What's on the Menu for Metastatic Urothelial Cancer?

Debates and Didactics in Hematology and Oncology

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Sea Island, GA

Bradley C. Carthon, MD. Ph.D.
Professor, Genitourinary Medical Oncology
Emory University, Atlanta, GA

Chief, Hematology/Oncology
Emory University Hospital Midtown

Disclosures

Consultant:

Exelixis

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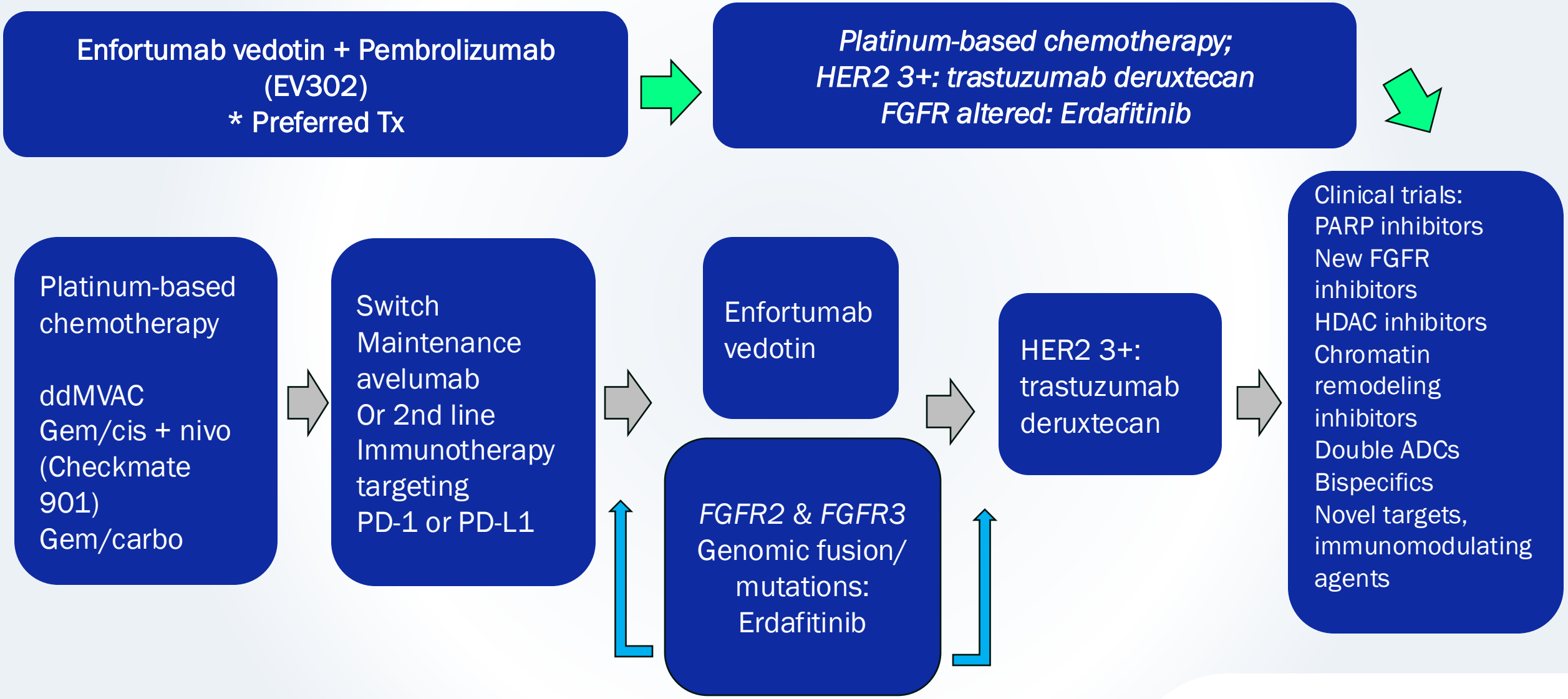
Astellas

Objectives

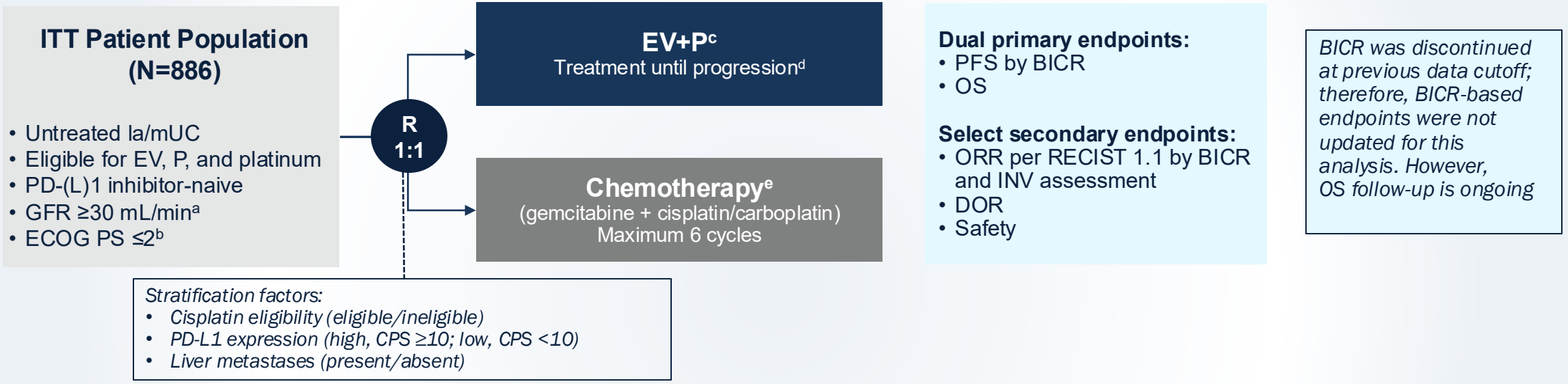
- Review of Urothelial Treatment Landscape & 1st Line Treatment Data
- Impact from Locally Advanced and Perioperative Systemic Approaches
- Subsequent & Novel Systemic Therapy Options Post EV

Current treatment landscape for metastatic urothelial cancer: 2026



Zhang, T. ASCO 2026

EV-302/KEYNOTE-A39 Design and Updates: ASCO 2026



This analysis evaluated efficacy and safety outcomes in the ITT population (median follow-up of 42.8 months)

–Additionally, exploratory subgroup analyses evaluated outcomes in patients who achieved CR (directly or after PR) as well as in patients treated with EV+P for a DOT >1 or 2 years

ClinicalTrials.gov ID, NCT04223856.

BICR, blinded independent central review; CPS, combined positive score; DOR, duration of response; DOT, duration of treatment; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; GFR, glomerular filtration rate; INV, investigator; IV, intravenously; ITT, intention to treat; NYHA, New York Heart Association; ORR, objective response rate; OS, overall survival; P, pembrolizumab; PD-(L)1, programmed death (ligand) 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

[a]Measured by Cockcroft-Gault formula, Modification of Diet in Renal Disease, or 24-hour urine; [b]Patients with an ECOG PS of 2 were required to also meet additional criteria: hemoglobin ≥10 g/dL and GFR ≥50 mL/min but may not have NYHA class III heart failure. [c]Patients received 3-week cycles of EV (1.25 mg/kg IV) on Days 1 and 8 and P (200 mg IV) on Day 1. No maximum number of treatment cycles for EV; maximum of 35 cycles for P. [d]Treatment until progression by BICR, clinical progression, unacceptable toxicity, or if applicable, maximum cycles. [e]Cisplatin eligibility and assignment/dosing of cisplatin vs carboplatin were protocol defined.

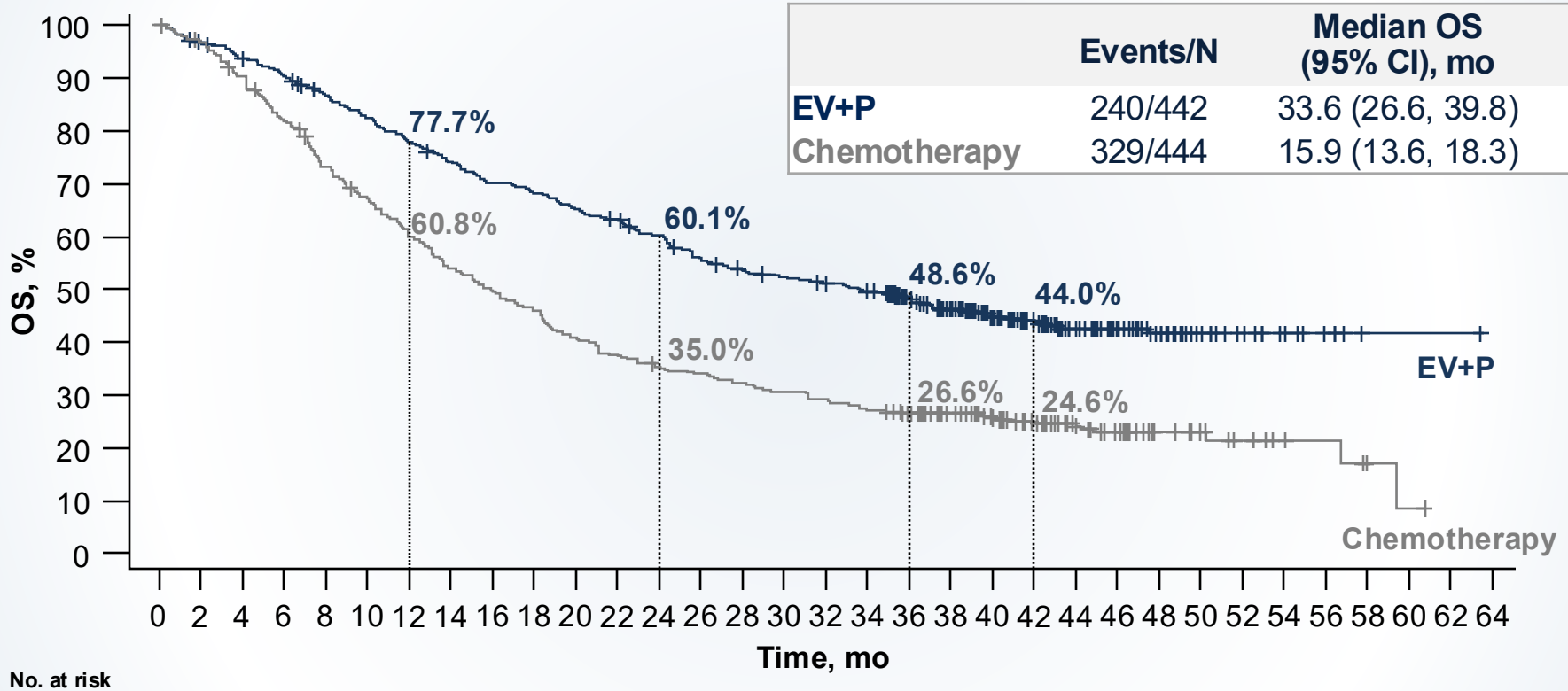
1. Powles T, et al. N Engl J Med. 2024;390(10):875-88.

Powles, T. ASCO 2026

EV-302/KEYNOTE-A39 - Updated OS (ITT Population)

At 3.5 years, an estimated 44.0% of patients in the EV+P arm were alive vs 24.6% in the chemotherapy arm[a]

	Events/N	Median OS (95% CI), mo	Stratified HR (95% CI)
EV+P	240/442	33.6 (26.6, 39.8)	0.53 (0.45, 0.63)
Chemotherapy	329/444	15.9 (13.6, 18.3)	



No. at risk																															
EV+P	442	426	409	394	375	356	336	319	302	294	281	272	256	237	225	218	212	204	181	154	126	104	84	62	42	24	14	9	5	1	1	1	0
Chemotherapy	444	423	393	356	316	289	262	232	214	197	176	161	150	146	138	131	125	116	107	91	75	62	47	32	18	14	10	6	5	2	1	0	0

Data cutoff: October 6, 2025. Median follow-up, 42.8 mo.

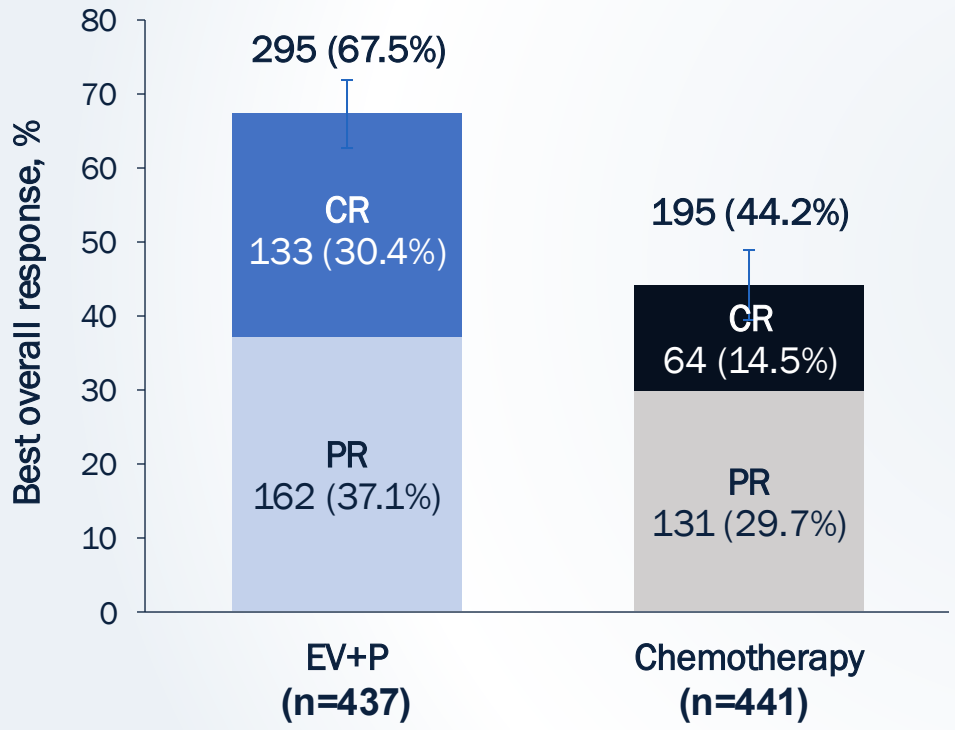
EV, enfortumab vedotin; ITT, intention to treat; OS, overall survival; P, pembrolizumab.

[a]Based on Kaplan-Meier estimates.

Objective Response and CR Rates in EV-302

The CR rate was approximately doubled in the EV+P vs chemotherapy arm

ORR[1]



CR evolution[2]

	Response-evaluable patients	
	EV+P (n=437)	Chemotherapy (n=441)
Patients achieving CR, n (%)	133 (30.4)	64 (14.5)
Patients achieving CR directly	45 (10.3)	26 (5.9)
Patients achieving CR after PR	88 (20.1)	38 (8.6)

- Among patients with confirmed CR in the EV+P arm (n=133), 66.2% achieved PR initially, then converted from PR to CR (n=88)[2]

Data cutoff: August 8, 2024. BICR was discontinued after this data cutoff; while OS follow-up remains ongoing, BICR-based endpoints were not updated for later data cutoffs.

BICR, blinded independent central review; response rate; CR, complete response; EV, enfortumab vedotin; ORR, objective response rate; P, pembrolizumab; PR, partial response.

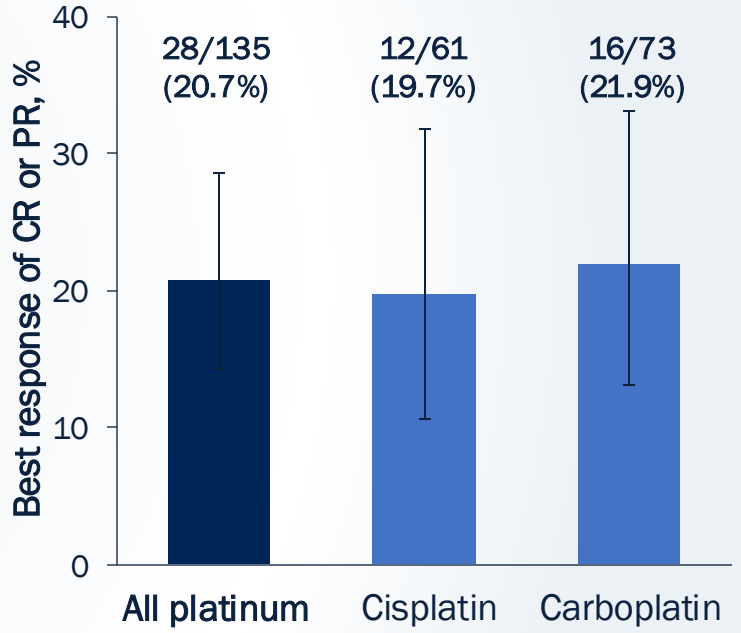
1. Gupta S, et al. ASCO 2025. Abstract 4502 (Oral). 2. Gupta S, et al. ASCO GU 2026. Abstract 746 (Poster).

Subsequent Therapy (ITT Population)

In the EV+P arm, the most common first subsequent treatment was platinum-based chemotherapy, which resulted in an ORR of 21% and median OS of 10.9 months

	EV+P (n=442)
Patients who received subsequent anticancer therapies, n (%)	192 (43.4)
Systemic therapy	173 (39.1)
First subsequent systemic therapy, n (%)	
Platinum-containing chemotherapy[a]	135 (30.5)
Carboplatin-based therapy	73 (16.5)
Cisplatin-based therapy	61 (13.8)
PD-(L)1 inhibitor therapy[b]	17 (3.8)
Maintenance	0
EV+P-based therapy	2 (0.5)
Other PD-(L)1 inhibitor therapy	15 (3.4)
Atezolizumab	1 (0.2)
Pembrolizumab	14 (3.2)
Other	21 (4.8)

ORR in evaluable patients receiving subsequent platinum-based chemotherapy[a,c]



- Median OS from start of platinum-based chemotherapy was 10.9 months (95% CI 8.3, 12.8)

Data cutoff: October 6, 2025.

CR, complete response; EV, enfortumab vedotin; ITT, intention to treat; ORR, objective response rate; OS, overall survival; P, pembrolizumab; PD-(L)1, programmed death (ligand) 1; PR, partial response.

[a]When platinum-based therapy and a PD-(L)1 inhibitor were given in the same line of therapy, the therapy was categorized as platinum-containing therapy; 1 patient received a platinum agent other than carboplatin or cisplatin.

[b]Patients could receive >1 PD-(L)1 agent in the same line of therapy; only agents used in >1% of patients in ≥1 arm are listed. [c]Subsequent response data were reported by the study sites and were not collected systematically across patients.

NCCN 1L Therapy for Locally Advanced or Metastatic Disease: v1.2026

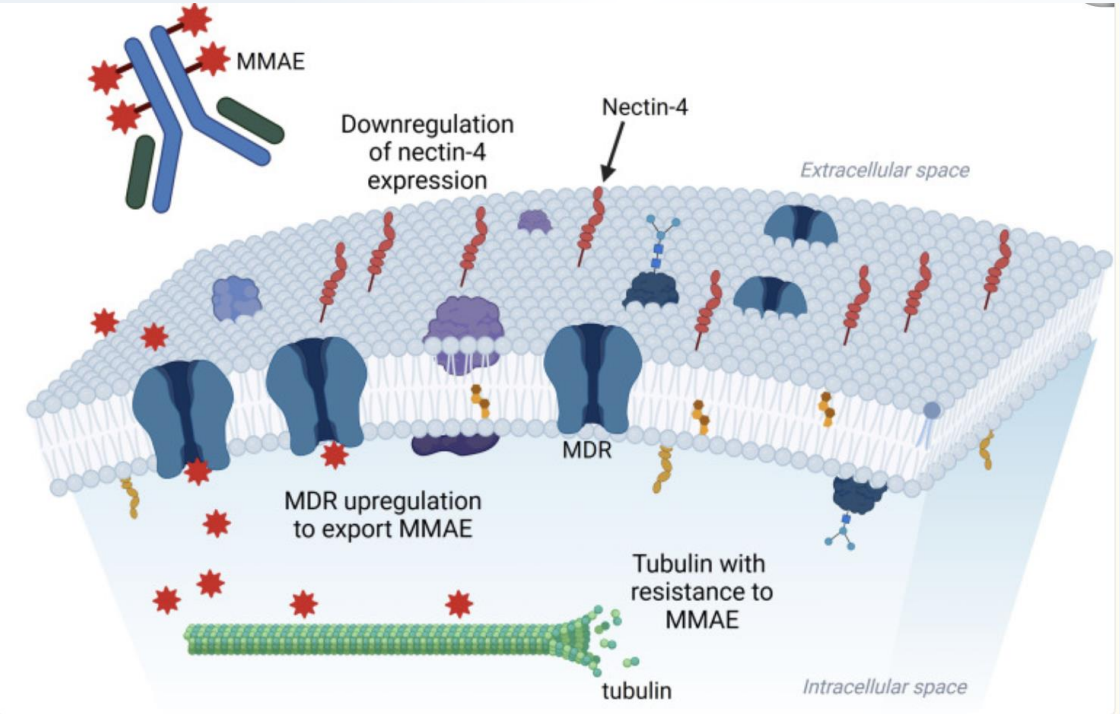
PRINCIPLES OF SYSTEMIC THERAPY[a]

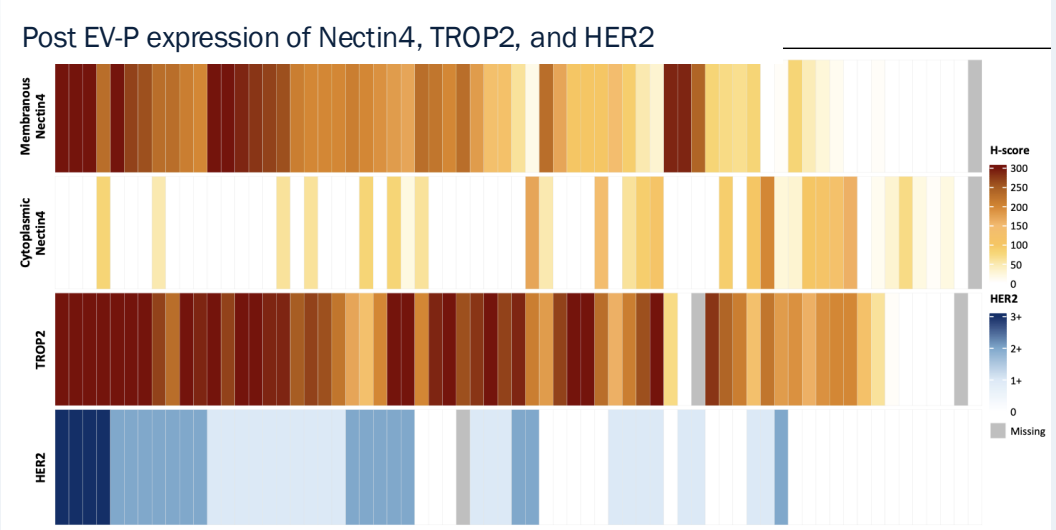
First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)		
Preferred • Enfortumab vedotin-ejfv[13,14] + Pembrolizumab (category 1)	**Other recommended** • Cisplatin/Gemcitabine[4] (category 1) followed by Avelumab maintenance therapy (category 1)[c,15] • Cisplatin/Gemcitabine + Nivolumab (category 1) followed by Nivolumab maintenance therapy[16] (category 1) • DDMVAC with growth factor support[2,11] (category 1) followed by Avelumab maintenance therapy (category 1)[c,15]	**Useful in certain circumstances** • Carboplatin/Gemcitabine[17] followed by Avelumab maintenance therapy (category 1)[c,15] • Pembrolizumab (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy)[18] • Atezolizumab[19] (only for patients whose tumors express PD-L1[d] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 2B)

Regimen	CR Rate	RR	Median OS	Hazard Ratio
EV + Pembo (EV-302) N Engl J Med. 2024 Mar 7;390(10) ASCO 2026	30.4%	67.5%	33.6 mos (25.4-NE)	0.53 P <0.001
Gem/Cis/Nivo ->Nivo (CheckMate 901) N Engl J Med. 2023 Nov 9;389(19):1778-1789	21.7%	57.6%	21.7 mos (18.6-26.4)	0.78 P=0.02
Cis/Carbo + Gem -> Avelumab (Javelin Bladder 100) N Engl J Med. 2020 Sep 24;383(13):1218-1230; J Clin Oncol 2023 Jul 1;41(19):3486-3492	25.7%*	72%*	23.8 mos (18.9-26.1)	0.76 P<0.0036

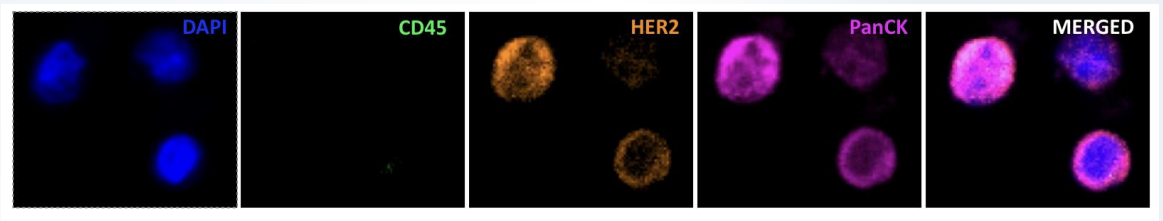
NCCN, Bladder Cancer 2026.

What Happens to Drug Targets During Resistance?





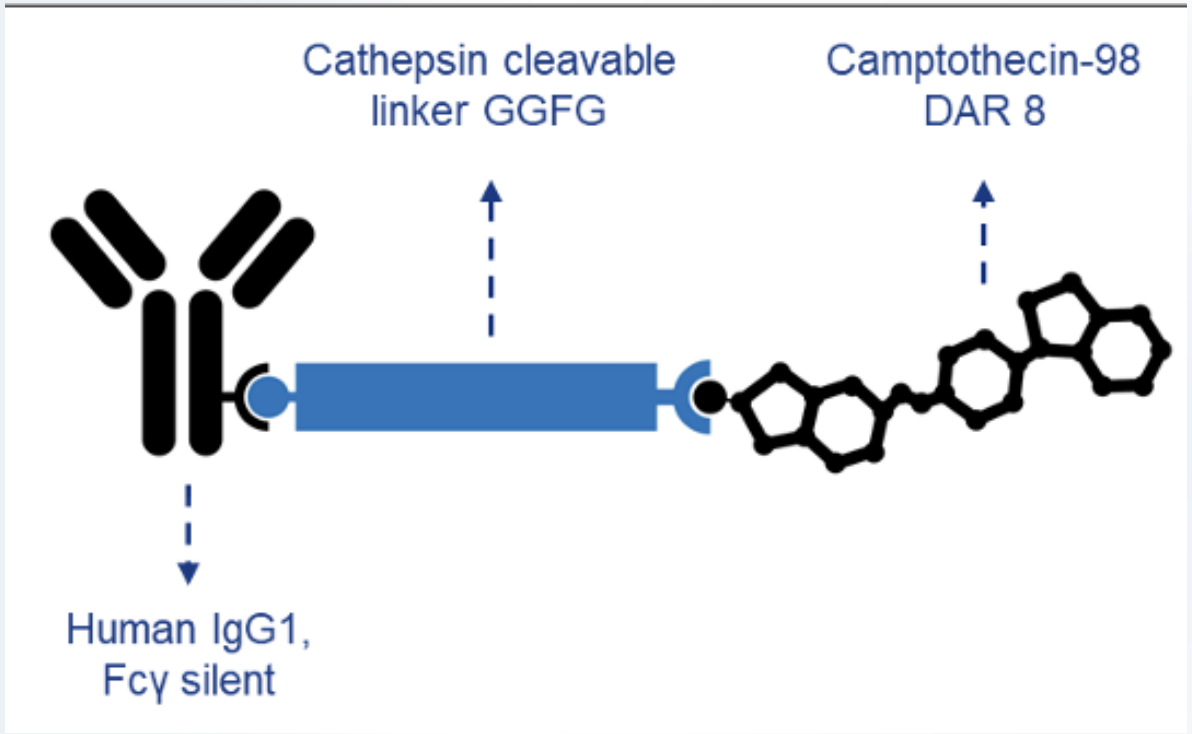
HER2 expression on CTC from [illegible] EVP-refractory mUC



Resistance to cell surface ligand or payload?
Other pathways involved in resistance?
Better ways to detect and target early treatment resistance?

Jang A & Brown J, *Explor Target Antitumor Ther*, 2025
Michal Sternschuss et al, ASCO 2026
Issa W et al, ASCO 2026
Zhang, T, ASCO 2026

NEXUS-01, a phase 1 study of LY4052031, an antibody-drug conjugate targeting Nectin-4, in participants with advanced or metastatic urothelial carcinoma



Disease Characteristics of Special Interest in mUC (n=95)	
CrCl mL/min, n (%)	
≤30-49	18 (19)
50-59	16 (17)
≥60	61 (64)
Visceral metastases, n (%)	54 (57)
Liver metastases, n (%)	27 (28)
Median prior systemic regimens (range)	3 (1-12)
Prior Therapy, n (%)	
Platinum chemotherapy	85 (89)
EV with or without pembrolizumab	66 (69)
EVP	39 (41)
IO[b]	90 (95)
ADC – Topo-I	25 (26)
Reason for EV discontinuation, n (%)	
Toxicity	5 (8)

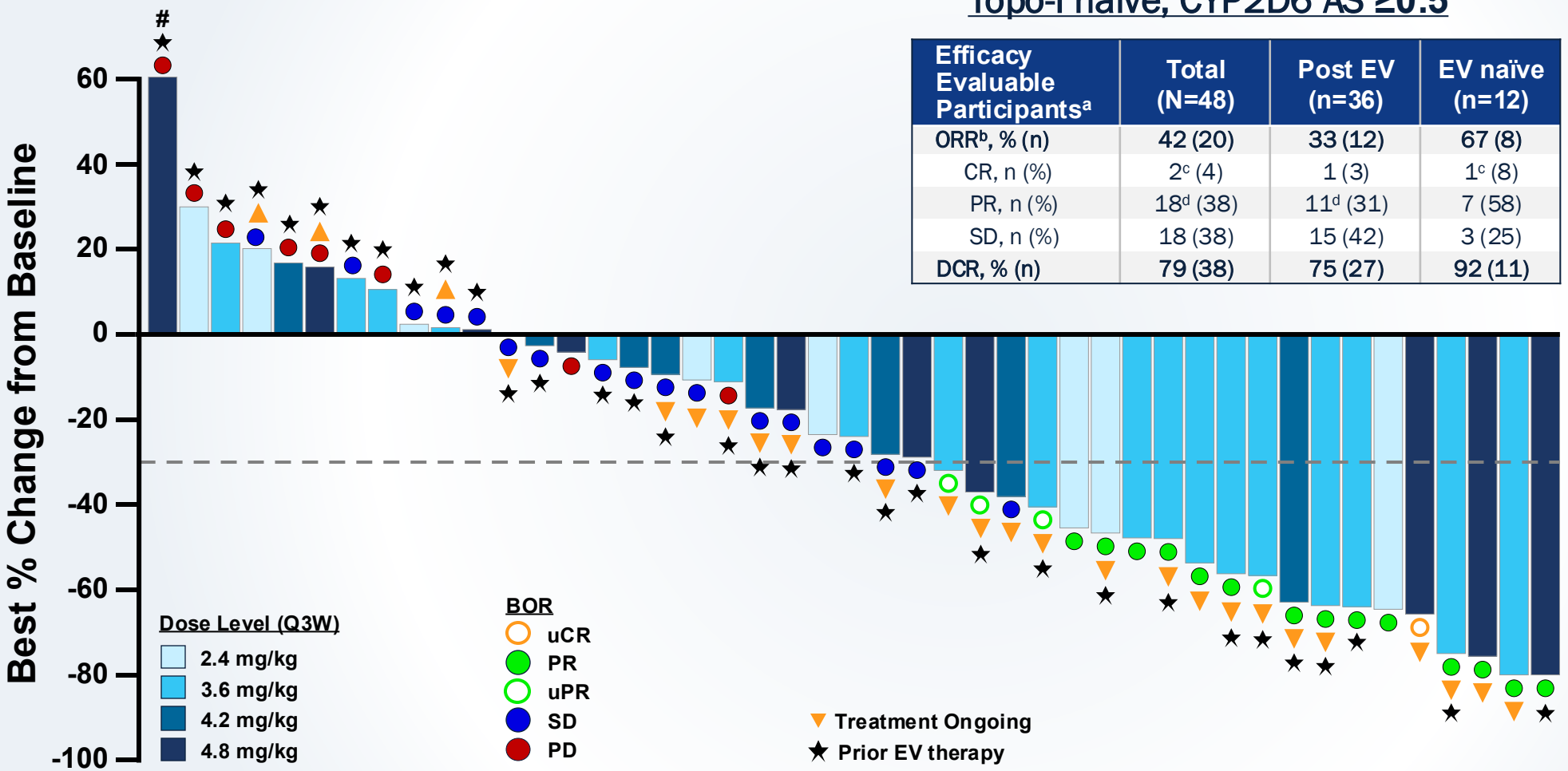
- 95 patients with metastatic urothelial cancer
- 69% had EV with or without pembrolizumab
- 57% visceral metastatic disease

Iyer G et al, ASCO 2026

NEXUS-01: LY4052031 responses in EV Naïve & refractory disease

Topo-I naïve, CYP2D6 AS ≥0.5

Efficacy Evaluable Participants[a]	Total (N=48)	Post EV (n=36)	EV naïve (n=12)
ORR[b], % (n)	42 (20)	33 (12)	67 (8)
CR, n (%)	2[c] (4)	1 (3)	1[c] (8)
PR, n (%)	18[d] (38)	11[d] (31)	7 (58)
SD, n (%)	18 (38)	15 (42)	3 (25)
DCR, % (n)	79 (38)	75 (27)	92 (11)



- Min. Responses in Topo1 Pretreated
- 33 patients with EV-P refractory mUC
- 33% objective responses post EV
- 79% disease control rate overall
- Option vs. 2nd line Chemo?
- Nectin -4 utility in EV-P refractory mUC
- Low CYP2D6 with toxicity, neutropenia

Iyer, G, et al. ASCO 2026

Perioperative SHR-A2102, a novel nectin-4-targeted antibody-drug conjugate, in combination with adebrelimab for patients with muscle-invasive bladder cancer

Key Eligible Criteria:

- Pathologically and radiographically confirmed T2-4aN0M0 or T1-4aN1M0 MIBC
- Eligible for RC + PLND
- ECOG: 0-1
- Adequate organ function, CrCl ≥30 mL/min

Neoadjuvant

SHR-A2102
8 mg/kg
+
Adebrelimab
1200 mg
Q3W×4 cycles

Within 6 weeks*

Radical Cystectomy

Adjuvant

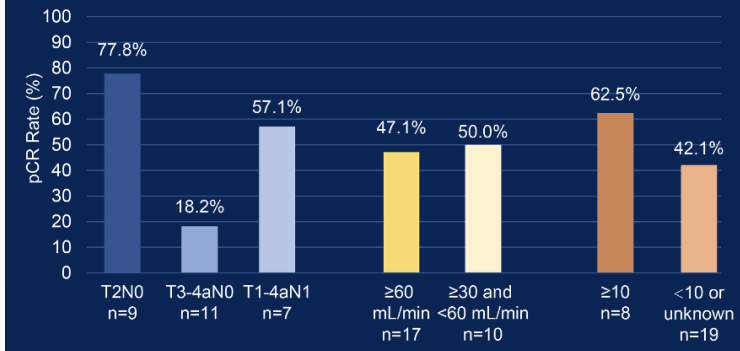
SHR-A2102 8 mg/kg
Q3W×5 cycles
+
Adebrelimab
1200 mg
Q3W×13 cycles

Survival follow-up

Primary endpoints:
- Recommended phase 3 dose (RP3D)#
- Investigator-assessed pathological complete response (pCR, defined as pT0N0)

Secondary endpoints&:
- EFS, DFS, OS
- Preoperative ORR, DCR
- Safety

Pathologic Response	Evaluable Patients (N=27)
pCR (ypT0N0), n (%)	13 (48.1)
95% CI	28.7, 68.1
pDS (<ypT2N0), n (%)	16 (59.3)
95% CI	38.8, 77.6

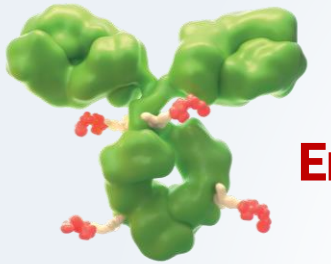


Subgroup analysis for pCR rate

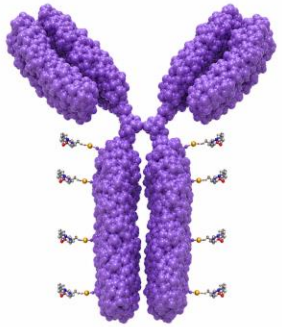
- SHR-A2102: Nectin-4 ADC, with topoisomerase inhibitor, combined with anti PD-1
- Phase 2 muscle invasive or node positive urothelial cancer
- Pathologic CR rate 48% (13/27)

Shen, et al. ASCO 2026

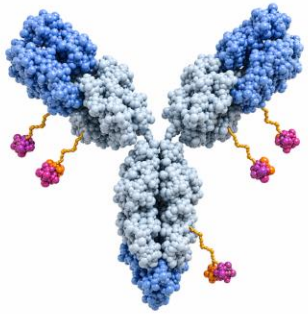
Nectin-4 Targeted Agents in Use & Development



Enfortumab Vedotin



LY4052031



SHR-A2102

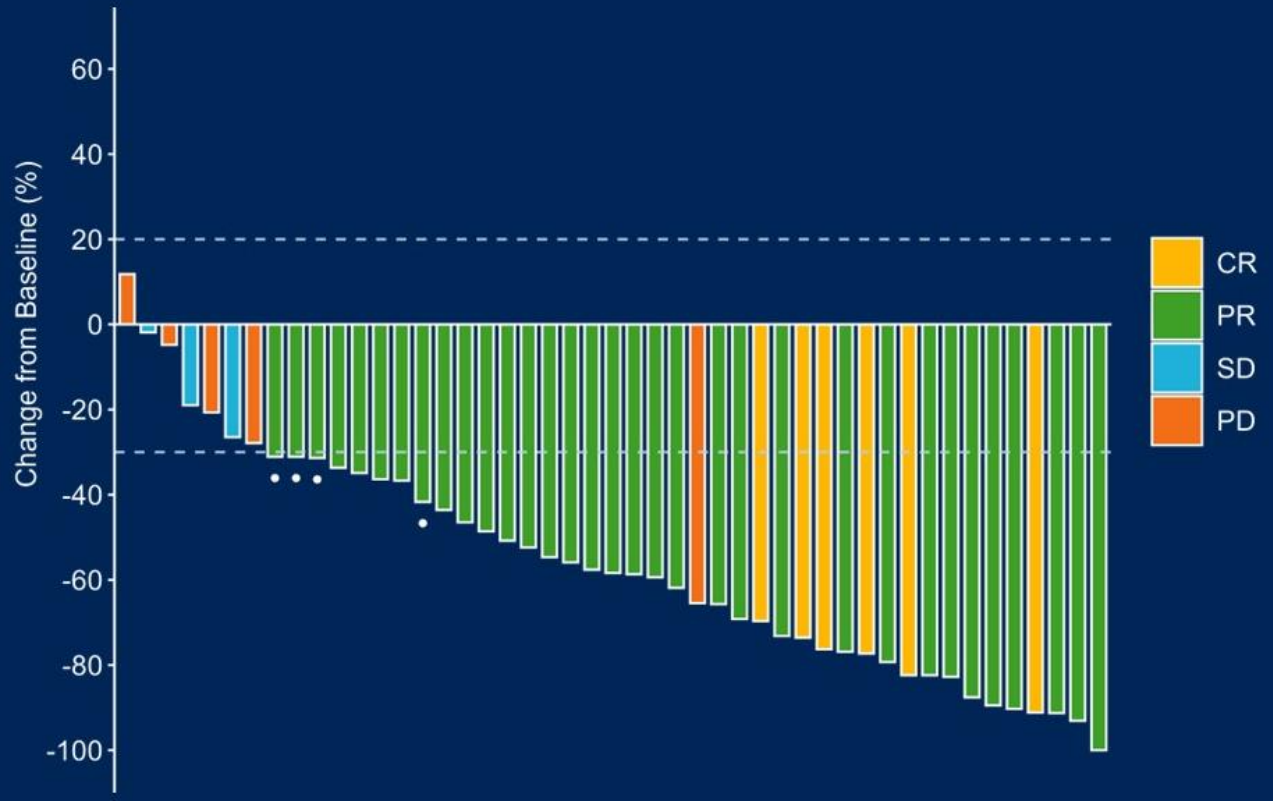
Nectin 4 Targeted agents under development	Payload	Linker
Zelenectide pevedotin (BT8009)	MMAE	Bicycle Drug Conjugate peptidase-cleavable sarcosine spacer chain / valine-citrulline
Bulumtatug fuvedotin (9MW2821)	MMAE	protease-cleavable
CRB-701 (SYS6002)	MMAE	Cleavable
ETx-22 (LY4101174)	Topo-1 Exatecan	Cleavable Maleimide-beta-glucuronide poly-sarcosine
BAT8007	Topo-1	Enzymatically cleavable
IPH4502	Topo-1 Exatecan	Cleavable, hydrophilic
ADRX-0706	AP052 (tubulin inhibitor)	Protease-cleavable

Apolo, A. ASCO 2026

Phase 1b/2 Study of Bulumtatug fuvedotin (9MW2821) + Torapilimab in Patients with Locally Advanced and Metastatic Urothelial Cancer

47 patients with la/mUC had at least one tumor assessment after baseline according to RECIST v1.1.

- 7 pts had been previously treated for la/mUC and other 40 pts were treatment-naïve for la/mUC.
- ORR 83.0% (95%CI 69.2-92.4); DCR 89.4% (95%CI 76.9-96.5) in the overall population.



✓ Treatment-naïve patients for la/mUC (n=40; all BFv 1.25mg/kg combination):
ORR 87.5%, DCR 92.5%

✓ Previously treated patients for la/mUC (n=7; 3 pts for BFv 1.0mg/kg combination, 4 pts for BFv 1.25mg/kg combination):
ORR 57.1%, DCR 71.4%

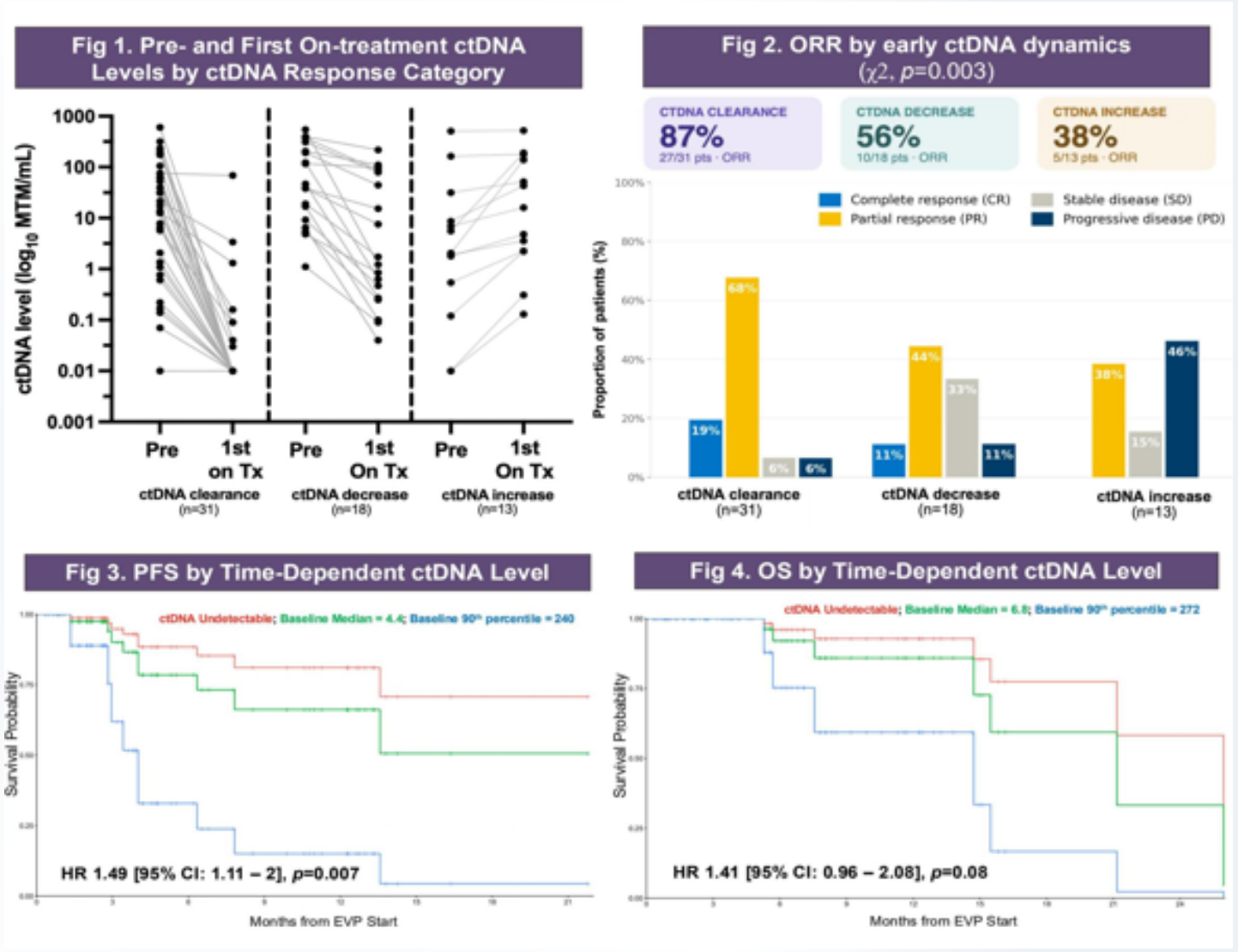
- BFv 1.0mg/kg (n=3), all chemo progressed only, ORR 33.3%, DCR 66.7%.
- BFv 1.25mg/kg (n=4), all chemo progressed including 3 pts ICI progressed, ORR 75.0%, DCR 75.0%.

Sheng, X., Gao, J. et al. ASCO 2026

Circulating tumor DNA (ctDNA) dynamics as early biomarkers of response to enfortumab vedotin plus pembrolizumab (EVP) in advanced urothelial carcinoma (aUC)

- Retrospective institutional cohort
- 302 patients (pts) with aUC treated with EVP at MDACC.
- 79 pts with baseline and serial ctDNA testing using a tumor-informed assay (Signatera) (08/23–01/26)
- Early cTDNA dynamics provide a clinically meaningful measure of response to EVP in aUC and correlate with imaging outcomes.
- ctDNA clearance identifies patients with deep and durable benefit, while lack of clearance flags early resistant

Moussa, M.J., et al. ASCO 2026



NCCN 2nd Line and Subsequent Therapy in Metastatic Urothelial CA

PRINCIPLES OF SYSTEMIC THERAPY[a]

Second-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)		
Previous immunotherapy and enfortumab vedotin-ejfv (no previous chemotherapy)		
Preferred • Biomarker-directed therapy (see biomarker-directed therapy table, BL-G 5 of 8) • Cisplatin/Gemcitabine[4] • DDMVAC with growth factor support[2,11] • Carboplatin/Gemcitabine (category 2B)	Other recommended • Gemcitabine[20] • Paclitaxel[21] or Docetaxel[22]	Useful in certain circumstances • Cisplatin/Gemcitabine + Nivolumab (category 2B)
Previous chemotherapy (no previous immunotherapy or enfortumab vedotin-ejfv)[e]		
Preferred • Enfortumab vedotin-ejfv + Pembrolizumab[14]	Other recommended • Pembrolizumab (category 1 post-platinum)[23] • Biomarker-directed therapy (see biomarker-directed therapy table, BL-G 5 of 8) • Enfortumab vedotin-ejfv[24] • Avelumab[25,26] (category 2B) • Nivolumab[27] (category 2B)	Useful in certain circumstances • Gemcitabine[20] • Paclitaxel[21] or Docetaxel[22] • Cisplatin/Gemcitabine[4] (category 2B) • DDMVAC with growth factor support[2,11] (category 2B) • Doxorubicin/Gemcitabine/Ifosfamide[28] (category 2B) • Gemcitabine/Paclitaxel[29] (category 2B)
Previous immunotherapy (no previous chemotherapy or enfortumab vedotin-ejfv)		
Preferred • Biomarker-directed therapy (see biomarker-directed therapy table, BL-G 5 of 8) • Carboplatin/Gemcitabine • Cisplatin/Gemcitabine[4] • DDMVAC with growth factor support[2,11] • Enfortumab vedotin-ejfv[24] • Enfortumab vedotin-ejfv + Pembrolizumab	Other recommended • Gemcitabine[20] • Paclitaxel[21] or Docetaxel[22]	Useful in certain circumstances • Cisplatin/Gemcitabine + Nivolumab (category 2B) • Doxorubicin/Gemcitabine/Ifosfamide[28] (category 2B) • Gemcitabine/Paclitaxel[29] (category 2B)
Previous chemotherapy and immunotherapy (no previous enfortumab vedotin-ejfv)[f,g]		
Preferred • Enfortumab vedotin-ejfv[30,31] (category 1) • Biomarker-directed therapy (see biomarker-directed therapy table, BL-G 5 of 8)	Other recommended • Cisplatin/Gemcitabine[4] • DDMVAC with growth factor support[2,11] • Enfortumab vedotin-ejfv + Pembrolizumab • Gemcitabine[20] • Paclitaxel[21] or Docetaxel[22] • Doxorubicin/Gemcitabine/Ifosfamide[28] (category 2B)	Useful in certain circumstances • Sacituzumab govitecan-hziy[32]

PRINCIPLES OF SYSTEMIC THERAPY

Subsequent-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)[f,g]		
Previous chemotherapy, immunotherapy, and enfortumab vedotin-ejfv		
Preferred • Biomarker-directed therapy (see biomarker-directed therapy table)	Other recommended • Gemcitabine[20] • Paclitaxel[21] or Docetaxel[22] • Doxorubicin/Gemcitabine/Ifosfamide[28] (category 2B) • Gemcitabine/Paclitaxel[29] (category 2B)	Useful in certain circumstances • Sacituzumab govitecan-hziy[32]

Biomarker-Directed Therapy (pan-cancer tumor-agnostic treatments can be considered for patients with actionable mutations)
• Erdafitinib (susceptible FGFR3 genomic alterations)[33] (Category 1 for patients who have already received platinum and a checkpoint inhibitor if eligible.) • Fam-trastuzumab deruxtecan-nxki (HER2-positive, IHC 3+, IHC 2+).[34,h,i]

NCCN, Bladder Cancer 2026.

Destiny – PanTumor02: A Phase 2 Study of T-Dxd for HER2-Expressing Solid Tumors

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1

T-DXd
5.4 mg/kg
q3w

n≈40 per cohort planned

(Cohorts with no objective responses in the first 15 patients were to be closed)

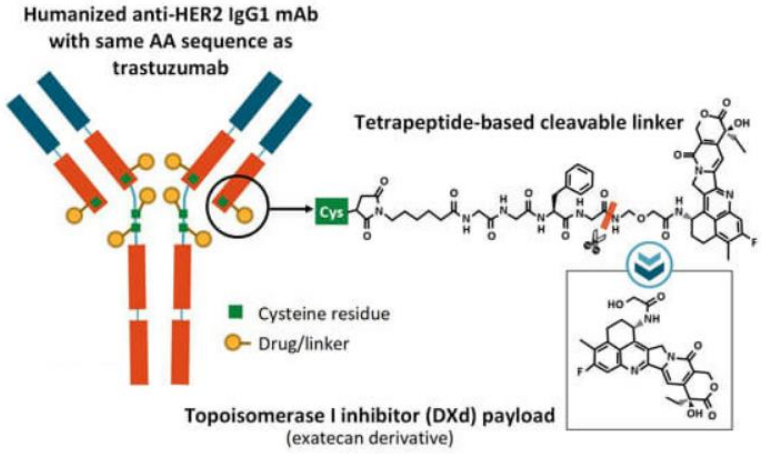
- Cervical cancer
- Endometrial cancer
- Ovarian cancer
- Biliary tract cancer
- Pancreatic cancer
- Bladder cancer
- Other tumors[b]

Primary endpoint
- Confirmed ORR (investigator)[c]

Secondary endpoints
- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

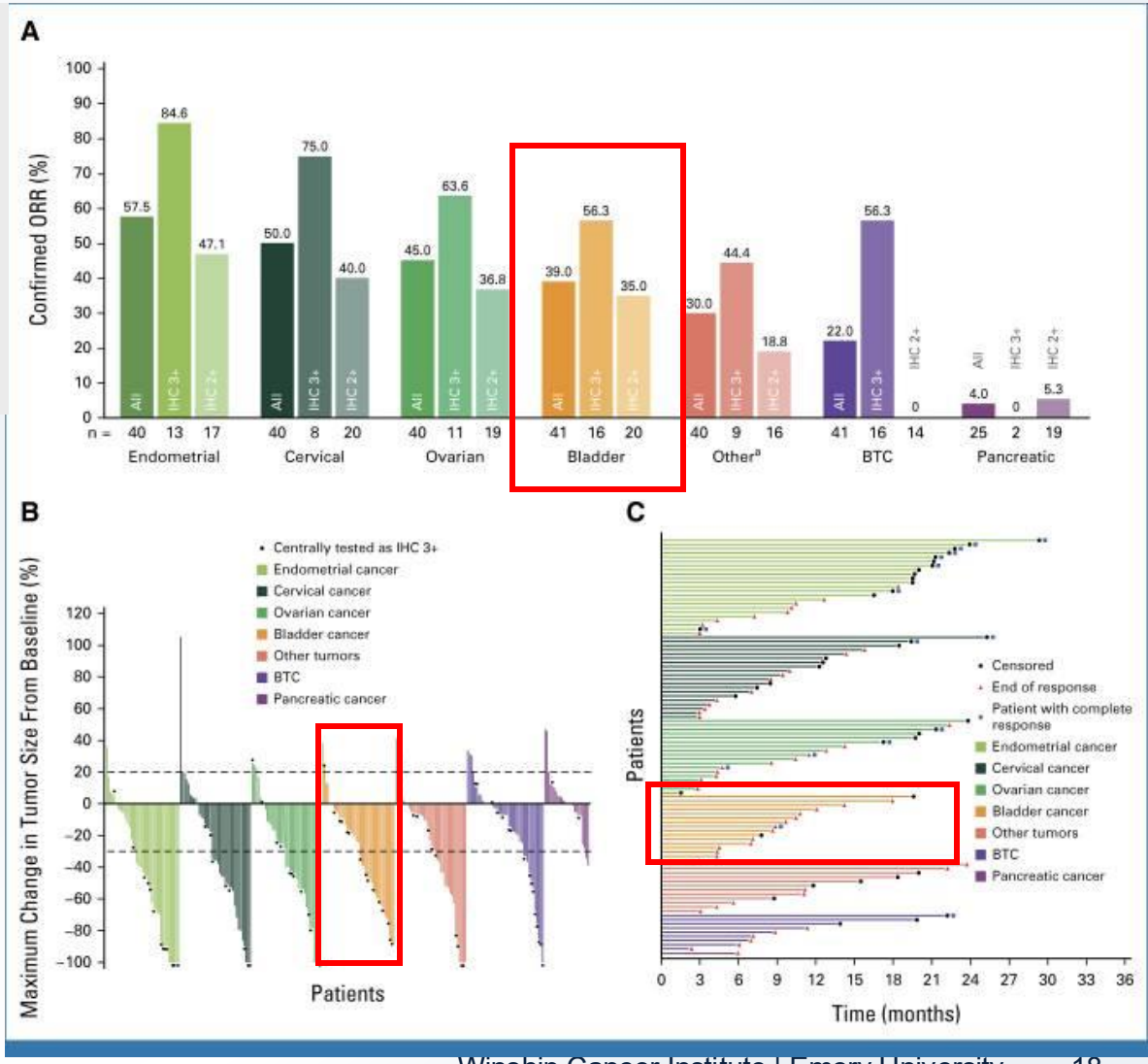
Data cut-off for analysis:
- Nov 16, 2022

HER2-Targeted ADC: Trastuzumab Deruxtecan



- High drug:antibody ratio: ~8
- Stable linker-payload
- Tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life
- Bystander killing effect

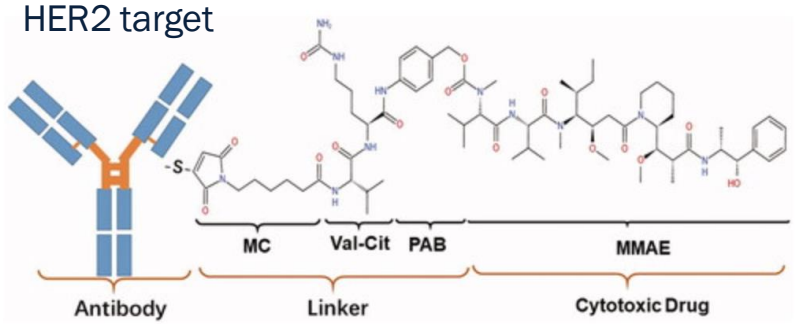
Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. Trail. Pharmacol Ther. 2018;181:126. Ogitani. Cancer Sci. 2016;107:1039.



Disitamab Vedotin (DV) plus Toripalimab in HER2-Expressing Advanced Urothelial Cancer

- Disitimab vedotin: HER2-targeted ADC
- Combined with PD-1 inhibitor vs chemotherapy

- HER2 1+/2+/3+ metastatic UC



RC48-C016 Study Design (NCT05302284)

Key Inclusion criteria

- No prior systemic treatment for unresectable locally advanced or metastatic UC
- Central lab-confirmed HER2 IHC 1+, 2+, or 3+
- Measurable disease per RECIST v1.1
- Eligible for ciscplatin or carboplatin
- ECOG PS 0 or 1

R 1 : 1

N=243 **Disitamab vedotin + Toripalimab**
no set maximum cycles

N=241 **Gemcitabine + Cisplatin/Carboplatin**
a maximum of 6 cycles

Dual primary endpoints:

- PFS assessed by BIRC
- OS

Secondary endpoints:

- PFS assessed by investigators
- ORR (per RECIST v1.1), DCR, and DoR assessed by BIRC and investigators
- Safety
- QoL, PK, and immunogenics

Stratification factors

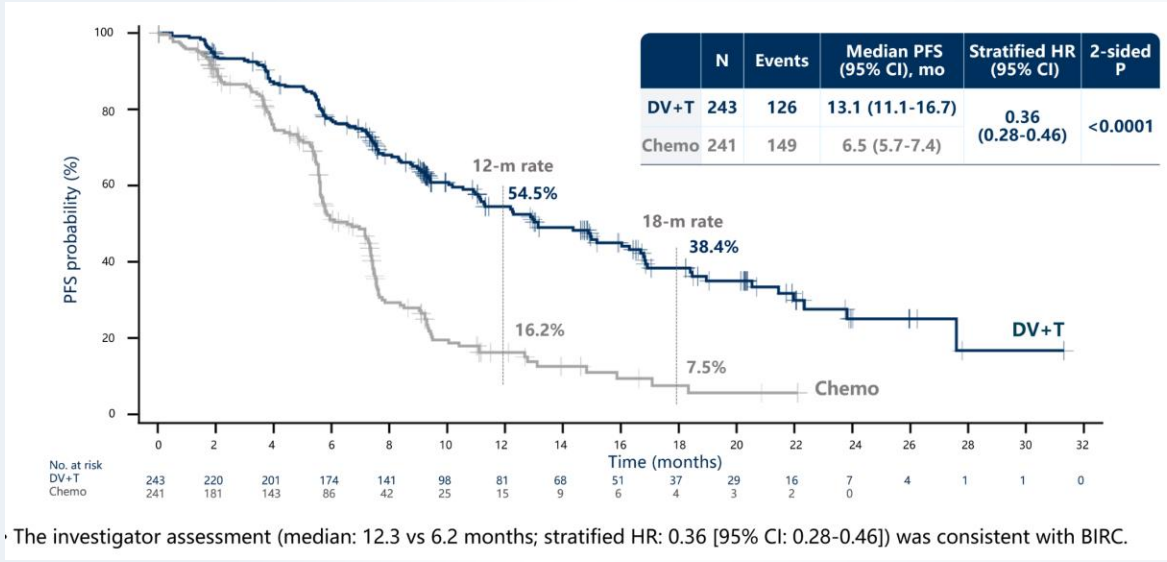
- Cisplatin-eligibility (eligible vs ineligible)
- HER2 expression status (1+ vs 2+/3+)
- Visceral metastases (present vs absent)

- Treatment continued until disease progression/death, intolerable toxicity, or consent withdrawal.
- In the Chemo group, assignment of cisplatin or carboplatin was protocol-defined. Chemo was administered for a maximum of 6 cycles.
- Statistical plan for analysis: the first analysis was planned to be performed after approximately 278 PFS (final) and 183 OS events (interim).

Sheng, X, et al. NEJM 2025; Sheng X et al, ESMO Annual Congress 2025; Zhang, T, ASCO 2026

Disitamab Vedotin plus Toripalimab in HER2-Expressing Advanced Urothelial Cancer

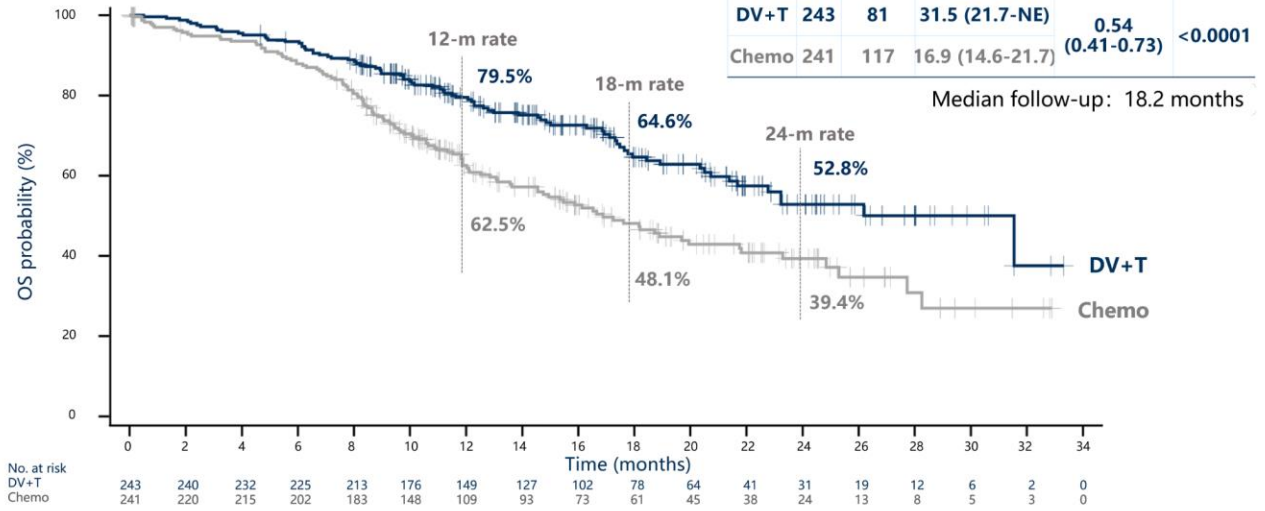
Progression free survival



	N	Events	Median PFS (95% CI), mo	Stratified HR (95% CI)	2-sided P
DV+T	243	126	13.1 (11.1-16.7)	0.36 (0.28-0.46)	<0.0001
Chemo	241	149	6.5 (5.7-7.4)		

The investigator assessment (median: 12.3 vs 6.2 months; stratified HR: 0.36 [95% CI: 0.28-0.46]) was consistent with BIRC.

Overall survival



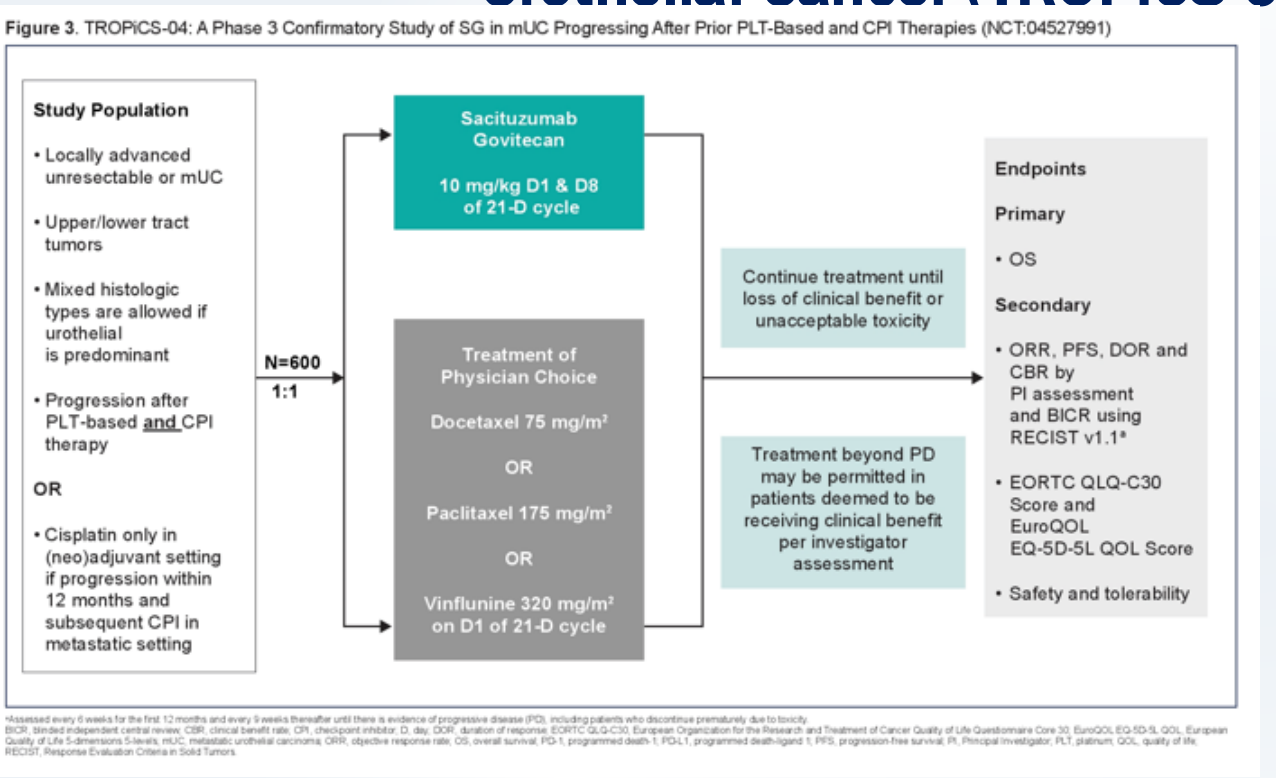
	N	Events	Median OS (95% CI), mo	Stratified HR (95% CI)	2-sided P
DV+T	243	81	31.5 (21.7-NE)	0.54 (0.41-0.73)	<0.0001
Chemo	241	117	16.9 (14.6-21.7)		

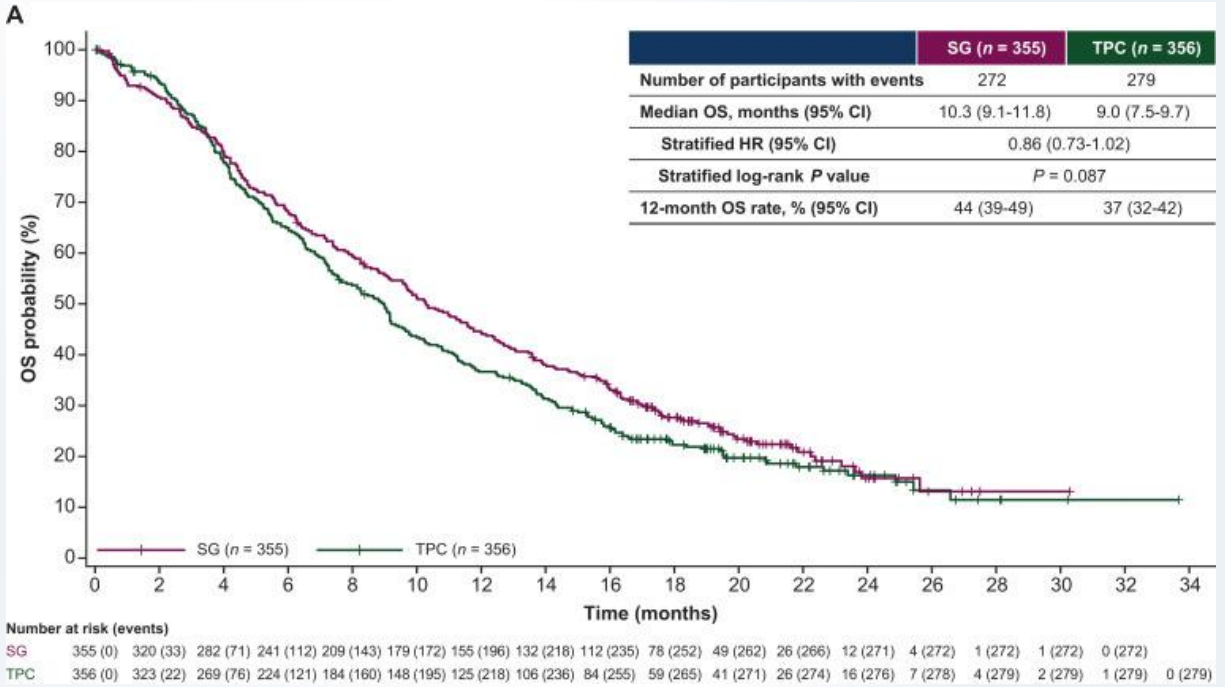
Median follow-up: 18.2 months

- Median PFS 13.1 months and median OS 31.5 months
- *First for HER2 selection in front-line metastatic urothelial cancer*
- ORR 76%

Sheng, et al. NEJM 2025

Sacituzumab Govitecan (IMMU-132) in Metastatic or Locally Advanced Unresectable Urothelial Cancer (TROPiCS-04) Failed to Show OS Benefit





	SG (*n* = 355)	TPC (*n* = 356)
Number of participants 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)

- April 13, 2021, accelerated approval
- Neither overall survival (OS) nor progression-free survival (PFS) were improved with SG.
- SG demonstrated objective response rate of 23%.
- SG arm had 16 grade 5 neutropenic complications
- November 22, 2024, the FDA announced the final withdrawal of the approval

Vulsteke, C. GU ASCO 2022; Powles T, Ann Oncol. 2025 May;36(5):561-571.

ECOG ACRIN EA8231: A Phase III Randomized Trial of Pembrolizumab in Combination with Sacituzumab Govitecan vs Standard of Care in Anti-PD-(L)1-Resistant aUC

SCHEMA

N=320 **1:1 Randomization**

Metastatic or locally advanced / unresectable UC

1. ECOG PS 0-2
2. Anti-PD(L)1 therapy exposure required in any disease setting and no tumor progression on prior anti-PD(L)1 therapy within 12 weeks of initial ICI initiation (from starting prior ICI)
3. Prior exposure to EV, or Nectin-4-, or MMAE containing Rx unless contraindicated
4. ≥1 lines of systemic therapy for advanced disease [*FGFR3*-altered tumors must have received FGFR inhibitor unless contraindicated; If EV+P is given in the peri-operative setting, subjects are eligible if PD ≤12mo from last dose]
5. Bellmunt score 0-2

Stratification Factors:

- ❑Bellmunt score (0-1 vs 2)
- ❑Prior lines of therapy (≤2 lines vs >2 lines)
- ❑Prior exposure to platinum-based chemo (*yes* vs *no prior exposure and platinum-eligible per physician discretion* vs *no prior exposure and platinum-ineligible per physician discretion*)
- ❑Duration of prior anti PD-(L)1 therapy (≤6 vs >6 months)

ARM A: TPC (Therapy per Physician Choice)

Platinum-based doublet [up to 6 cycles]

- ❑Carboplatin + Gemcitabine
- ❑Cisplatin + Gemcitabine

- ❑Docetaxel [treatment until progression or unacceptable toxicity]
- ❑Paclitaxel [treatment until progression or unacceptable toxicity]

ARM B: Sacituzumab (SG) + Pembrolizumab

❑SG 10 mg/kg on Days 1/8 + Pembrolizumab 200mg Day 1 (q21-day cycle) [SG until progression or unacceptable toxicity; Pembrolizumab up to 35 cycles]

G-CSF prophylaxis strongly recommended with SG!

Biomarker & HRQOL are being collected

Primary endpoint:
Overall survival

Secondary endpoints:

1. PFS
2. ORR
3. Clinical benefit rate (CR/PR/SD)
4. QoL/PRO
5. Duration of Response
6. Safety/toxicity

Biomarkers:

1. NGS: DNA/RNA tumor tissue
2. TROP2 IHC
3. PD-L1 IHC
4. TMB/MSI status
5. ctDNA in blood
6. Urine biomarker

ClinicalTrials.gov: NCT06524544
Study actively enrolling; 7/320 enrolled; 62 sites in process of activation as of April 2026

References & Acknowledgements

References:

1. Sacituzumab govitecan in metastatic urothelial carcinoma after platinum-based chemotherapy and checkpoint inhibitors (TROPHY-U-01): a multicohort, open-label, phase II study. J Clin Oncol.2021;39(22):2474-85.
2. Sacituzumab govitecan in advanced urothelial carcinoma: TROPiCS-04, a phase III randomized trial. Annals of Oncology. 2025.
3. Sacituzumab govitecan in combination with pembrolizumab for patients with metastatic urothelial cancer: results from TROPHY-U-01 cohort 3. Journal of Clinical Oncology. 2024;42(12):1415–25.
4. Pembrolizumab Retreatment in Patients with Advanced or Metastatic Urothelial Carcinoma Who Responded to First-course Pembrolizumab-based Therapy. European Urology. 2025;87(4):390–5.

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ECOG-ACRIN cancer research group

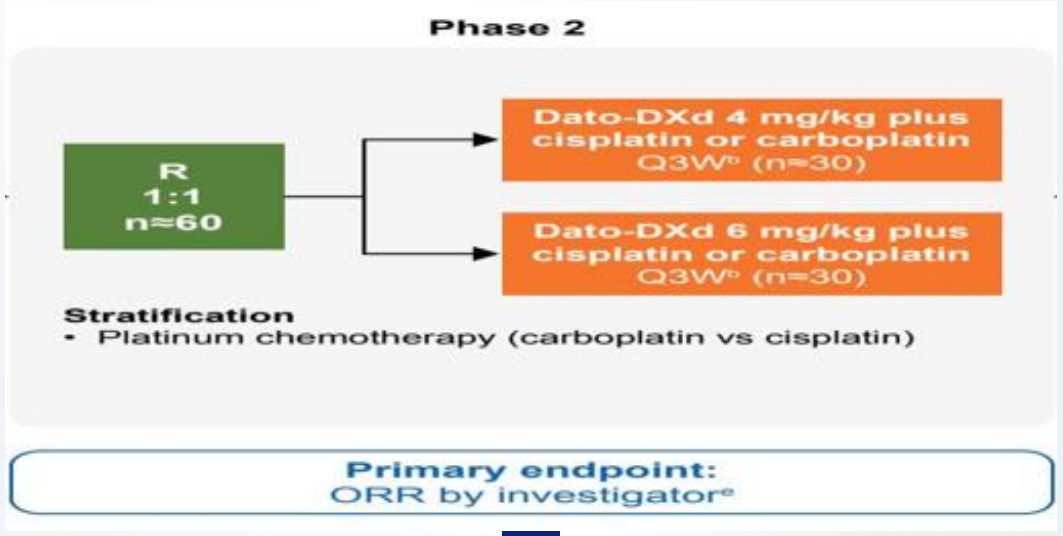
Winship PI: Dr. Jacqueline Brown

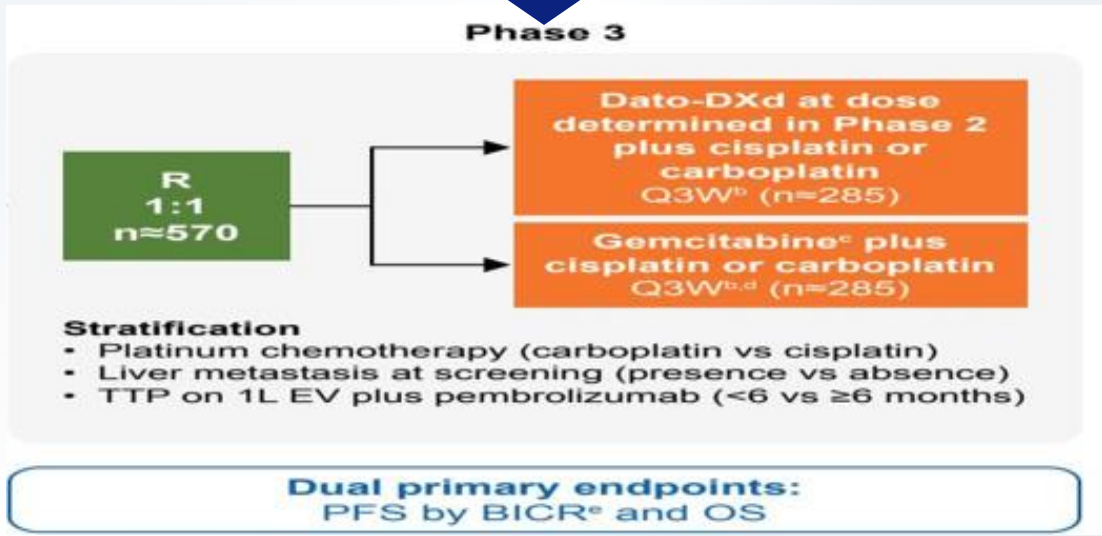
Joshi, M, et al. ASCO 2026. Trials in Progress

TROPION-Urothelial03: A phase 2/3 study of Trop 2 targeted datopotamab deruxtecan (Dato-DXd) + platinum chemotherapy (CT) vs gemcitabine + platinum CT

Key inclusion criteria

- Unresectable la/mUC
- Measurable disease on CT/MRI per RECIST 1.1[a]
- ≥18 years of age or minimum legal adult age
- Radiographic progression or relapse during or after 1L EV plus pembrolizumab
- Tumor tissue sample of sufficient quantity from archival or newly obtained tissue
- Eligible to receive cisplatin- or carboplatin-containing chemotherapy
- Eastern Cooperative Oncology Group performance status of 0 or 1

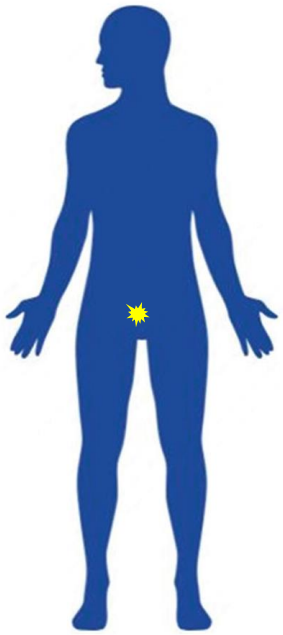




Galsky, M., et al. ASCO 2026. Trials in progress.

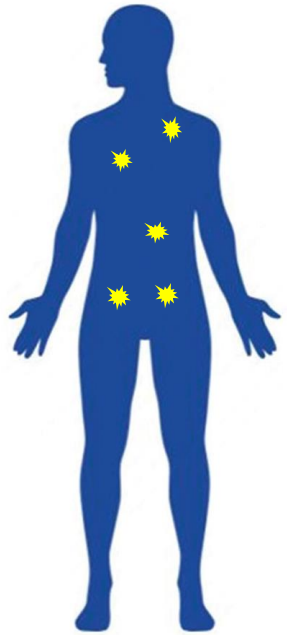
Evolving Treatment Algorithm for Urothelial Carcinoma

Muscle-Invasive



- **EV+ Pembro**

First-Line



Cisplatin-eligible

- **Cisplatin + gemcitabine**
- **Dose-dense methotrexate + vinblastine + doxorubicin + cisplatin (ddMVAC)**

Cisplatin-ineligible

- **Carboplatin + gemcitabine**

- Erdafitinib (tumor + FGFR 3 genetic alterations)
- Trastuzumab deruxtecan (if tumor Her2 2/3+)

Second-Line and Beyond

- Platinum based chemotherapy
- Erdafitinib (tumor + FGFR 3 genetic alterations)
- Trastuzumab deruxtecan (if tumor Paclitaxel, docetaxel, or vinflunine
- Clinical trial
- Her2 2/3+)
- ***Sacituzumab govitecan + GCSF

Apolo AB et al., Cancer 2025 Aug 15;131(16):e70020; Apolo, A, ASCO 2026

Take Home Points:

- EV + P continues to be standard 1st Line Agent in Metastatic UC
- EV + P now approved in perioperative setting, along with platinum therapies
- CT DNA role in postoperative care suggests increasing role in metastatic disease
- 2nd and subsequent line therapies will be patient specific and actionable
- Clinical trials remain necessary given unmet and ongoing need

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