

LIVE PODCAST

Will New Antibody Drug Conjugates (ADCs) Cure Bladder Cancer?



MODERATOR

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Princess Margaret
Cancer Center

ADC in platinum advanced bladder cancer	Enfortumab Vedotin	Sacituzumab Govitecan (n=113)	Disitamab Vedotin (n=109)	T-DXD (n=16)	BT8009 (n=45)	BL-B01D1 (n=27)
Target	NECTIN-4	TROP-2	HER-2	HER-2	NECTIN-4	HER3/EGFR
Payload	MMAE	TOPO-1	MMAE	TOPO-1	MMAE	TOPO-1
Biomarker selection	None	None	1-3+	3+	None	None
Randomised phase III studies	301,302,303,304 VOLGA	TROPICS-4	1st line R3 (China and Global)	None	1st line R3 Global	Planned (China)
Grade 3+ TRAEs	51%	65%	45%	45-55%	22%	52%
Response rates in platinum-refractory disease	 41%	 28%	 50%	 56%	 45%	 41%
Response rates in combination with PD-1 therapy	 68% (420)	 34% (41)	 75% (20)	 36% (26)		

Study EV-103 Dose Escalation/Cohort A (DE/A): 5y Follow-Up of First-Line (1L) Enfortumab Vedotin (EV) + Pembrolizumab (P) in Cisplatin (Cis)-Ineligible Locally Advanced or Metastatic Urothelial Carcinoma (la/mUC)

Jonathan E. Rosenberg¹, Peter H. O' Donnell², Daniel Petrylak³, Thomas W. Flaig⁴, Christopher J. Hoimes⁵,
Shilpa Gupta⁶, Nataliya Mar⁷, Terence W. Friedlander⁸, Scott Tagawa⁹, Mehmet Asim Bilen¹⁰, Jason Brown¹¹,
Rana R. McKay¹², Jaime R. Merchan¹³, Sandy Srinivas¹⁴, Aditya Shetty¹⁵, Blanca Homet Moreno¹⁶, Griffith Davis¹⁷,
Heidi S. Wirtz¹⁷, Yalin Zhu¹⁷, Matthew I. Milowsky¹⁸

Figure 2.
Time to response and DOR in patients achieving confirmed CR or PR by BICR

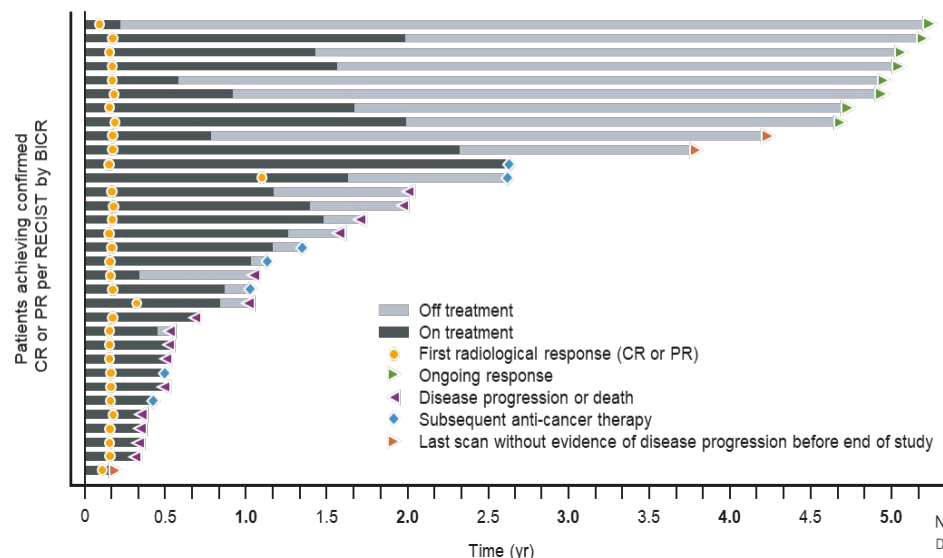
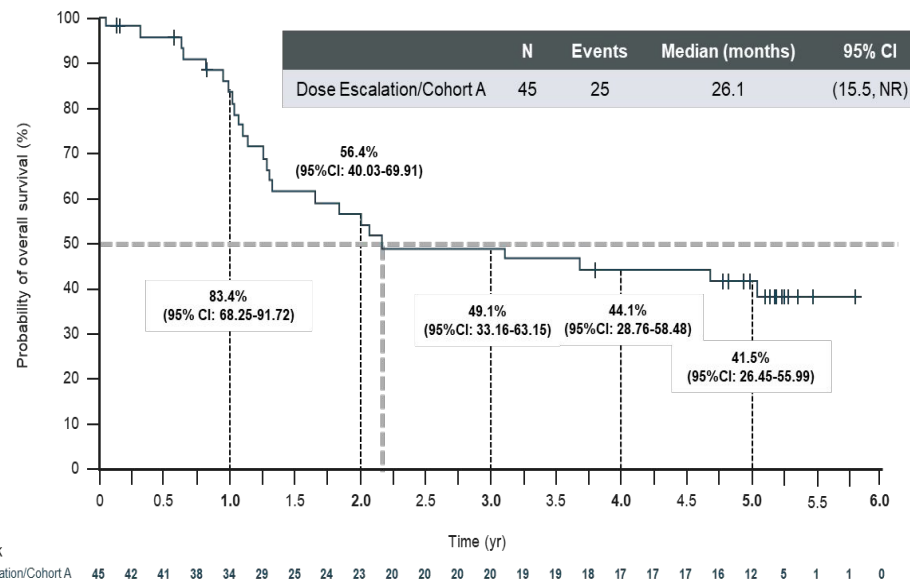
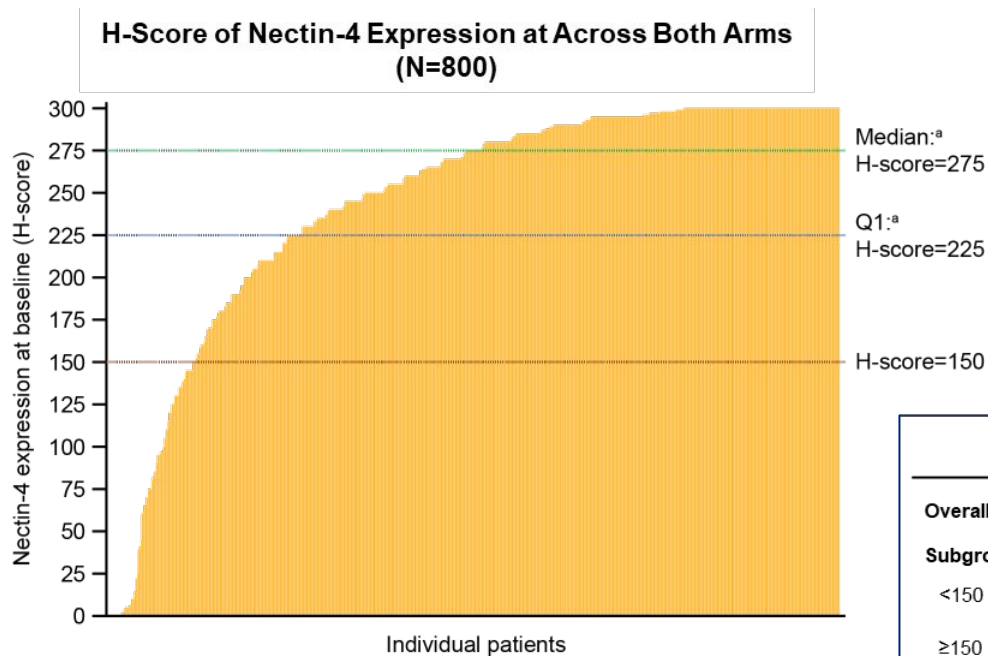


Figure 5. OS



NECTIN-4 as a biomarker for enfortumab vedotin and pembrolizumab vs chemotherapy in the EV302 study.



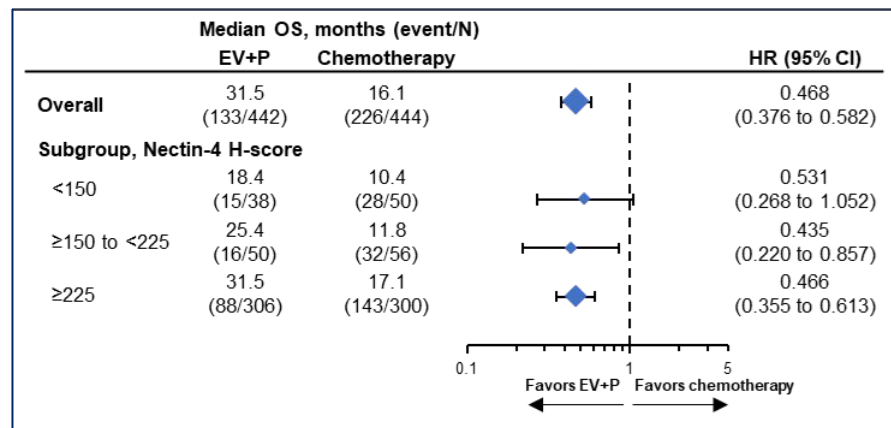
Data cutoff: 8 August 2023.

EV, enfortumab vedotin; IQR, interquartile range; P, pembrolizumab.

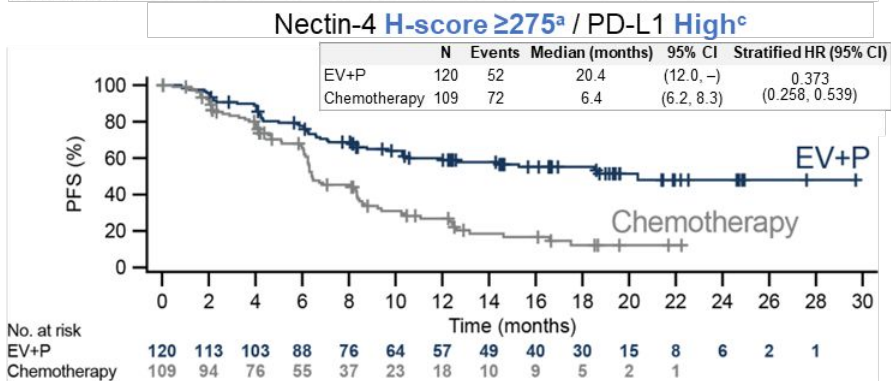
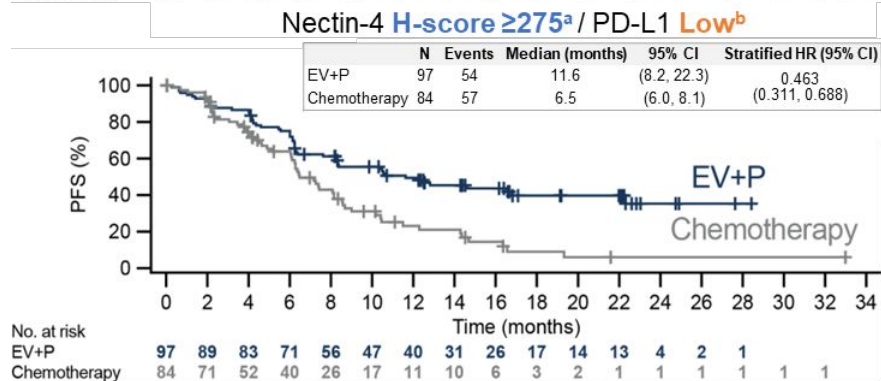
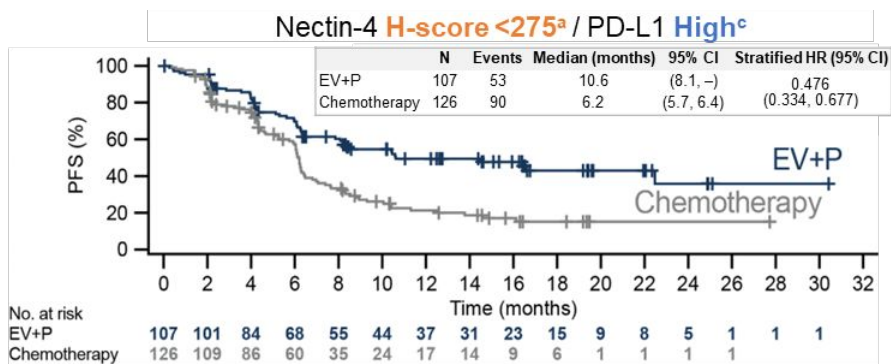
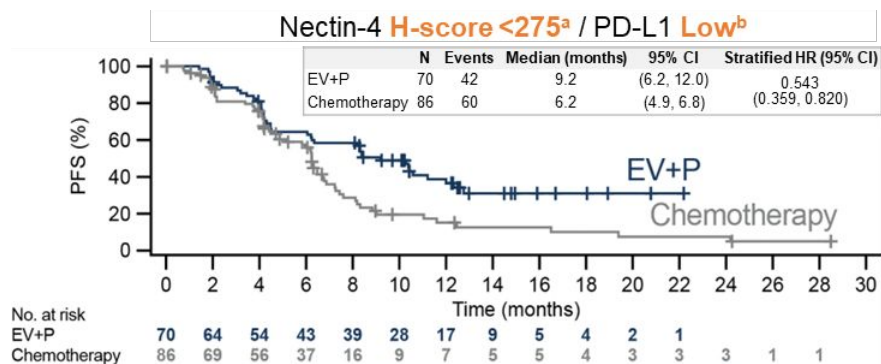
^aIncluding all patients across both arms.

Variable	EV+P (n=394)	Chemotherapy (n=406)
H-score, median (IQR)	280 (230-298)	270 (215-297)
Subgroup, H-score, n (%)		
<150	38 (9.6)	50 (12.3)
≥150 to <225	50 (12.7)	56 (13.8)
≥225	306 (77.7)	300 (73.9)
Patients with H-score 0, n (%)	3 (0.8)	6 (1.5)

OS



Consistent PFS Benefit with EV+P Across Nectin-4 and PD-L1 Subgroups

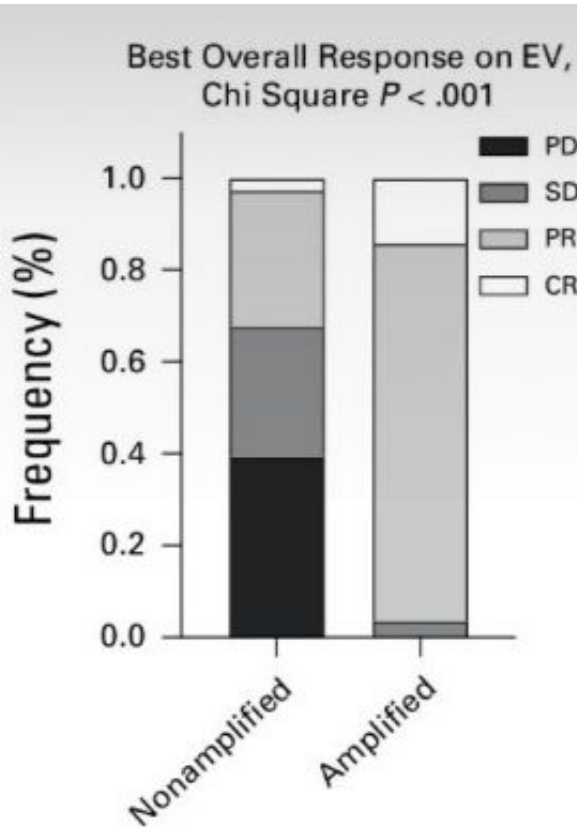
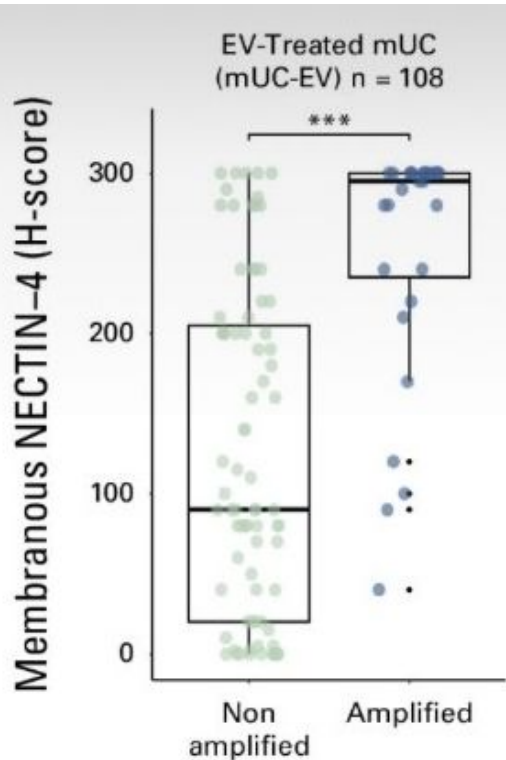


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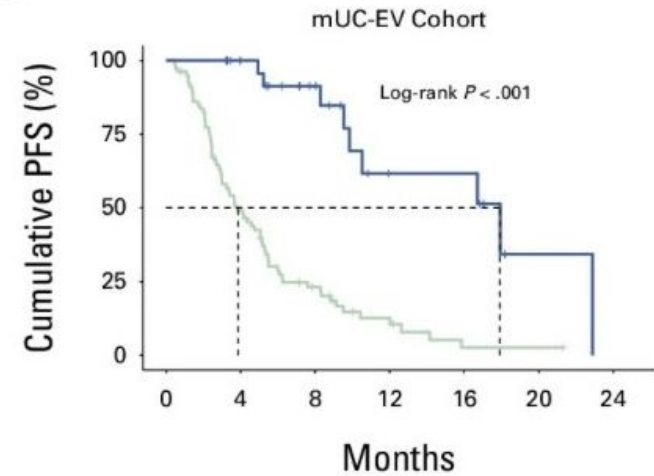
CPS, combined positive score; EV, enfortumab vedotin; P, pembrolizumab; PD-L1, programmed death ligand 1.

^aThe median Nectin-4 H-score was 275 across patients in both arms. ^bCPS <10. ^cCPS ≥10.

NECTIN-4 amplification and response to EV monotherapy



G











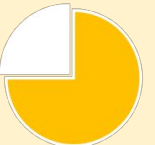


No. at risk:

Nonamplified	80	38	15	6	1	1	0
Amplified	28	23	15	6	6	1	0

Neoadjuvant durvalumab/tremelimumab/enfortumab vedotin resulting in high ctDNA clearance

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Cystectomy	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N
Clinical stage at baseline	T2	>T2	T2	T2	T2	T2	T2	T2	T2	T2	T2	>T2	T2	>T2	T2	T2	>T2
Pathological assessment at RC			pCR				Downstaged			No change		Upstaged			NA	NA	NA
Baseline ctDNA status	+	+	+	+	+	-	-	-	-	+	+	+	+	+	-	-	NS
Pre-RC ctDNA status	-	-	-	-	-	-	NS	-	-	-	-	+	+	+	-	NS	NS

- At baseline, the overall ctDNA-positive rate was 62.5% (10/16 patients) and the overall ctDNA-negative rate was 37.5% (6/16 patients)
- After neoadjuvant treatment, the pre-RC ctDNA-negative rate was 78.6% (11/14 patients)
- A total of **7 out of 10 patients had ctDNA clearance** (baseline ctDNA positive, then pre-RC ctDNA negative)

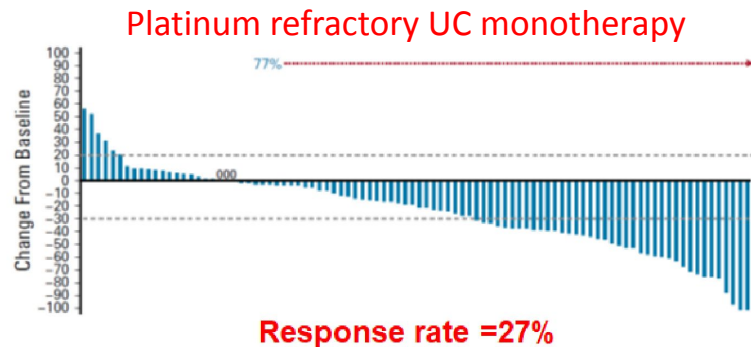
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Sacituzumab Govitecan alone and with PD-1 therapy

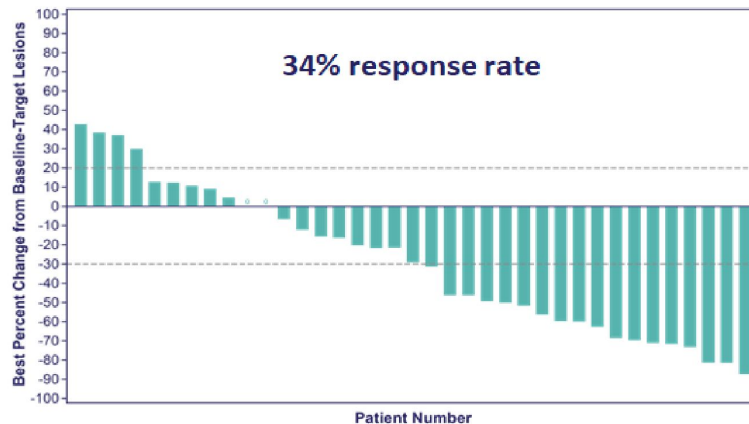
4 cycles of neoadjuvant therapy was associated with responses but also 8% treatment-related deaths

Median follow-up: 7.1 months

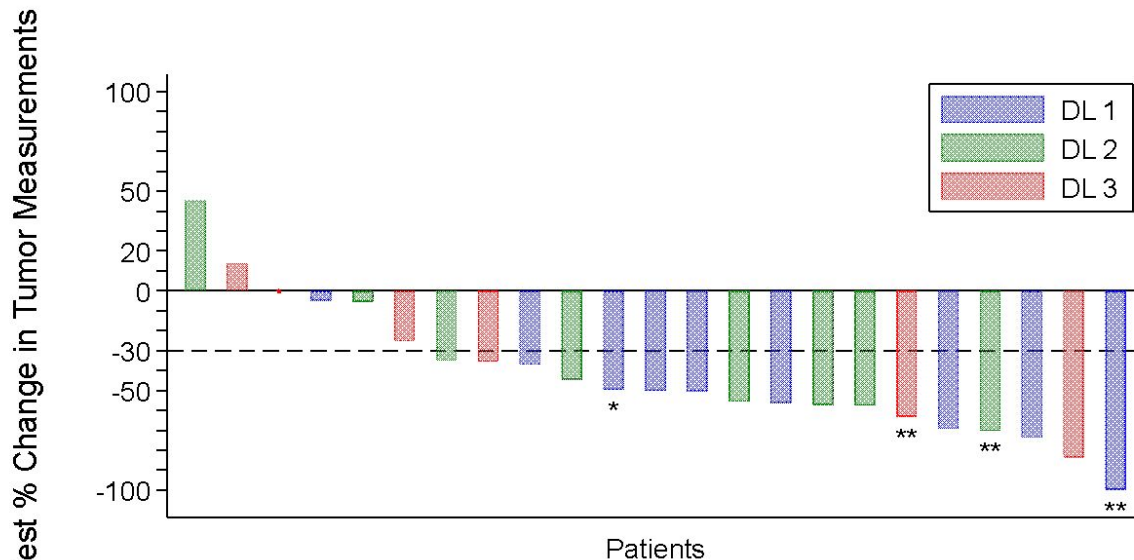
Outcome	N (%)
Total N=11 RC-evaluable patients	
• ypT0N0 (95%CI)	4 (36.4; 14.9–64.8)
• ypT≤1N0 (95%CI)	5 (45.4; 21.2–72.0)
Total N=21 ITT patients	
• ypT0N0-x (95%CI)	10 (47.6; 28.3–67.6)
• ypT≤1N0-x	11 (52.4)
• ypT2Nx ^a	1 (4.7)
• ypT3-4N0 ^b	3 (14.3)
• ypT _{any} N+ ^b	3 (14.3)
Relapse/progression during or post-SG	1 (4.7)



Platinum refractory UC combination with PD1 inhibitor














Enfortumab vedotin with Sacituzumab vedotin in pretreated advanced urothelial cancer









One patient who did not undergo any post-baseline scans was marked as having 0 percentage change.

* One patient experienced progressive disease due to the emergence of a new non-target lesion, despite the reduction in a target lesion.

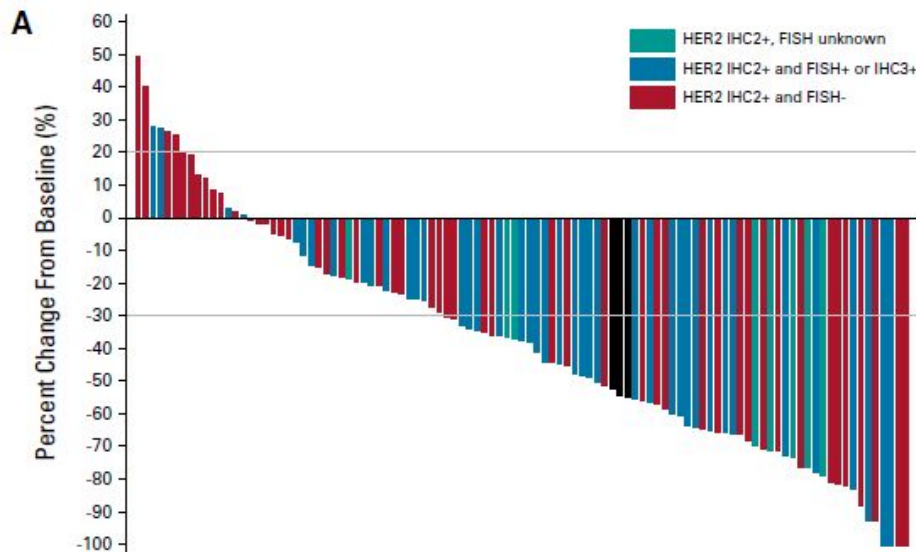
** Among three patients with complete response, two had lymph node lesions and the sum of lesions was not zero for those achieving a complete response.

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⑧ Efficacy and Safety of Disitamab Vedotin in Patients With Human Epidermal Growth Factor Receptor 2–Positive Locally Advanced or Metastatic Urothelial Carcinoma: A Combined Analysis of Two Phase II Clinical Trials

Xinan Sheng, MD¹ ; Lin Wang, MD²; Zhisong He, MD³; Yanxia Shi, MD⁴; Hong Luo, MD⁵; Weiqing Han, MD⁶; Xin Yao, MD⁷; Benkang Shi, MD⁸; Jijian Liu, MD⁹ ; Changlu Hu, MD¹⁰; Ziling Liu, MD¹¹; Hongqian Guo, MD¹² ; Guohua Yu, MD¹³; Zhigang Ji, MD¹⁴; Jianming Ying, MD¹⁵ ; Yun Ling, MD¹⁶; Shiyong Yu, MD¹⁶; Yi Hu, MD¹⁷; Jianming Guo, MD¹⁸; Jianmin Fang, PhD^{19,20} ; Aiping Zhou, MD²; and Jun Guo, MD¹ 

DOI <https://doi.org/10.1200/JCO.22.02912>



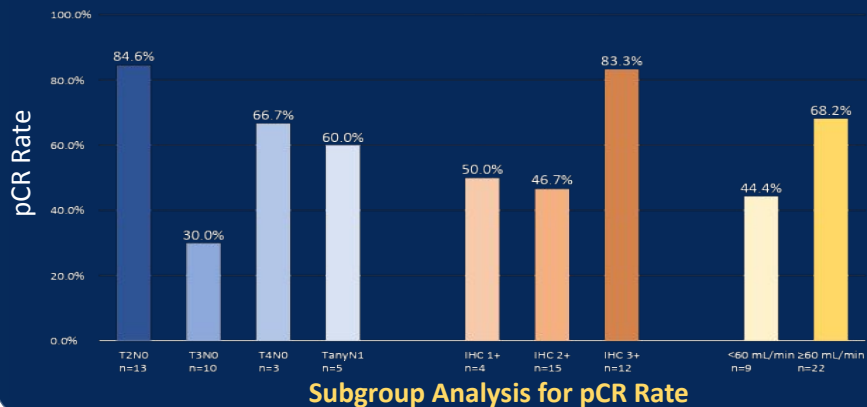
	C005 (N=43)	C009 (N=64)	Pooled (N=107)
HER2-Positive IHC3+ or 2+/FISH+	60%	64%	62.2%
HER2-Low IHC2+/FISH- IHC2+/FISH Unknown	40% 66%	39.4% 50%	39.6% 55.6%

Most frequent TRAE All grades (≥30%)

Any event	100%
Peripheral sensory neuropathy	68%
Leukopenia	51%
AST increase	42%
Neutropenia	42%
Alopecia	40%
Asthenia	39%
ALT increase	36%
Decreased appetite	32%

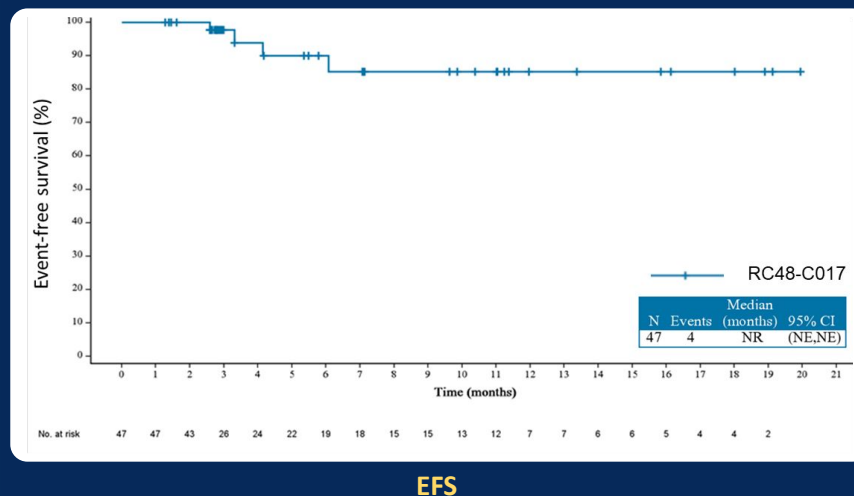
Disitamab Vedotin plus Toripalimab in muscle invasive bladder cancer (MIBC): data on 31/47 patients

Pathologic Response	Evaluable Patients N=31
pCR (ypT0N0), n (%) 95% CI	19 (61.3) 42.2, 78.2
pPR (<ypT2, and N0), n (%) 95% CI	23 (74.2) 55.4, 88.1





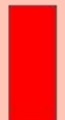
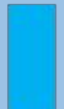







Xinan Sheng, MD

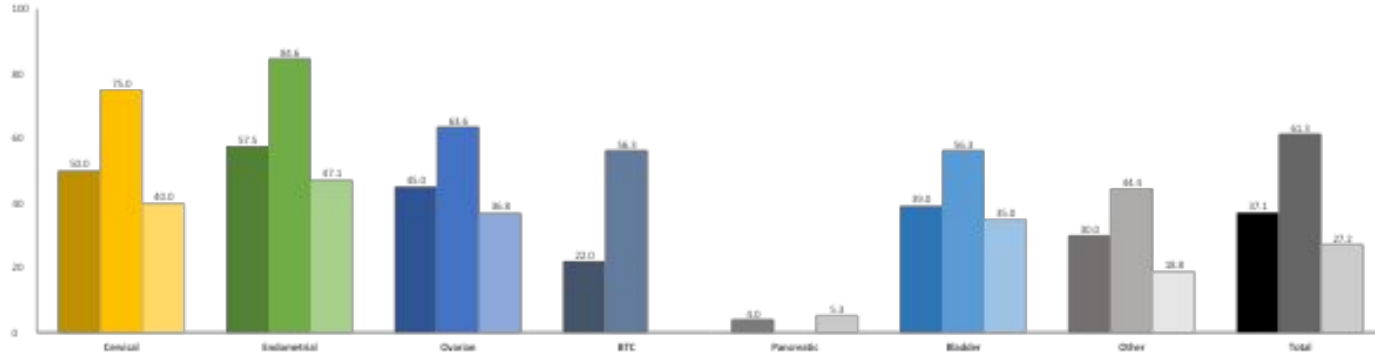
- The median event-free survival (EFS) follow-up was 5.4 months. The median EFS not yet mature and EFS rate at 12 months was 85.0% (95%CI: 64.0%, 94.0%).
- The median DFS and OS not yet mature and will be reported later.














EFS

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A Phase 2 study of T-DXd in patients with HER2-expressing solid tumours in 2L and later patient population

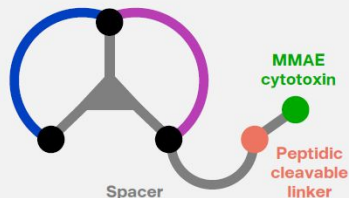


ILD/pneumonitis adjudicated as T-DXd-related						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
All patients (N=267)	6 (2.2)	12 (4.5)	1 (0.4)	0	1 (0.4)	20 (7.5)
Left ventricular dysfunction ^a						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
Ejection fraction decreased						
All patients (N=267)	1 (0.4)	4 (1.5)	1 (0.4)	0	0	7 (2.6) ^b
Cardiac failure						
All patients (N=267)	0	0	1 (0.4)	0	0	1 (1.04)

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BT8009 (zelenectide pevedotin) = peptide drug conjugate

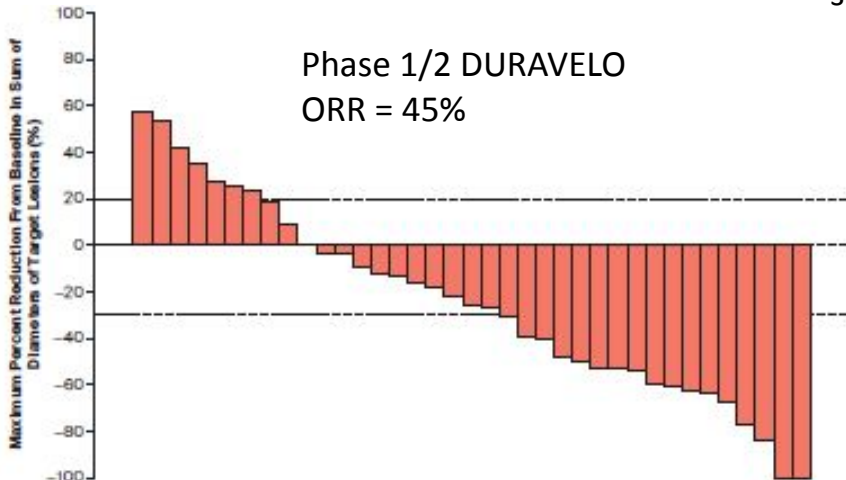
Nectin-4 targeting Bicycle® molecule



Molecular weight ⁵	4.2 kDa
Half-life ¹	<1 hr
Affinity for Nectin-4 (K _D) ¹	2.5 nM

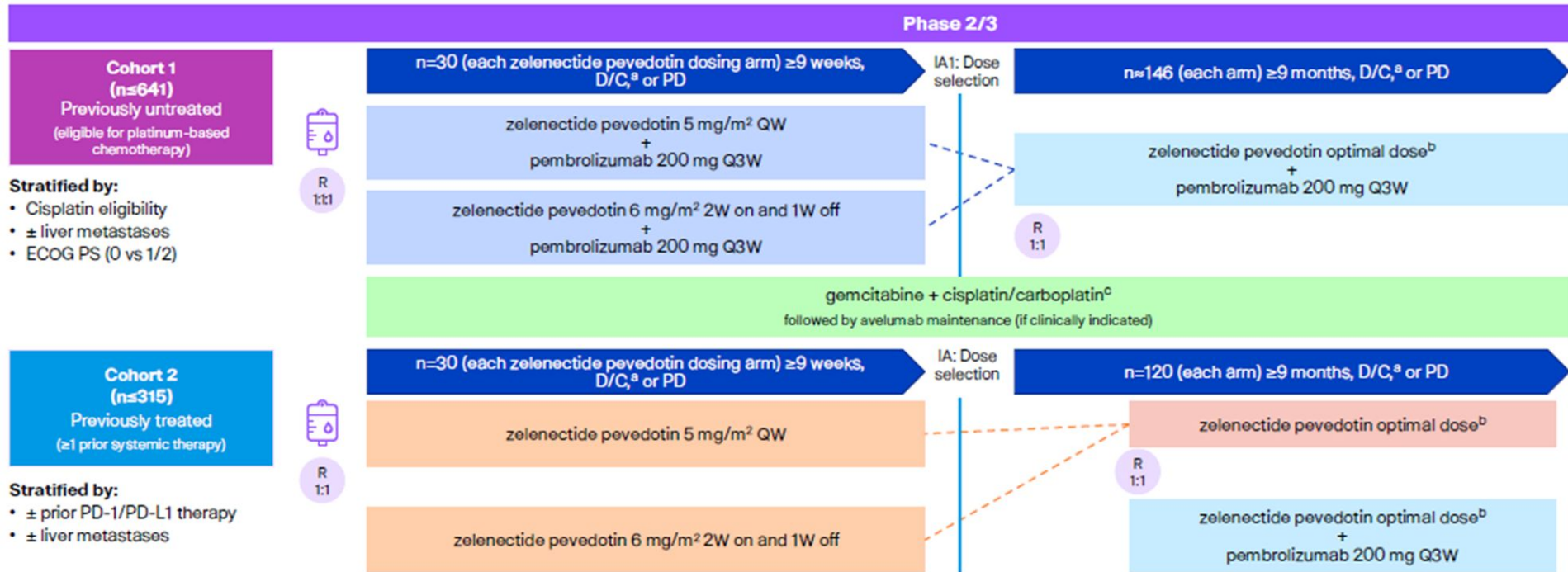
- Small conjugated molecule
- Short linear peptides into a stabilized bi-cyclic structure using a central chemical scaffold
- BT-8009 can quickly leave the vasculature and distribute rapidly to target tissues and tumors, enabling delivery directly to the required site of action












Phase 1/2 DURAVELO
ORR = 45%



Event type	Patients* (N=45)					Total, n (%)
	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)	
Peripheral neuropathy ^a	9 (20)	7 (16)	0	0	0	16 (36)
Peripheral sensory neuropathy ^c	6 (13)	0	0	0	0	6 (13)
Hyperglycemia ^a /diabetes mellitus ^c	2 (4)	0	1 (2)	0	0	3 (7)
Skin reactions ^d	6 (13)	2 (4)	0	0	0	8 (18)
Neutropenia ^c	2 (4)	2 (4)	2 (4)	0	0	6 (13)
Eye disorders ^a	2 (4)	1 (2)	0	0	0	3 (7)

DURAVELO-2 STUDY (NCT04561362)



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BL-B01D1, an EGFR x HER3 Bispecific Antibody-drug Conjugate (ADC), in Patients with Locally Advanced or Metastatic Urothelial Carcinoma (UC)

Dingwei Ye¹

Xiaojie Bian¹, Tiejun Yang², Shusuan Jiang³, Manming Cao⁴, Sa Xiao⁵, Hongwei Wang⁶, Hai Zhu⁶, Yi Zhu⁷

¹ Urinary surgery, Fudan University Shanghai Cancer Center, Shanghai, China;

² Urinary surgery, Henan Cancer Hospital/Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China;

³ Urinary surgery, Hunan Cancer Hospital, Changsha, China;

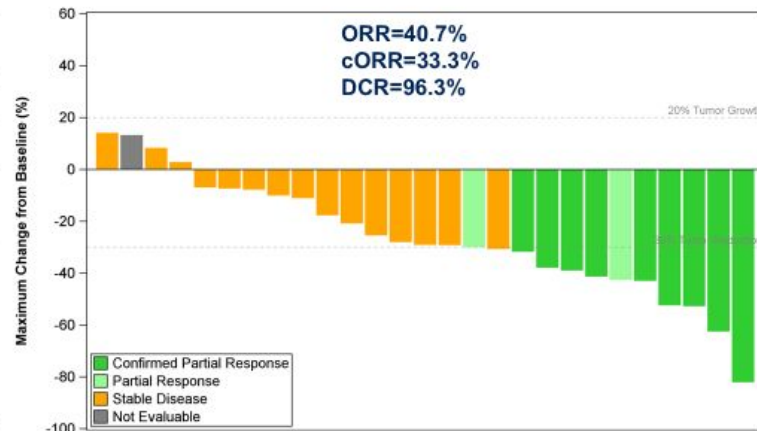
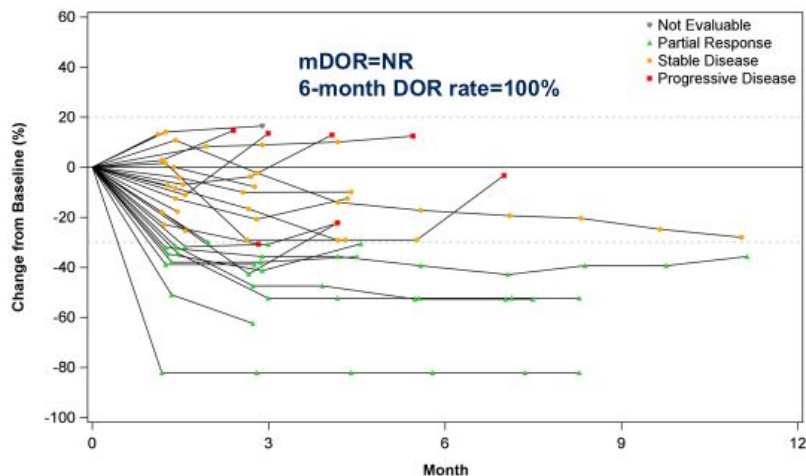
⁴ Breast Oncology Dept., Zhujiang Hospital of Southern Medical University, Guangzhou, China;

⁵ Baili-Bio (Chengdu) Pharmaceutical Co., Ltd., Chengdu, China; ⁶ SystImmune Inc., Redmond, United States of America; ⁷ Sichuan Biokin Pharmaceutical Co., Ltd, Chengdu, China
Shanghai, China 9/13/2024



Depth and Duration of Response

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



Where to explore new ADC

Neoadjuvant

ctDNA positives

1st line vs EVP

2nd line post EVP
vs platinum
therapy

3rd line post EVP
and platinum vs
paclitaxel

SG

TDXD

NECTIN-4 bicycle

DV

EGFR/HER3 TOPO-1

Other
TROP-2/TOPO-1

Monotherapy all comers

Monotherapy
biomarker driven

Combinations

Audience Question

Which of the following is likely to have the biggest impact on bladder cancer care in the future?

1. Sacituzumab Govitecan
2. Disitamab Vedotin
3. T-DXD
4. BT8009 (bicycle)
5. BL-BO1D1 (HER3/EGFR)
6. D-DXD or another TROP-2 ADC