	40% (6/15) [IHC 2+ or 1+ and HR-]	38% (15/39) [H-score 100-200]		
Low expression ORR (%) (# of patients) [criteria]			NA	49% (105/214) [IHC 1+]	31% (4/13) [IHC 1+]	28% (9/32) [IHC 2+ or 1+ and HR+]	22% (6/27) [H-score <100]	18% (11/62) [H-score 10-100]	24% (9/38) [H-score <120]
No expression ORR (%) (# of patients) [criteria]		30% (11/37) [IHC 0]	NA	NA	NA	NA		24% (8/34) [H-score ≤10]	

Table 1. Overall response rates for different approved ADCs in patients with different target expression levels. See QR code at the top right for a comprehensive analysis.

Anti-tumor response rates for selected ADCs reveal that:

- Best response rates are achieved in patients with higher antigen expression.
- Many ADCs work well in antigen-low or antigen-null patients, highlighting concomitant mechanisms in addition to targeted payload delivery.

Analytes		AUC (%) (Payload AUC/Total mAb AUC*100)			C_{max} (%) (Payload C_{max}/Total mAb C_{max}*100)		
ADC	Payload or payload metabolite	Humans	Monkeys	Rats (*Rabbits)	Humans	Monkeys	Rats (*Rabbits)
Multiple vedotin ADCs	MMAE	5-13%	0.02-0.10%	0.01-0.10%	2-3%	0.01-0.03%	0.04-0.05%
Enhertu	DXd	1.3%	0.06%	0.04%	1.8%	0.10%	0.06%
Elahere	DM4	0.5%	0.06%	0.02%*	0.6%	0.07%	0.12%*
	S-Me-DM4	1.7%	BLQ	0.002%*	1.0%	NA	0.01%*

Table 2. Payload AUC and C_{max} expressed as percentage of total antibody AUC and C_{max} in different species for approved ADCs. See QR code at top right for a comprehensive analysis.

Intrinsic ADC stability is similar across species, yet we have identified that serum payload exposures (as a percentage of ADC exposure) are significantly higher in humans, highlighting species-specific dependency in ADC and payload metabolism and disposition.

Circulating free payload concentrations often achieve pharmacologically active levels in humans

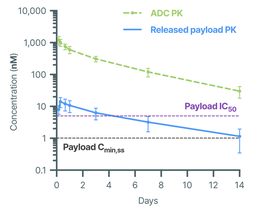


Figure 5. Example of typical exposures of an ADC and its released payload in plasma compared to payload $C_{min,ss}$ and cell-based payload IC_{50}. See Tarcsa et al. for further discussion.[2]

- ADCs with moderate drug-linker stability benefit from both targeted and untargeted mechanisms.
- ADCs with stable drug-linkers rely instead on full ADC catabolism to release the active payload.

ADC stability impacts payload disposition and the premise of payload delivery

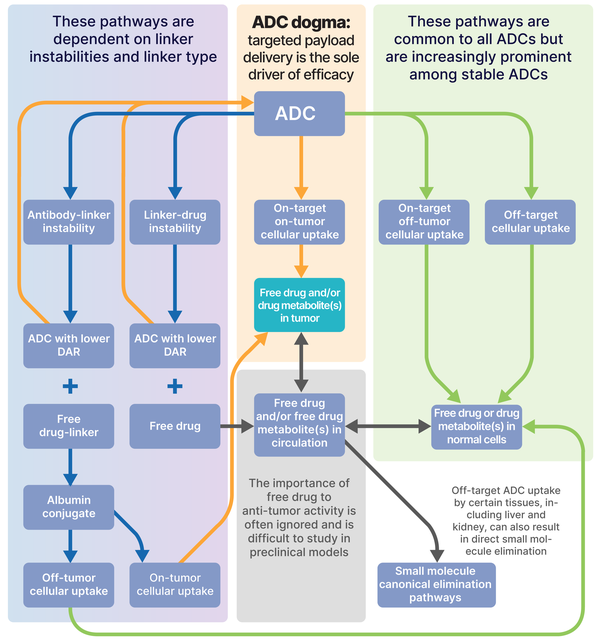


Figure 6. The complex disposition of an ADC and its catabolites: ADC properties, including antibody-linker and linker-drug instabilities, influence the fate of each ADC.

- It is estimated that <1% of injected therapeutic antibodies reaches tumors in humans, highlighting the need to contemplate additional mechanisms.
- ADC efficacy is likely driven by a complex combination of targeted payload delivery, free payload exposure, and tumor subtype sensitivity.
- Drug-linker instabilities and target expression influence sites and rates of ADC disposition, and in turn payload tumor, tissue, and systemic exposures.
- Preclinical models do not accurately recapitulate the effects of linker instabilities (degradation or deconjugation) in the clinic and may overemphasize the benefit of stable ADCs.
- Unexpected toxicities caused by antibody conjugated payload are apparent with more stable ADC conjugation technologies.

References

1) Colombo R, Rich JR. The therapeutic window of antibody drug conjugates: A dogma in need of revision. *Cancer Cell*. **2022**, *40*, 1255-1263.
2) Tarcsa E, Guffroy MR, Falahatpisheh H, Phipps C, Kalvass JC. Antibody-drug conjugates as targeted therapies: Are we there yet? A critical review of the current clinical landscape. *Drug Discov Today Technol*. **2020**, *37*, 13-22.

Revisiting the dogma of antibody drug conjugates (ADCs): Emerging data challenge the benefit of linker stability and the primacy of payload delivery

Raffaele Colombo, Stuart D. Barnscher, Jamie R. Rich
ADC Therapeutic Development, Zymeworks Inc., Vancouver, BC, Canada

AACR Annual Meeting 2023
Poster #1538

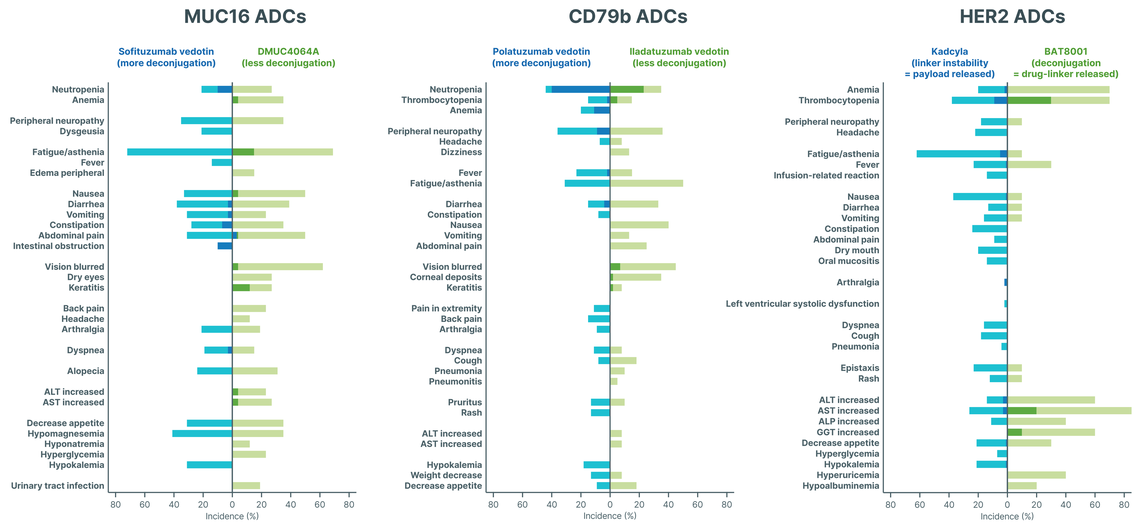
Extended tables and figures

	T-DM1	T-DM1	T-DM1	T-DXd	T-DXd	T-DXd	T-DXd	T-DXd	T-DXd	T-DXd	T-DXd	T-DXd	RC48	RC48	SYD985	SG	SG	SG	SKB264	HER3-DXd	UpRi	STRO-002	STRO-002	Mirv	Mirv	ABBV-647	ABBV-647	ABBV-647	TV	TV
Trial #	NCT00679341	NCT00509769	NCT02289833	NCT04132960	NCT02564900	NCT02564900	NCT03734029	NCCHE, Kashiwa, Japan	NCT03329690	NCT03505710	NCT03384940	UMIN000029506	NCT02881138 and NCT03052634	NCT04073602	NCT02277717	NCT01631552	NCT02574455	NCT03901339	NCT04152499	NCT03260491	NCT03319628	NCT03748186	NCT03748186	NCT01609556	NCT02631876	NCT04189614	NCT04189614	NCT04189614	NCT02001623	NCT03438396
Tumor	BC	BC	NSCLC	BC	BC	BC	BC	BC	GC	NSCLC	CRC	UCS	BC	mUC	BC	NSCLC	TNBC	TNBC	TNBC	NSCLC	OC	OC	OC	OC	OC	NSCLC	TNBC	OC	CC	CC
Target	HER2	HER2	HER2	HER2	HER2	HER2	HER2	HER2	HER2	HER2	HER2	HER2	HER2	HER2	HER2	TROP2	TROP2	TROP2	TROP2	HER3	NaPi2b	FRα	FRα	FRα	FRα	PTK7	PTK7	PTK7	TF	TF
High expression ORR (%) (# of patients) [criteria]	**34%** (25/74) [IHC 3+]	**41%** (33/80) [IHC 3+]	**20%** (4/20) [IHC 3+]	**71%** (48/68) [IHC 3+ or ISH+]	**63%** (97/154) [IHC 3+]	NA	NA	**50%** (5/10) [IHC 3+]	**41%** (52/126) [IHC 3+]	**20%** (2/10) [IHC 3+]	**58%** (23/40) [IHC 3+]	**53%** (12/22) [IHC 3+ or 2+]	**43%** (9/21) [IHC 3+]	**60%** (12/20) [IHC 3+]	**33%** (16/48) [IHC 3+]	**11%** (2/19) [IHC 3+]	**44%** (37/85) [H-score >200]	**23%** (33/142) [H-score ≥100]	**55%** (16/29) [H-score ≥200]	**50%** (7/14) [H-score ≥200]	**35%** (13/37) [TPS ≥75]	**44%** (7/16) [TPS >75]	**40%** (8/20) [TPS >75]	**27%** (6/22) [PS2+ ≥75]	**29%** (34/116) [PS2+ ≥75]	**50%** (3/6) [H-score >190]	**33%** (2/6) [H-score >210]	**44%** (4/9) [H-score >120]	**21%** (5/24) [H-score ≥120]	**29%** (11/38) [H-score ≥120]
Medium expression ORR (%) (# of patients) [criteria]	**5%** (1/21) [IHC 2+, 1+, or 0]	**20%** (3/15) [IHC 2+, 1+, or 0]	**0%** (0/29) [IHC 2+]	**38%** (27/72) [IHC 2+ or 1+]	**46%** (13/28) [IHC 2+ and ISH+]	**39%** (10/26) [IHC 2+]	**57%** (90/159) [IHC 2+]	**73%** (8/11) [IHC 2+ or 1+]	**33%** (7/21) [IHC 2+]	**26%** (10/39) [IHC 2+]	**8%** (1/13) [IHC 2+ and ISH+]		**43%** (15/35) [IHC 2+]	**40%** (8/20) [IHC 2+]	**40%** (6/15) [IHC 2+ or 1+ and HR-] *and* **28%** (9/32) [IHC 2+ or 1+ and HR+]	**40%** (2/5) [IHC 2+]	**38%** (15/39) [H-score 100-200]		**23%** (6/26) [H-score <200]	**50%** (7/14) [H-score 100-199]		**33%** (1/3) [TPS 50-75]	**33%** (4/12) [TPS 25-75]	**29%** (4/14) [PS2+ 50-75]	**28%** (29/103) [PS2+ 50-75]	**0%** (0/7) [H-score 120-190]	**14%** (1/7) [H-score 110-210]	**27%** (3/11) [H-score 50-120]		
Low expression ORR (%) (# of patients) [criteria]			NA		NA	**36%** (10/28) [IHC 1+]	**49%** (105/214) [IHC 1+]		**18%** (4/22) [IHC 1+]	NA	**0%** (0/18) [IHC 1+]	**70%** (7/10) [IHC 1+]	**31%** (4/13) [IHC 1+]	**25%** (2/8) [IHC 1+ or 0]		**0%** (0/1) [IHC 1+]	**22%** (6/27) [H-score <100]	**18%** (11/62) [H-score 10-100]		**14%** (1/7) [H-score <100]	**9%** (2/22) [TPS <75]	**33%** (2/6) [TPS 25-50]	**11%** (1/9) [TPS ≤25]	**25%** (2/8) [PS2+ 25-50]	**16%** (18/114) [PS2+ ≤50 and TPS>50]	**17%** (1/6) [H-score <120]	**0%** (0/5) [H-score <110]	**20%** (2/11) [H-score <50]	**30%** (6/20) [H-score <120]	**24%** (9/38) [H-score <120]
No expression ORR (%) (# of patients) [criteria]			NA	**30%*** (11/37) [IHC 0]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**0%** (0/1) [IHC 0]		**24%** (8/34) [H-score ≤10]				**13%** (1/8) [TPS ≤25]		NA	NA					

Extended Table 1. Overall response rates for different approved ADCs in patients with different target expression levels.

		AUC (%) (Payload AUC/Total mAb AUC*100)			Cmax (%) (Payload Cmax/Total mAb Cmax*100)		
		Humans	Monkeys	Rats (*Rabbits)	Humans	Monkeys	Rats (*Rabbits)
Adcetris	**MMAE**	4.6%	0.04%	0.1%	2.8%	0.03%	0.04%
Aidexi	**MMAE**	9.5%	0.10%		2.3%	0.03%	
Tivdak	**MMAE**	4.8%	0.08%		3.0%	0.03%	
Padcev	**MMAE**	13%	0.05%	0.13%	3.2%	0.02%	0.05%
Polivy	**MMAE**	5.8%	0.015%	0.014%	3.2%	0.01%	
Enhertu	**DXd**	1.3%	0.06%	0.04%	1.8%	0.1%	0.06%
Kadcyla	**DM1**	1.3% (Chinese) NA (Western) 0.21% (Japanese)	0.12%	0.21%	3.5% (Chinese) 1.3% (Western) 0.9% (Japanese)	1.1%	1.1%
Elahere	**DM4**	0.5%	0.06%	0.02%*	0.6%	0.07%	0.12%*
Elahere	**S-Me-DM4**	1.7%	BLQ	0.0016%*	1.0%	NA	0.01%*
Trodelvy	**SN-38**	2.1% (27% of total ADC)	3.9%		16%	9%	
Trodelvy	**SN-38-G**	0.6% (7% of total ADC)	NA		2.3%	NA	
Blenrep	**Cys-MC-MMAF**	0.3%	0.3%	0.4%	0.3%	0.4%	0.3%
Zynlonta	**SG3199**	0.02%			0.4%	0.2%	

Extended Table 2. Payload AUC and C_{max} expressed as percentage of total antibody AUC and C_{max} in different species for approved ADCs.



Extended Figure 4. Comparisons of adverse events (lighter shade, G<3; darker shade, G≥3) of ADCs with identical antibody paratopes and payloads, but different linker technologies.