Novel Antibody-Drug Conjugates

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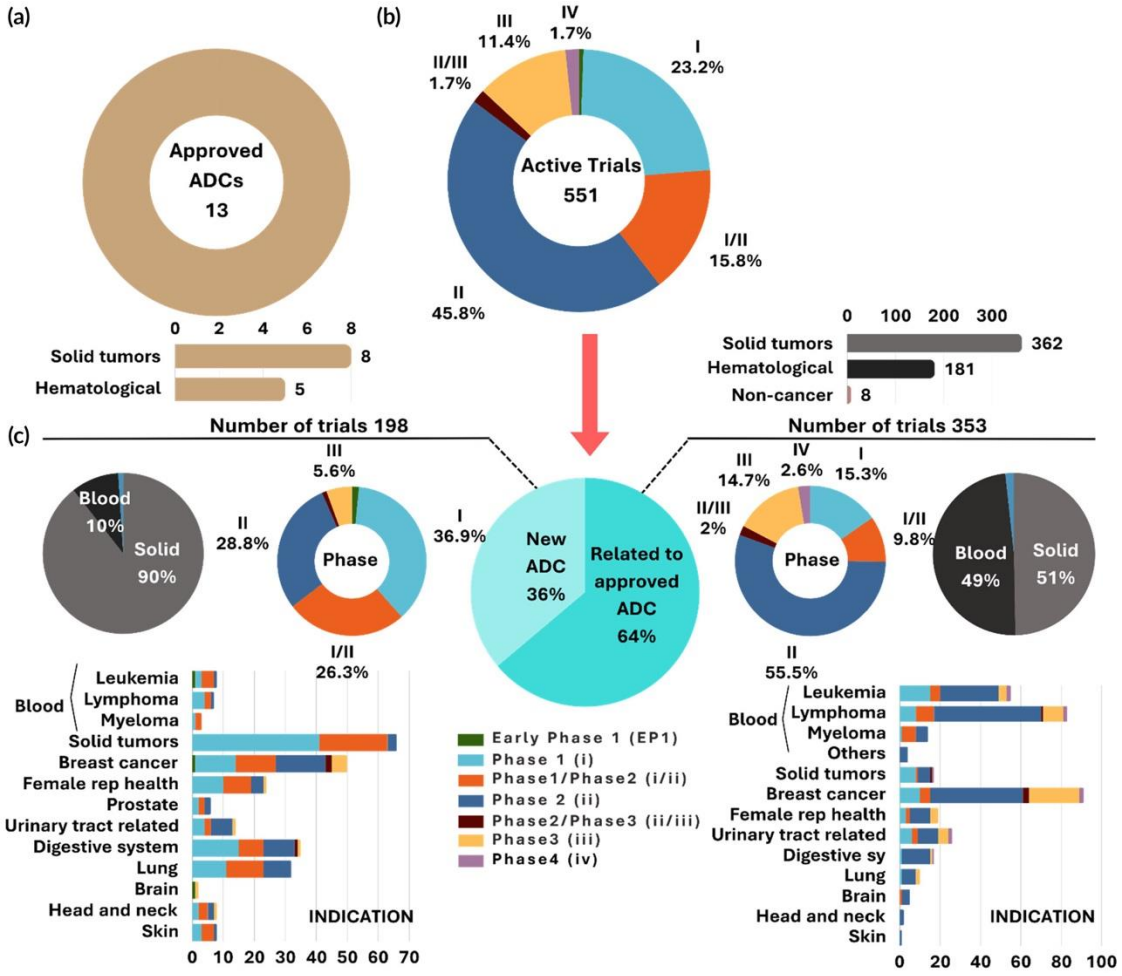
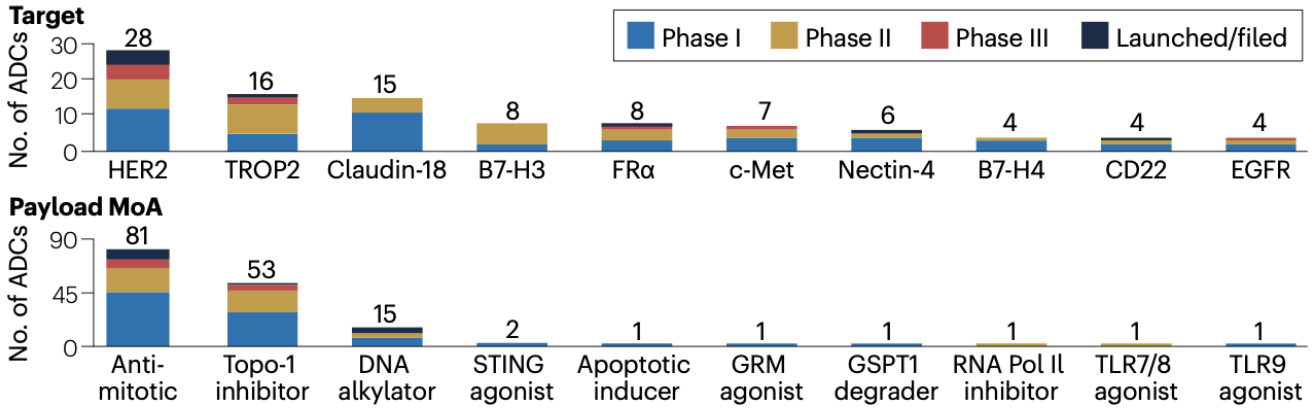
The Antibody Drug Conjugate Revolution





Flynn *et al. Nature Reviews Drug Disc* 2023
Tarantino *et al. Nature Reviews Clin Oncol* 2023

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ADCs Approved for Solid Tumor Indications

ADC	Target	Linker	Payload	Average DAR	Tumor Types	First Approval Date
Enfortumab vedotin	Nectin-4	mc–VC–PABC	MMAE	3.8	**Urothelial Cancer**	December 2019
Trastuzumab deruxtecan	HER2	tetrapeptide	DXD	7-8	Breast cancer, GC, NSCLC, **Tumor agnostic**	December 2019
Disitamab Vedotin	HER2	mc–VC–PABC	MMAE	4	**Urothelial Cancer**, GC	June 2021 (China)
Sacituzumab govitecan	TROP2	CL2A	SN-38	7.6	Breast cancer (mTNBC)	April 2020
Trastuzumab emtansine	HER2	SMCC	DM1	3.5	Breast cancer	February 2013
Tisotumab vedotin	TF	mc–VC–PABC	MMAE	4	Cervical cancer	September 2021
Mirvetuximab soravtansine	FRα	Sulfo-SPDB	DM4	3.3-5	Ovarian cancer	November 2022

Liu et al., Molecular Cancer 23: 62, 2024

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ADCs In Urothelial Cancer

- Two ADCs with current FDA approval in mUC
  - **Enfortumab vedotin** (unselected population, multiple settings) → **Targets Nectin-4**
  - **Trastuzumab deruxtecan** (HER2 IHC 3+, treatment-refractory) → **Targets HER2**

- Recently withdrawn FDA approval: Sacituzumab govitecan → Targets Trop2

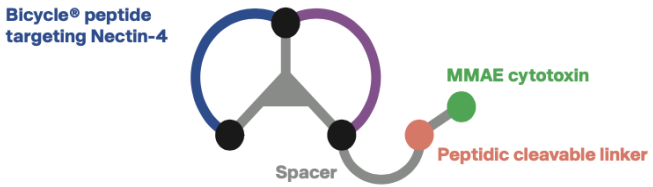
- Other targets with ongoing and future trials
  - EGFR/HER3 dual targeting ADC
  - CDH6
  - B7H3
  - ROR1
  - HER3

Nectin-4

Enfortumab Vedotin Data

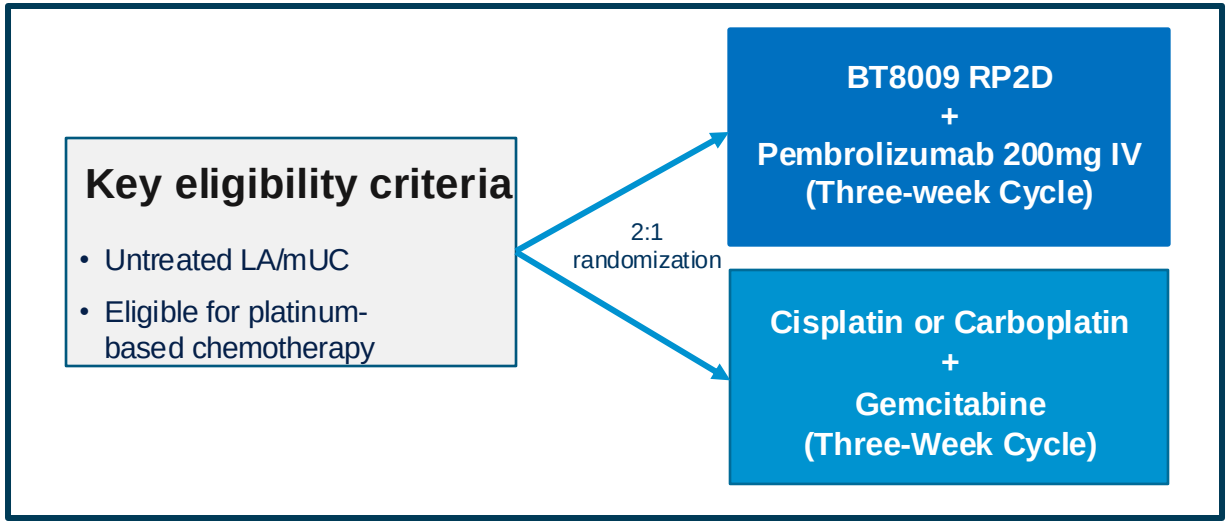
EV monotherapy (Treatment-refractory): ORR 41%; mOS 12.9 months
EV / Pembrolizumab (Front-line population): ORR 68%; mOS 33.8 months

BT8009 (Zelenectide pevedotin): Small molecule targeting Nectin-4 with MMAE payload



Duravelo-1: Urothelial Cancer Patients (Post-Platinum/ICI, no EV) Treated with BT8009 Monotherapy (N=38)	
ORR	45%
Disease Control Rate	61%
Median Duration of Response	11.1 months
Peripheral Neuropathy Rate	36%

Phase II/III: Duravelo-2 Trial of Zelenectide Pevedotin (BT 8009: Nectin4-Targeting Peptide with MMAE Payload) + Pembrolizumab



Torras *et al. ESMO* 2024, Powles *et al.* ASCO GU 2025

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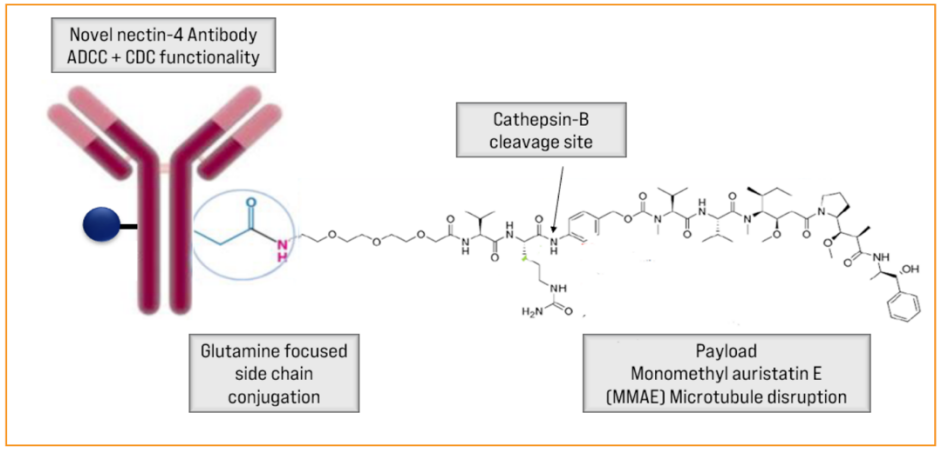
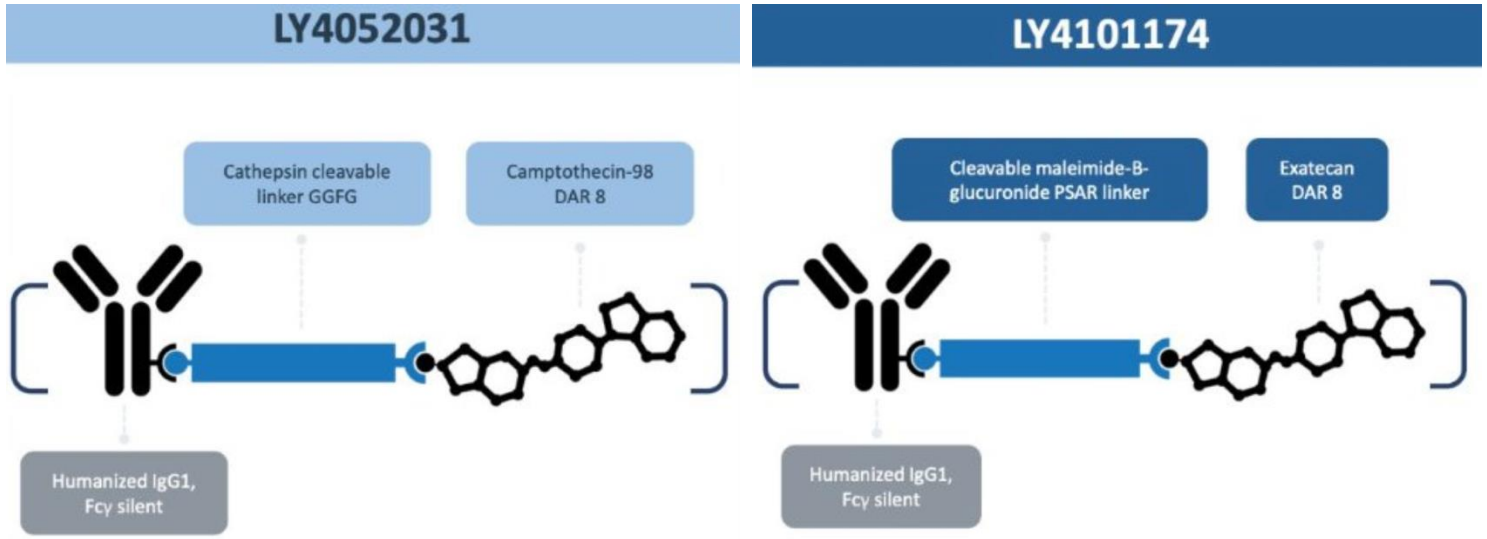
Novel Nectin-4 Targeting ADCs

CRB-701 Next-gen Nectin-4 Antibody-Drug conjugate



Nectin-4 ADCs With Non-MMAE Payloads (Topo1)



Sun et al., AACR-NCI-EORTC 2023 ; Sagar *et al.* AACR 2024; Rosenberg *et al*., AACR 2024

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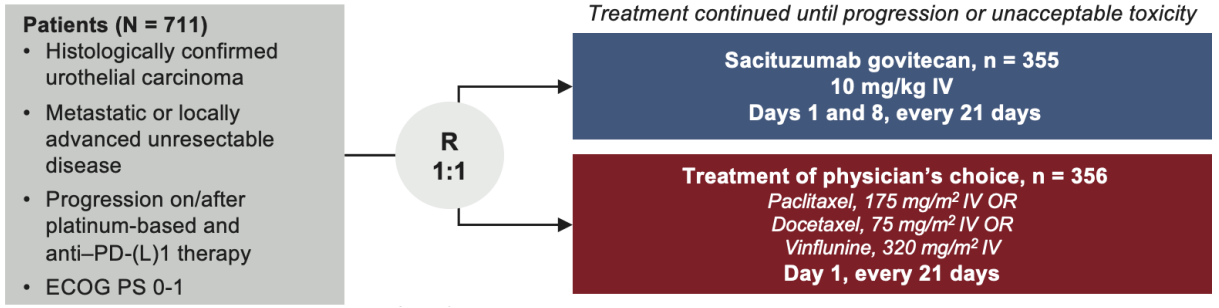
Trop-2: Sacituzumab govitecan

Phase 2 Trophy-U01: Non-randomized cohort of mUC patients post platinum/ICI treated with Sacituzumab govitecan

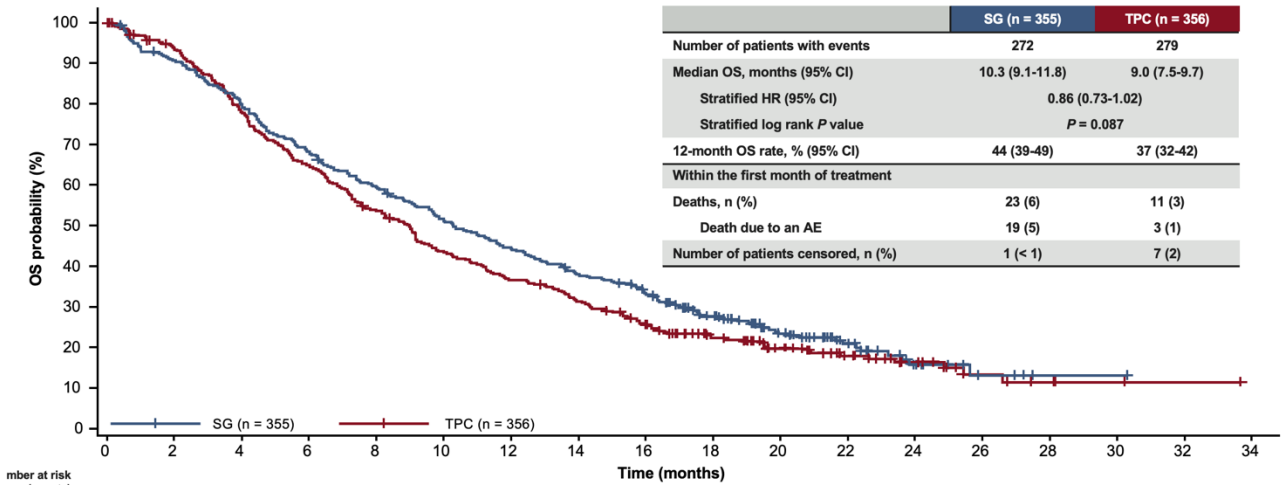
Sacituzumab Govitecan (N=113)	TROPHY-U01 Cohort 1 (post-platinum/ICI)
ORR	28%
Median PFS, months	5.4
Median OS, months	10.9

Accelerated approval: April 2021

TROPiCS-04: Phase 3 Study of Sacituzumab govitecan vs Chemotherapy



Primary End Point: Overall Survival



	SG (n = 355)	TPC (n = 356)
Number of patients with events	272	279
Median OS, months (95% CI)	10.3 (9.1-11.8)	9.0 (7.5-9.7)
Stratified HR (95% CI)	0.86 (0.73-1.02)	
Stratified log rank *P* value	*P* = 0.087	
12-month OS rate, % (95% CI)	44 (39-49)	37 (32-42)
Within the first month of treatment		
Deaths, n (%)	23 (6)	11 (3)
Death due to an AE	19 (5)	3 (1)
Number of patients censored, n (%)	1 (< 1)	7 (2)

Negative Trial: OS Primary Endpoint Not Met

SG's FDA Accelerated Approval Withdrawn Voluntarily

Tagawa *at al. JCO* 2021, Grivas *et al.* ESMO Asia 2024

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Trop-2: Datopotamab deruxtecan (Dato-DXd)

Phase 1: TROPION PanTumor01 Study

Key eligibility criteria
- Unresectable locally advanced/metastatic (stage III or IV) urothelial carcinoma (included renal pelvis, ureter, urinary bladder, and urethra)
- Previous treatment with ≥1 line of therapy including an immune checkpoint inhibitor
- ECOG PS 0–1
- Unselected for TROP2 expression
- No prior treatment with DXd-ADCs or TROP2-directed therapies

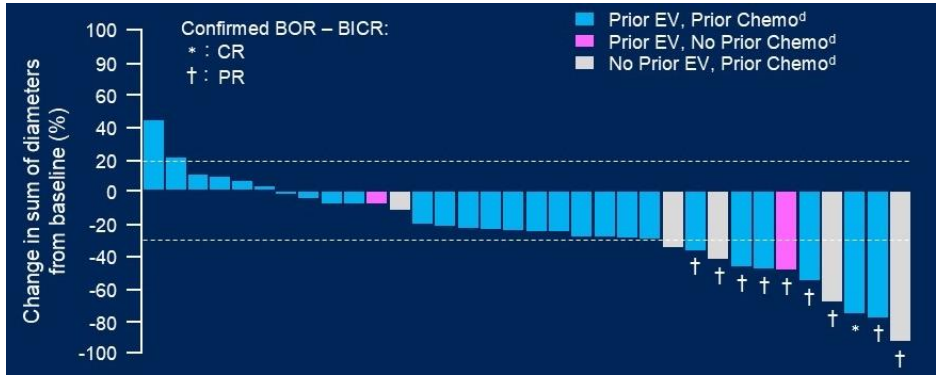
→ **Dato-DXd** 6 mg/kg Q3W **(N=40)**

Primary endpoints
- Safety and tolerability

Secondary endpoints (by BICR[a])
- ORR
- DOR
- DCR
- PFS

Characteristic, n (%)	Dato-DXd (N=40)
Age, years, median (range)	66.5 (44–83)
Sex, male	31 (78)
ECOG PS	
0	19 (48)
1	21 (53)
Stage	
III	2 (5)
IV	33 (83)
History of brain metastases[a]	2 (5)
Time from diagnosis to study treatment, months, median (range)	24 (3–342)

Characteristic, n (%)	Dato-DXd (N=40)
Number of prior lines of therapy (locally advanced/metastatic)	
1	5 (13)
2	11 (28)
≥3	24 (60)
Median (range)	3 (1–7)
Prior systemic treatment (any setting)	
Immunotherapy	40 (100)
Platinum-based chemotherapy	36 (90)
Taxane chemotherapy	7 (18)
Enfortumab vedotin[b]	33 (83)



Response by BICR[a]	Dato-DXd (N=40)
ORR[b], n (%) [95% CI]	**10 (25.0)** [12.7–41.2]
DCR[c], n (%) [95% CI]	**31 (77.5)** [61.5–89.2]
BOR, n (%)	
CR	1 (2.5)
PR	9 (22.5)
SD	20 (50.0)
Non-CR/non-PD	1 (2.5)
PD	5 (12.5)
NE	4 (10.0)
DOR, median (95% CI)**, months**	NE (2.6–NE)
6-month DOR rate, % (95% CI)	76.2 (33.2–93.5)

ORR by investigator was 30.0% (n=12); all were PR

Upcoming Phase 3 Trial in mUC:
Datopotamab-Deruxtecan in patients with mUC after prior Enfortumab Vedotin plus Pembrolizumab

Meric-Bernstam *at al.* ASCO GU 2025

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Trop-2: Sacituzumab Tirumotecan (Sac-TMT)

Phase 1/2 MK-2870-001 Study: mUC Cohort

Key Eligibility Criteria for Cohort 9

- Aged ≥18 y
- Histologically or cytologically confirmed locally advanced or metastatic UC (mixed histology eligible if urothelial component >50% and plasmacytoid component <10%)
- Progressed on/after prior first-line platinum-based therapy and received anti–PD-(L)1 inhibitor therapy[a]
- Measurable lesion by CT or MRI
- ECOG PS 0 or 1

→ Sac-TMT 5 mg/kg IV Q2W until disease progression, unacceptable toxicity, or patient withdrawal

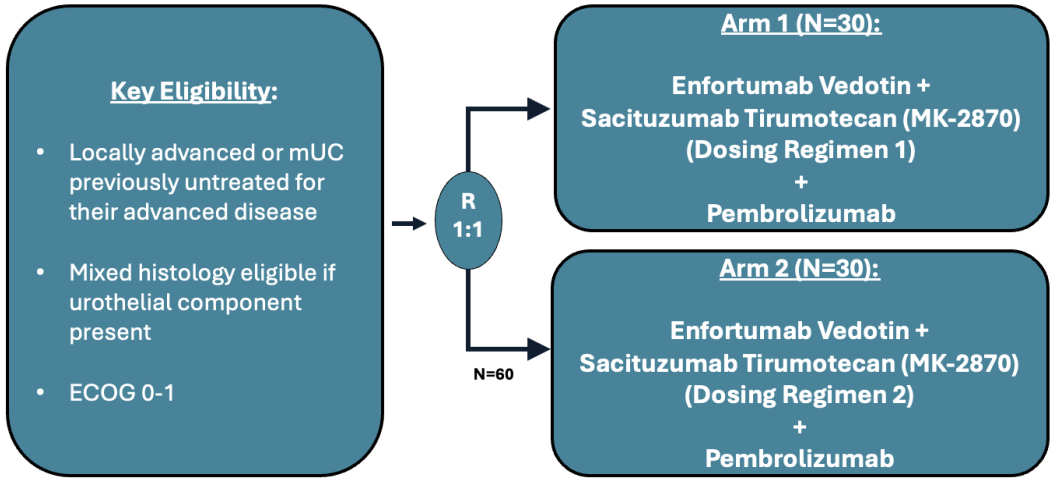
Primary endpoint
- ORR per RECIST version 1.1 by investigator

Secondary endpoints
- DOR per RECIST version 1.1 by investigator
- PFS per RECIST version 1.1 by investigator
- OS
- Safety

Outcome	UC 2L (n = 11)	UC 3L+ (n = 38)	Total (N = 49)
Confirmed ORR,[a] % (95% CI)	45.5 (16.7–76.6)	26.3 (13.4–43.1)	30.6 (18.3–45.4)
Best confirmed overall response, n (%)			
CR	1 (9.1)	0	1 (2.0)
PR	4 (36.4)	10 (26.3)	14 (28.6)
SD	3 (27.3)	17 (44.7)	20 (40.8)
PD	2 (18.2)	10 (26.3)	12 (24.5)
NE	1 (9.1)	1 (2.6)	2 (4.1)
Confirmed + unconfirmed ORR,[a] % (95% CI)	45.5 (16.7–76.6)	28.9 (15.4–45.9)	32.7 (19.9–47.5)
Median DOR[b] (range), mo	NE (3.5+–13.9+)	NE (2.1–16.5+)	NE (2.1–16.5+)

Current / Upcoming Trials in mUC

Keymaker U04C: Phase 1/2 Trial of Sac-TMT plus Enfortumab Vedotin with and without Pembrolizumab in treatment-naïve patients



Pending Phase 3 trial of Sac-TMT in treatment-refractory patients with mUC

Ye *at al.* ASCO GU 2025

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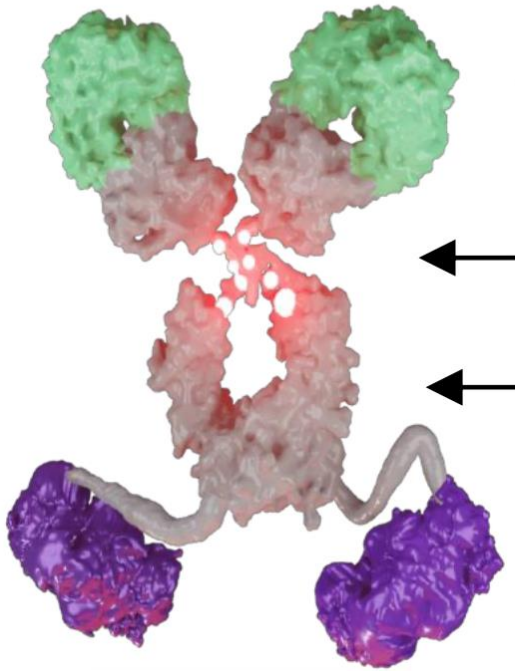
Izalontamab Brengitecan: HER3/EGFR Dual Targeting ADC

BL-B01D1 (EGFRxHER3 ADC)



αEGFR
Human EGFR
Affinity: High

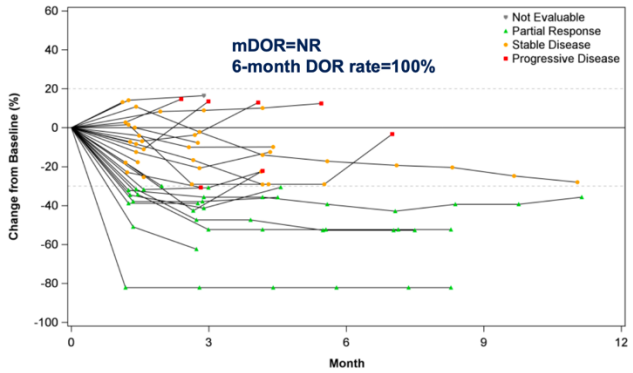
DAR = 8
Cat B cleavable linker
Ed-04 (TOPI inhibitor)

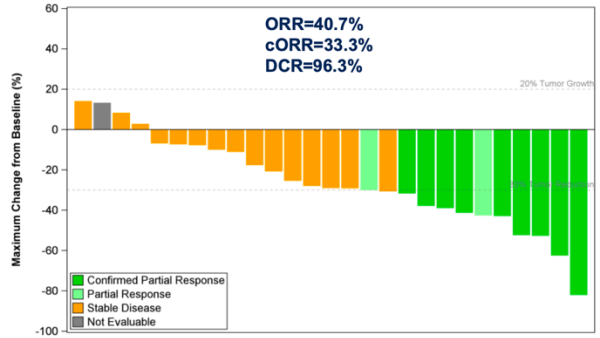
wt Fc IgG1

αHER3
Human HER3
Affinity: Low

Izalontamab Brengitecan
First-in-class ADC: EGFRxHER3 bispecific antibody bound to a Topoisomerase I inhibitor payload via a cleavable linker

Patients at 2.2 mg/kg D1D8 Q3W (N=27)





	2.2 mg/kg D1D8Q3W	
	Total (N = 27)[1]	1 Prior line of chemo (PBC or ADC) (N=12)[2]
Prior line of therapy, median (range)	2 (1-7)	1 (1-2)
Best Overall Response (BOR), n		
PR	11	9
Confirmed PR	9	9
SD	15	3
PD	0	0
NE	1	0
ORR, % (95%CI)	40.7 (22.4, 61.2)	75.0 (42.8, 94.5)
cORR, % (95%CI)	33.3 (16.5, 54.0)	75.0 (42.8, 94.5)
DCR, % (95%CI)	96.3 (81.0, 99.9)	100 (73.5, 100.0)
Median DOR (months) (95% CI)	NR (NR, NR)	NR (NR, NR)
6-month DOR rate, %, (95% CI)	100 (100.0, 100.0)	100 (100.0, 100.0)
Median PFS (months) (95% CI)	NR (4.2, NR)	NR (NR, NR)
6-month PFS rate, %, (95% CI)	62.4 (32.2, 82.2)	100 (100.0, 100.0)

[1] Among of the 27 patients, 24 patients had received anti-PD-(L)1, 24 patients had received PBC, and 14 patients had received 1-2 prior lines of ADCs.
[2] Among of the 12 patients, 11 patients had received anti-PD-(L)1, 9 patients had received PBC, 2 patients had received ADCs, and 1 patient had received anti-PD-(L)1 + gemcitabine.
ORR was calculated based on response evaluable population defined as at least 1 post-baseline scan; CI: confidence interval; cORR: confirmed objective response rate; NE: not evaluable; NR: not reached; PD: progressive disease; PR: partial response; SD: stable disease.

Pending Phase 3 trial: In patients with mUC post EV/P

Bian *et al. ESMO* 2024

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Combining ADCs and Immune Checkpoint Inhibitors in mUC

ADC	Enfortumab Vedotin	Sacituzumab govitecan	Trastuzumab deruxtecan	Disitamab vedotin	BT8009	BL-B01D1
Target	NECTIN4	TROP2	HER2	HER2	NECTIN4	EGFR/HER3
Biomarker Population	All-comers	All-comers	HER2-high (IHC 2+/3+)	HER2-expressing (IHC 1+/2+/3+)	All-comers	All-comers
Payload	MMAE	Top1 Inhibitor	Top1 Inhibitor	MMAE	MMAE	Top1 Inhibitor
ORR as Monotherapy	41%	23-28%	39%	39% IHC 1+ 51% IHC 2+/3+	45%	41%
ORR in Combination with ICI	68%	41%	37%	75%	?	?

Powles *et al. NEJM* 2024, Grivas *et al. JCO* 2024, Hamilton *et al. CCR* 2024, Galsky *et al. ESMO* 2024

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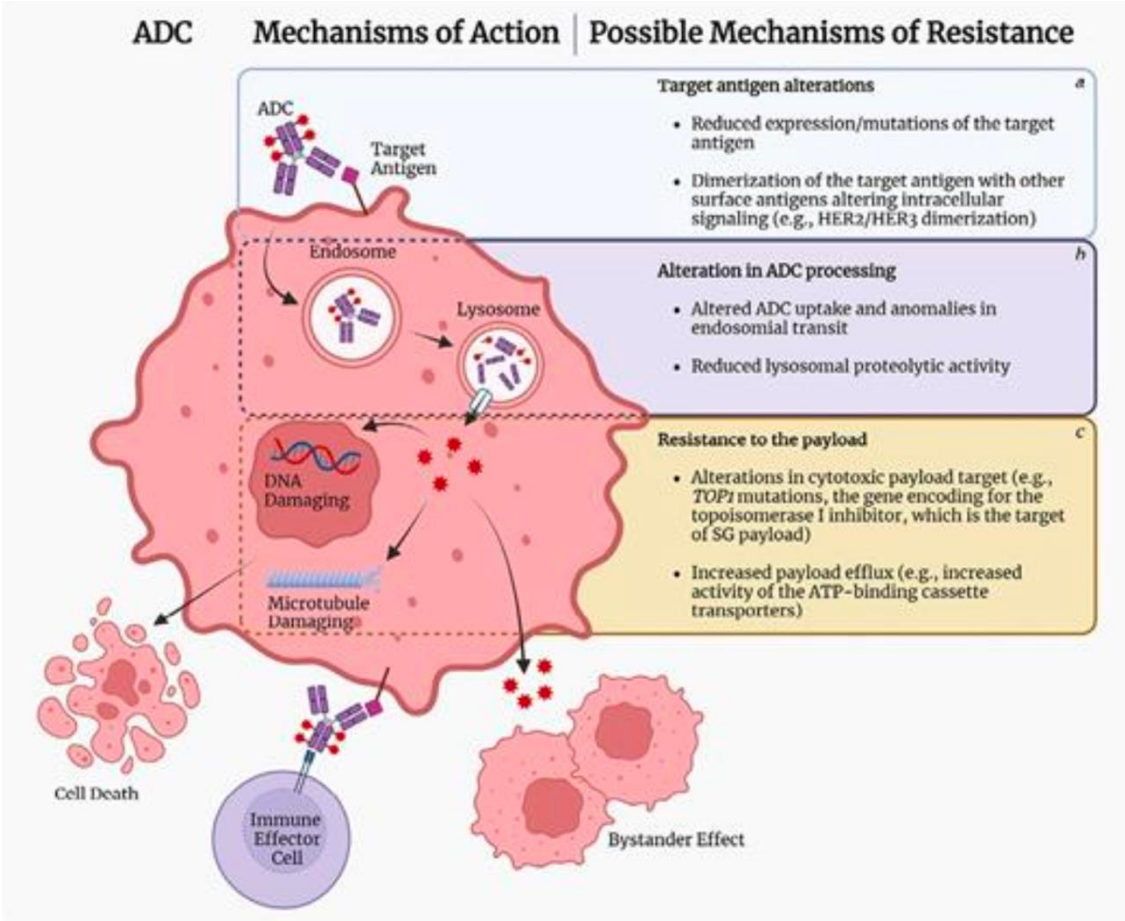
Where Will Novel ADCs Fit Into the mUC Treatment Landscape?

- Many mUC patients will receive EV/P as initial treatment
  - In first-line metastatic or perioperative setting
- Most ADCs being developed for la/mUC will need to show efficacy following EV/P or in combination with EV/P (or EV/ICI)
- Potential role for other ADC-based regimens as initial treatment, based on biomarker selection or toxicity considerations
- Optimal treatment sequencing relies on improved understanding of ADC resistance mechanisms



Ascione *et al.*, *Oncologist* 2023

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Summary

- ADCs are taking center stage across the oncology landscape and in mUC
- In mUC, many novel ADCs in development for existing targets
  - Nectin-4, Trop2, HER2
- Novel targets for treatment are also being explored
  - Next generation ADCs with improved linker technology, different payloads
- Future directions will focus on novel combinations of these drugs, earlier treatment settings, improved understanding of primary and acquired resistance

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