Genitourinary Masterclass

ADCs and the LA/mUC treatment landscape

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EV as first-line therapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer. Combination therapy with pembrolizumab.

EV as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 or programmed death-ligand 1 inhibitor, and have received a platinum-containing chemotherapy

1L, first line; EV, enfortumab vedotin;
LA/mUC, locally advanced/metastatic urothelial carcinoma; P, pembrolizumab;
PD-1/L1, programmed cell death-1/ligand 1.
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Speaker disclosures

- I have provided scientific advice to: Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Johnson & Johnson Global Services, Merck KGaA, Merck Sharp & Dohme, Pfizer & Roche
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ADCs enable the targeted delivery of potent cytotoxic drugs into cancer cells

ADCs harness monoclonal antibodies that **specifically target tumor-associated antigens**, linked to a **cytotoxic payload** that can be delivered into cancer cells[1–3]

Key structural components of an ADC[2]

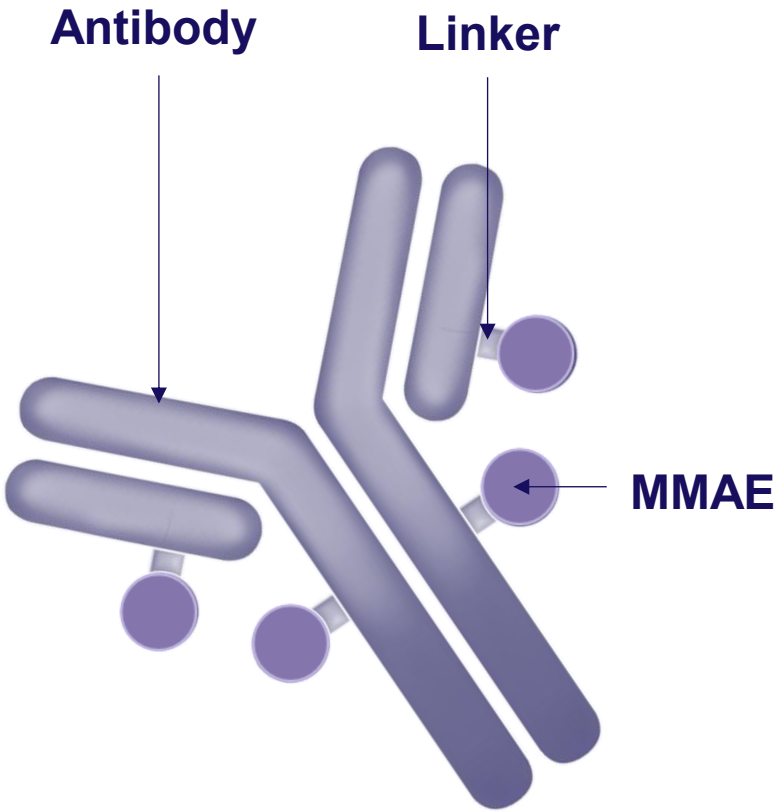


Image of EV antibody adapted from Jain N et al. 2015.[2]
ADC, antibody–drug conjugate.
1. Challita-Eid PM et al. *Cancer Res* 2016;76:3003–3013; 2. Jain N et al. *Pharm Res* 2015;32:3526–3540; 3. Hafeez U et al. *Molecules* 2020;25:4764.

ADCs may offer potential benefits vs. conventional chemotherapy

The **specificity of monoclonal antibodies** can be utilized to ensure targeted delivery of cytotoxic payloads to tumor cells, **improving the efficacy** of the payload[1]

By targeting antigens that are localized on the cell surface and highly expressed on tumor cells compared with healthy cells, ADCs may **limit the risk of off-target toxicities** vs. conventional chemotherapy, to which patients experience systemic exposure[1,2]

Key structural components of an ADC[2]

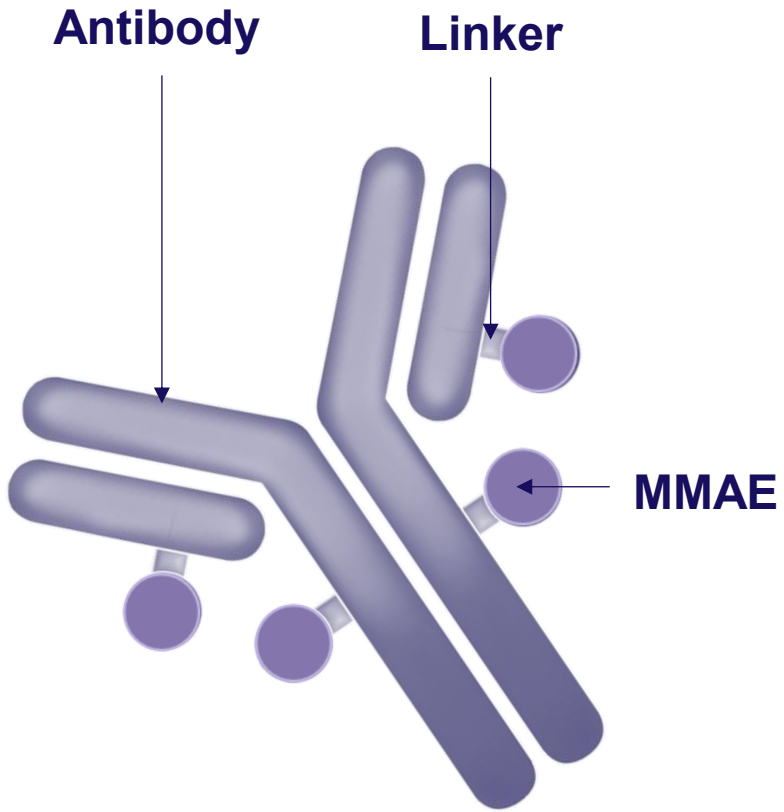
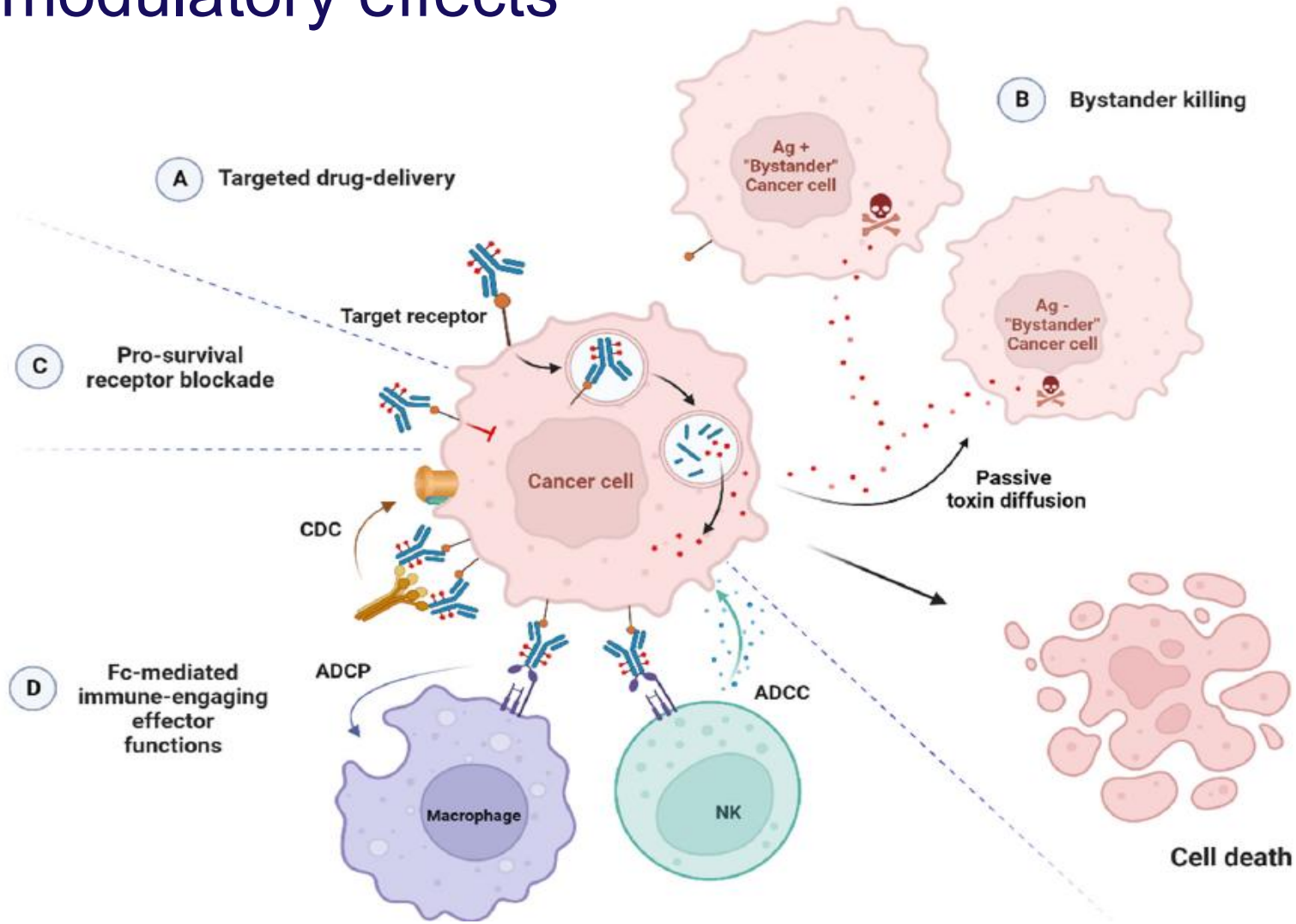


Image of EV antibody adapted from Jain N et al. 2015.[2]
ADC, antibody–drug conjugate.
1. Hafeez U et al. *Molecules* 2020;25:4764; 2. Jain N et al. *Pharm Res* 2015;32:3526–3540.

The mechanism of action of ADCs involves targeted immunomodulatory effects



Images reproduced from 'Antibody–Drug Conjugates: The Dynamic Evolution from Conventional to Next-Generation Constructs' Metrangolo V & Engelholm LH. *Cancers (Basel)* 2024;16:447.
Available at: https://www.mdpi.com/2072-6694/16/2/447. By CC: https://creativecommons.org/licenses/by-nc/4.0/
ADC, antibody–drug conjugate; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; Ag, antigen; CDC, complement-dependent cytotoxicity; Fc, fragment crystallizable; NK, natural killer.
Metrangolo V & Engelholm LH. *Cancers (Basel)* 2024;16:447.

There are many ADCs in clinical development for the treatment of solid tumors

Breast	Lung	GI	GU	Gynecologic	Brain	Solid tumors	Lymphoma	Myeloma	Acute leukemia
• **T-DM1** • **T-DXd** • Dato-DXd • LV • ***T-DM1*** • ***T-DXd*** • ***SG*** • *SGN-15* • *Dato-DXd* • *LV*	• SGN-15 • Teliso-V • Rova-T • ***SG*** • *Dato-DXd* • *T-DXd* • *AR*	• **T-DM1** • **T-DXd** • ***T-DXd*** • ***RC48*** • *AR*	• **RC48** • **SG** • **EV** • HuMax-TF • ***EV*** • ***SG*** • ***RC48*** • *T-DXd*	• MIRV • AR • HuMax-TF • *MIRV* • *ABT-414* • ***T-DXd*** • ***T-DM1*** • *HuMax-TF*	• ABT-414	• BMS-986148 • **SG** • *Rova-T* • ***SG*** • *AR* • ***T-DXd*** • *Teliso-V* • *HuMax-TF* • *Dato-DXd* • *LV*	• Brentuximab vedotin • Polatuzumab vedotin • *Brentuximab vedotin* • *Polatuzumab vedotin* • *Pinatuzumab vedotin*	• Belantamab vedotin • *Belantamab vedotin*	• Brentuximab vedotin • Gemtuzumab ozogamicin • *Gemtuzumab ozogamicin*

Italics indicate trials in progress

ADCs are a promising modality not only in UC, but also across multiple cancer types

Table adapted from Fuentes-Antrás J et al. 2023.[1]
ABT-414, depatuxizumab mafodotin; ADC, antibody–drug conjugate; AR, anetumab ravtansine; Dato-DXd, datopotamab deruxtecan; EV, enfortumab vedotin; GI, gastrointestinal; GU, genitourinary; HuMax-TF, tisotumab vedotin; LV, ladiratuzumab vedotin; MIRV, mirvetuximab soravtansine; RC48, disitamab vedotin; Rova-T, rovalpituzumab tesirine; SG, sacituzumab govitecan; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; Teliso-V, telisotuzumab vedotin; UC, urothelial carcinoma.

1. Fuentes-Antrás J et al. *Trends Cancer* 2023;9:339–354.

There are many ADCs in clinical development for the treatment of urothelial carcinoma [1/2]

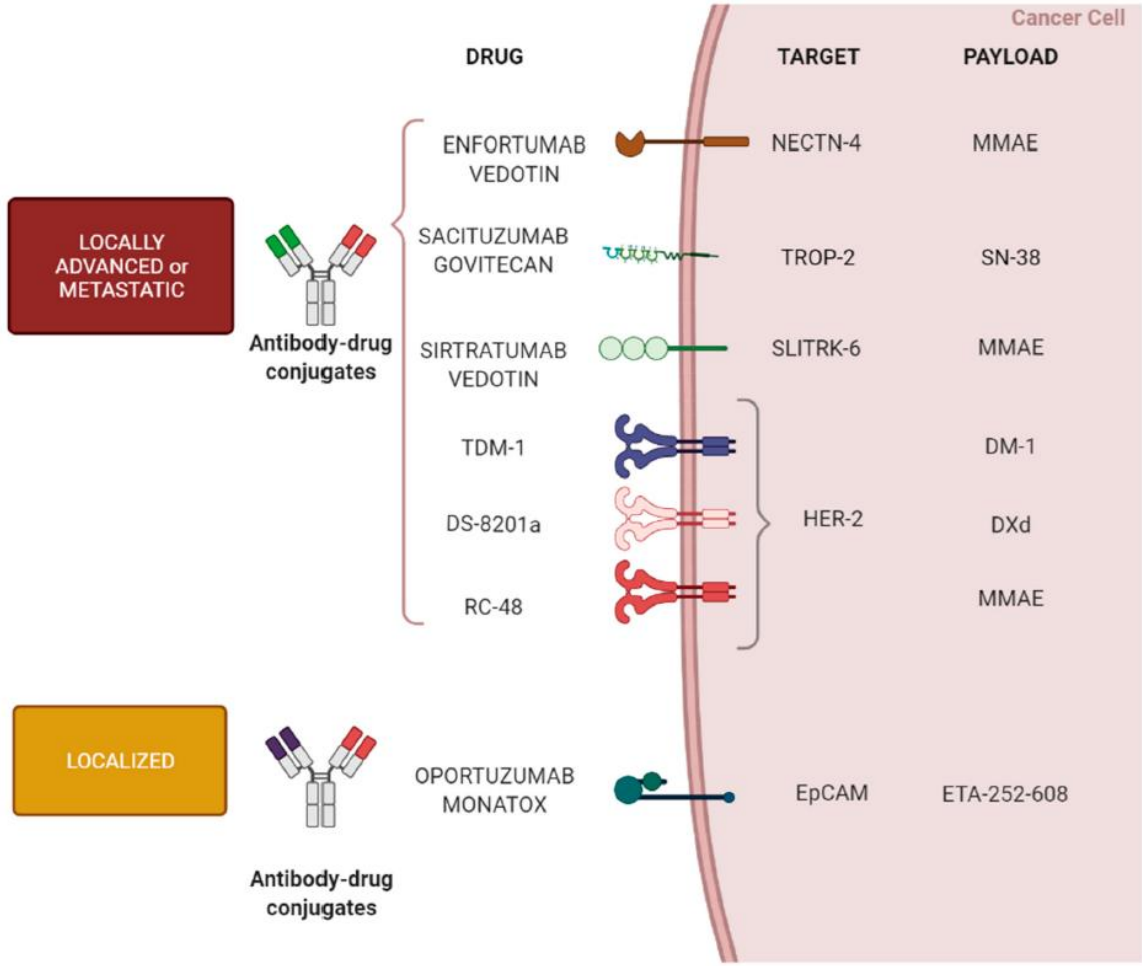


Figure 2. The main mechanisms of antibody drug conjugates investigated in urothelial carcinoma.

Images reproduced from 'Antibody-Drug Conjugates in Urothelial Carcinoma: A New Therapeutic Opportunity Moves from Bench to Bedside' Ungaro A et al. *Cells* 2022;11:803. Available at: https://www.mdpi.com/2073-4409/11/5/803. By CC: https://creativecommons.org/licenses/by-nc/4.0/.

ADC, antibody–drug conjugate; DM-1, emtansine; EpCAM, epithelial cell adhesion molecule; ETA, *Pseudomonas* aeruginosa exotoxin A; HER2, human epidermal growth factor receptor 2; MMAE, monomethyl auristatin E; RC48, disitamab vedotin; SLITRK6, SLIT and NTRK like family member 6; T-DM1, trastuzumab emtansine; TROP2, trophoblast cell surface antigen 2.

Ungaro A et al. *Cells* 2022;11:803.

There are many ADCs in clinical development for the treatment of urothelial carcinoma [2/2]

Clinical trial	Phase	Drug	Target antigen	Payload	Indication	Enrollment	Primary endpoint	Estimated completion date
NCT06483334	I/II	ST + EV ± P	ST: TROP2 EV: Nectin-4	SG: TOPO-1 EV: MMAE	Previously treated advanced UC	98	DLT, AE profile, ORR	Jul 2028
NCT05941507	I/II	LCB84 ± anti-PD-L1 Ab	TROP2	MMAE	Advanced solid tumors including UC	300	AE profile, RP2D, OS, ORR	May 2027
NCT05489211	II	Dato-DXd ± anticancer therapies	TROP2	TOPI inhibitor	Advanced solid tumors including UC	582	ORR, AE profile	Aug 2026
NCT05756559	II	EV + P	Nectin-4	MMAE	Advanced bladder cancer of variant histology	25	ORR	Dec 2027
NCT04879329	II	RC48 + P	HER2	MMAE	Previously treated advanced UC	332	AE profile, ORR, PK	Apr 2028
NCT06225596	II/III	BT8009-100* ± P vs. chemotherapy	Nectin-4	MMAE	Advanced solid tumors including UC	956	PFS, ORR	Dec 2030
NCT06524544	III	SG + P vs. SG	TROP2 (SG)	SN-38 (SG)	Previously treated advanced UC	384	OS	Dec 2028
NCT05302284	III	RC48 + toripalimab	HER2	MMAE	Treatment-naïve UC	452	PFS, OS	Apr 2028

There are further additional ADCs in development at various stages, including Phase I/Ib clinical trials

*Indicated bicycle therapy, which is not a conventional ADC.
Ab, antibody; ADC, antibody–drug conjugate; AE, adverse event; Dato-DXd, datopotamab deruxtecan; DLT, dose-limiting toxicity; EV, enfortumab vedotin; HER2, human epidermal growth factor receptor 2; MMAE, monomethyl auristatin E; ORR, objective response rate; OS, overall survival; P, pembrolizumab; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PK, pharmacokinetics; RC48, disitamab vedotin; RP2D, recommended Phase II dose; SG, sacituzumab govitecan; ST, sacituzumab tirumotecan; TOPI, topoisomerase I; TROP2, trophoblast cell surface antigen 2; UC, urothelial carcinoma.
Zarrabi KK et al. *Am Soc Clin Oncol Educ Book* 2025;45:e471924.

Particular ADCs of interest in the UC space: Sacituzumab govitecan

Sacituzumab govitecan[1]

Mechanism of action:
- Target: TROP2
- Payload: SN-38 (TOPI inhibitor)

Stage of clinical development: Phase III, approved in other solid tumors (e.g., breast)

TROPiCS-04 Phase III study[2]

Patients with:
- LA/mUC
- UT/LT tumors
- Progression within 12 months after PBCT and CPI or cisplatin only in (neo)adjuvant setting

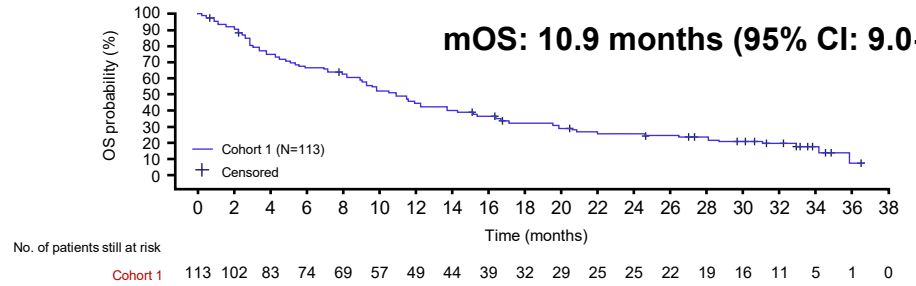
→ IV SG 10 mg/kg on D1 and D8, every 21 days

→ Treatment of physician's choice

SG did not meet the primary endpoint of OS in the ITT population[2]

TROPHY-U-01 Phase II Cohort 1:[3]

113 patients with LA/mUC who progressed after prior PBCT and a CPI, and received SG 10 mg/kg on D1 and D8, every 21 days



Endpoint	Cohort 1 (N=113)
Best overall response, n (%)	
CR	6 (5%)
PR	26 (23%)
SD	38 (34%)
PD	21 (19%)
NE	8 (7%)
Not assessed*	15 (13%)
ORR,† n (%) [95% CI]	31 (27%) [19–37]
Clinical benefit rate,‡ n (%) [95% CI]	42 (37%) [28–47]

*These patients have no post baseline radiologic tumor assessments; †Primary endpoint: CR+PR; ‡CR+PR+SD ≥6 months.
ADC, antibody–drug conjugate; CI, confidence interval; CPI, checkpoint inhibitor; CR, complete response; D, Day; ITT, intention-to-treat; IV, intravenous; LA/mUC, locally advanced/metastatic urothelial carcinoma; LT, lower tract; mOS, median overall survival; ORR, objective response rate; OS, overall survival; NE, not evaluable; PBCT, platinum-based chemotherapy; PD, progressive disease; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; TOPI, topoisomerase I; TROP2, trophoblast cell surface antigen 2; UC, urothelial carcinoma; UT, upper tract.

1. Trodelvy (sacituzumab govitecan). Summary of Product Characteristics; 2. Powles T, et al. *Ann Oncol* 2025;36:561–571; 3. Tagawa ST, et al. *J Clin Oncol* 2021 39:2474–2485.

Particular ADCs of interest in the UC space: Trastuzumab deruxtecan [1/2]

Trastuzumab deruxtecan[1]

Mechanism of action:

- Target: HER2
- Payload: DXd (TOPI inhibitor)

Stage of clinical development: Phase III, approved in other solid tumors (e.g., breast, NSCLC, gastric)

Open-label, multicenter, multicohort, Phase II study (DESTINY-PanTumor02)[2]

- Patients with previously treated HER2-expressing solid tumors
- Treatment: T-DXd 5.4 mg/kg IV Q3W (n=40 per cohort)
- Primary endpoint: Confirmed ORR
- Secondary endpoints: DOR, DCR, PFS, OS, safety and tolerability
- Exploratory: Subgroup analyses by: HER2 status and biomarkers

Characteristic*[2]		Bladder cancer (n=41)
Age, years	Median (range)	67.0 (43–85)
Race, n (%)	White	25 (61.0%)
	Asian	16 (39.0%)
ECOG PS, n (%)	0	19 (46.3%)
	1	22 (53.7%)
HER2 status by enrollment test, n (%)	IHC 3+	27 (65.9%)
	IHC 2+	14 (34.1%)
HER2 status by central testing, n (%)	IHC 3+	16 (39.0%)
	IHC 2+	20 (48.8%)
	IHC 1+	2 (4.9%)
	IHC 0	2 (4.9%)
	IHC unknown	1 (2.4%)
Number of prior regimens	Median (range)	2 (0–9%)
Prior regimens, n (%)	≤1	14 (34.1%)
	≥2	27 (65.9%)

*This table is a revised version of the original table to focus only on bladder cancer.

ADC, antibody–drug conjugate; DCR, disease control rate; DOR, duration of response; DXd, deruxtecan; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; TOPI, topoisomerase I; UC, urothelial carcinoma.

1. ENHERTU® (trastuzumab deruxtecan). Summary of Product Characteristics; 2. Meric-Bernstam F, et al. *J Clin Oncol* 2023;42:47–58.

Particular ADCs of interest in the UC space: Trastuzumab deruxtecan [2/2]

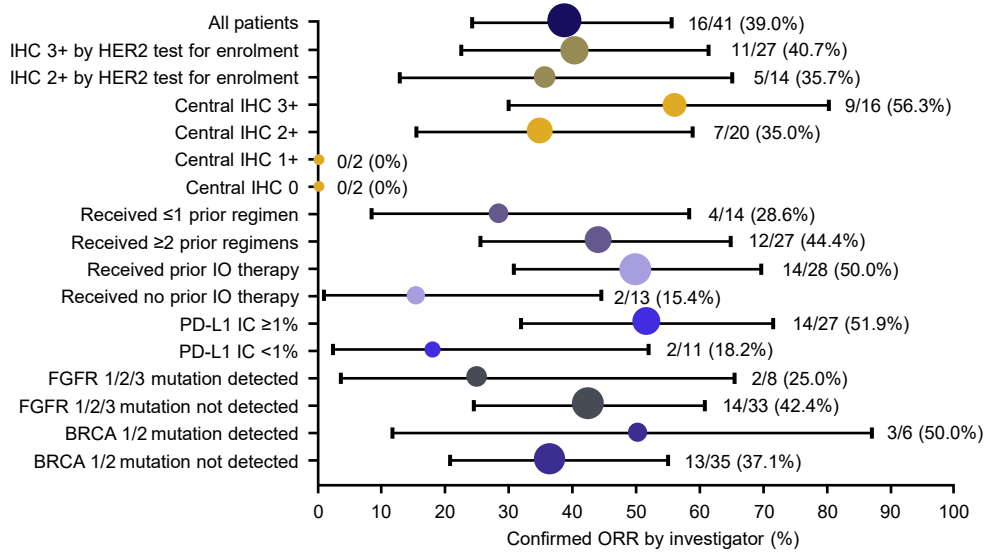
Trastuzumab deruxtecan[1]

Mechanism of action:

- Target: HER2
- Payload: DXd (TOPI inhibitor)

Stage of clinical development: Phase III, approved in other solid tumors (e.g., breast, NSCLC, gastric)

ORR (95% CI) in all patients and by subgroups



Characteristic	All patients	HER2 IHC 3+	HER2 IHC 2+	HER2 IHC 1+	HER2 IHC 0
n	41	16	20	2	2
Confirmed ORR, n (%) [95% CI]	16 (39.0%) [24.2–55.5]	9 (56.3%) [29.9–80.2]	7 (35.0%) [15.4–59.2]	0	0
Median DOR, months (95% CI)	8.7 (4.3–11.8)	8.7 (2.8–10.6)	10.3 (4.3–17.8)	-	-
Median PFS, months (95% CI)	7.0 (4.2–9.7)	7.4 (3.0–11.9)	7.8 (2.6–11.6)	5.5 (4.0–NE)	2.6 (1.0–NE)
Median OS, months (95% CI)	12.8 (11.2–15.1)	13.4 (6.7–19.8)	13.1 (11.0–19.9)	9.1 (4.8–NE)	3.0 (1.0–NE)
DCR at 12 weeks, % (95% CI)	70.7 (54.4–83.9)	75.0 (47.6–92.7)	70.0 (45.7–88.1)	100 (15.8–100)	50.0 (1.3–98.7)

ADC, antibody–drug conjugate; BRCA, breast cancer gene; CI, confidence interval; DCR, disease control rate; DOR, duration of response; DXd, deruxtecan; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; IC, immune cell; IHC, immunohistochemistry; IO, immunotherapy; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; TOPI, topoisomerase I; UC, urothelial carcinoma.

1. ENHERTU® (trastuzumab deruxtecan). Summary of Product Characteristics; 2. Wysocki PJ et al. *J Clin Oncol* 2024;42(Suppl 16):Abstract 4565.

Particular ADCs of interest in the UC space: Disitamab vedotin (RC48)

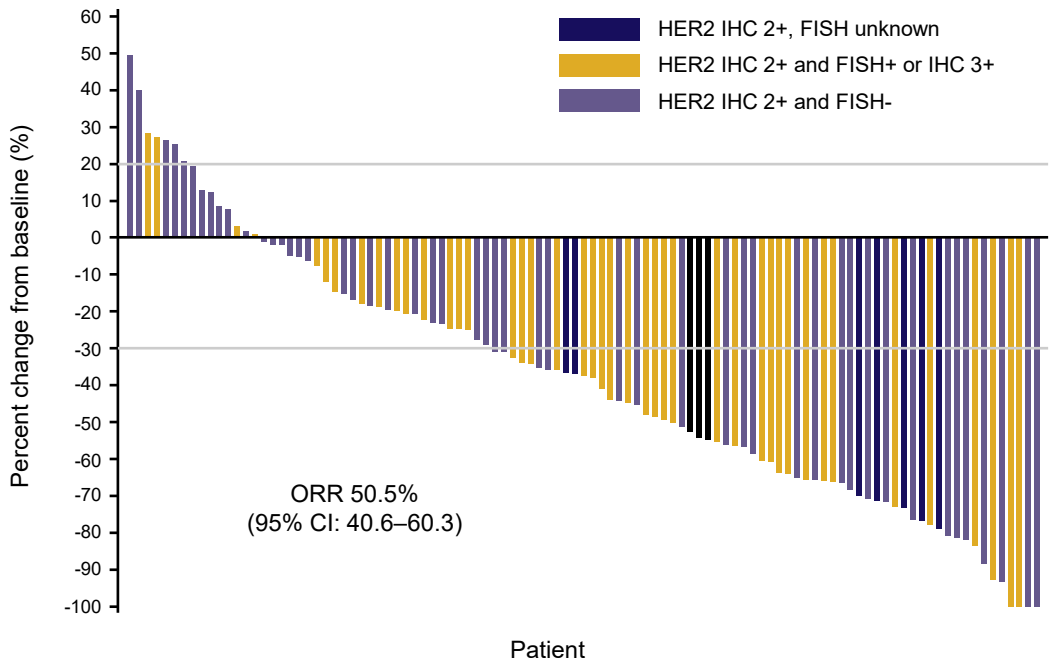
Disitamab vedotin[1,2]

Mechanism of action:
- Target: HER2
- Payload: MMAE

Stage of clinical development: Phase II studies, approved for use in LA/mUC in China, and in other solid tumors

Combined analysis of Phase II, open-label, multicenter single-arm studies (RC48-C005 & RC48-C009)[2]
- Unresectable, LA/mUC
- HER2 IHC 2+ or 3+
- Prior treatment with systemic chemotherapy
- Dosing: IV, 2 mg/kg every 2 weeks

Objective response rate[2]



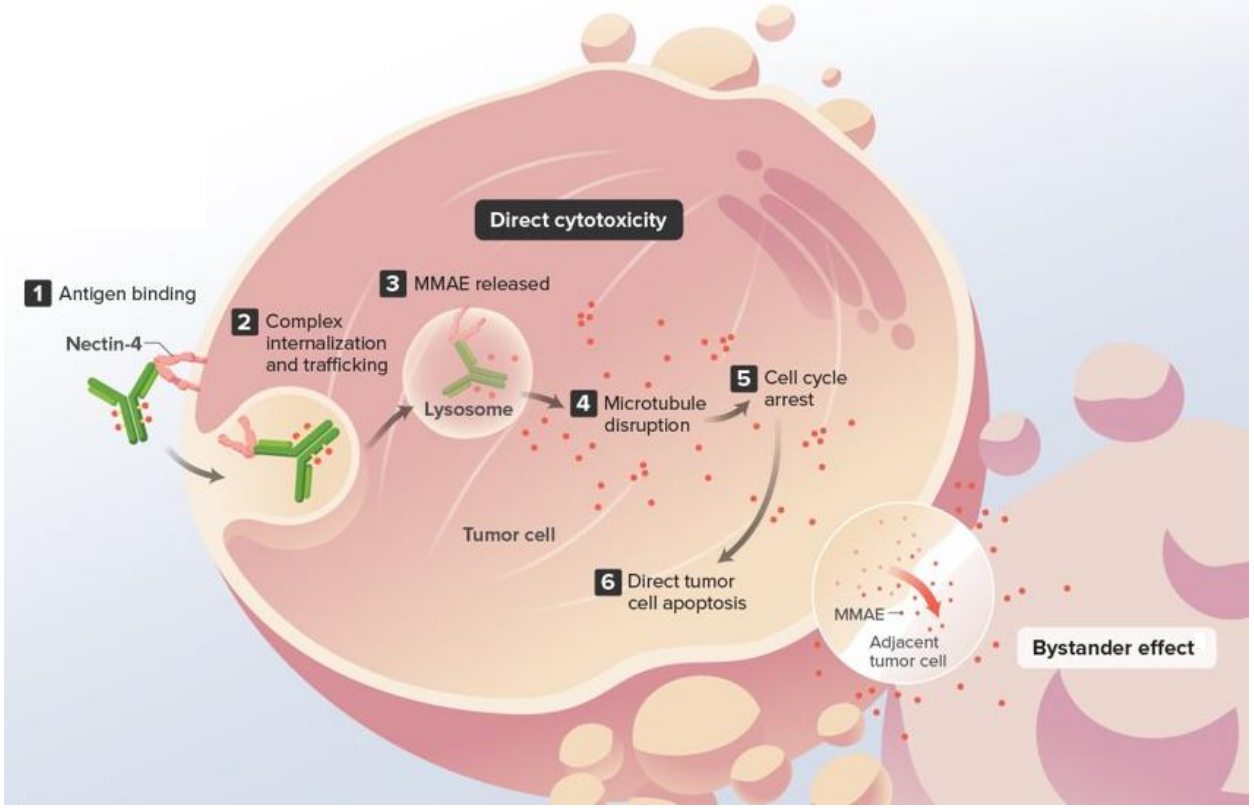
PFS[2]	
Median, months (95% CI)	5.9 (4.3–7.2)
12-month rate, % (95% CI)	24.7 (16.5–33.7)

OS[2]		Confirmed ORR, % (95% CI)[2]	
Median, months (95% CI)	14.2 (9.7–18.8)	**IHC 2+ and FISH+ or IHC 3+**	62.2% (46.5–76.2)*
18-month rate, % (95% CI)	42.2 (32.5–51.5)	**IHC 2+ and FISH−**	39.6% (26.5–54.0)*
OS follow-up, months, median	20.5	**IHC 2+ and FISH unknown**	55.6% (21.2–86.3)*

*There is no statistical difference among the three subgroups for RC48-C005, RC48-C09 and overall pooled population with p=0.441, p=0.1649 and p=0.0798, respectively.[2]
ADC, antibody–drug conjugate; CI, confidence interval; FISH, fluorescence *in situ* hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IV, intravenous; LA/mUC, locally advanced/metastatic urothelial carcinoma; MMAE, monomethyl auristatin E; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; UC, urothelial carcinoma.
1. Wang D et al. *BMC Cancer* 2025;25:812; 2. Sheng X et al. *J Clin Oncol* 2024;42:1391–1402.

EV is an ADC that delivers a cytotoxic payload into UC cells via Nectin-4[1]

- **EV** is an **ADC** consisting of a **Nectin-4–targeting** fully human monoclonal **antibody** attached to the cytotoxic drug **MMAE** via a **linker**[1,2]
- By **specifically targeting Nectin-4**, **EV** may **minimize** the risk of **off-target toxicities compared with conventional chemotherapy**[2,3]
  - **Moderate-to-strong Nectin-4 expression** is observed in a range of **UC subtypes**, whereas the expression of Nectin-4 in **normal tissue** is more **limited**[1]
- **Biomarker testing is not required for administration of EV**[1,4,5]



ADC, antibody–drug conjugate; EV, enfortumab vedotin; MMAE, monomethyl auristatin E; UC, urothelial carcinoma.

1. Challita-Eid PM et al. *Cancer Res* 2016;76:3003–3013; 2. Jain RK et al. *Cancer Manag Res* 2020;12:8379–8386; 3. Hafeez U et al. *Molecules* 2020;25:4764; 4. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics; 5. Powles T et al. *Ann Oncol* 2022;33:244–258; 6 Seagen. Enfortumab vedotin. Available at: https://www.seagen.com/science/pipeline/enfortumab-vedotin. Last accessed: January 2023.

EV was the first ADC to be approved for the treatment of LA/mUC and is now used globally

Approved indications for EV[1]

- As **monotherapy** for the treatment of adult patients with LA/mUC who have previously received a platinum-containing chemotherapy and a PD-1/L1 inhibitor
- In **combination** with pembrolizumab for the 1L treatment of adult patients with unresectable or mUC who are eligible for platinum-containing chemotherapy

Approvals were based on the EV-301 and EV-302 trials[2,3]

- In **EV-301**, the efficacy and safety of EV vs. PBCT were assessed in patients with LA/mUC who were previously treated with PBCT and a PD-1/L1 inhibitor
- In **EV-302**, the efficacy and safety of EV+P vs. PBCT were assessed in previously untreated patients with advanced mUC

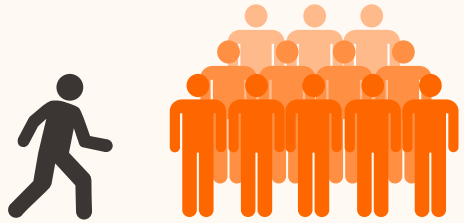
Disclaimer: Approval status may vary by country/region. All HCPs should refer to their own country's specific Prescribing Information.

1L, first-line; ADC, antibody–drug conjugate; EV, enfortumab vedotin; HCP, healthcare professional; LA/mUC, locally advanced/metastatic urothelial carcinoma; mUC, metastatic urothelial carcinoma; P, pembrolizumab; PBCT, platinum-based chemotherapy; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1.

1. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics; 2. Powles T et al. *N Engl J Med* 2021;384:1125–1135; 3. Powles T et al. *N Engl J Med* 2024;390:875–888.

EV-301 compared the efficacy and safety of EV with chemotherapy in patients with previously treated LA/mUC

An international, open-label, randomised Phase III study



Adult patients with unresectable LA/mUC (N=608)

- ECOG PS 0 or 1
- Disease progression during or after PD-1/L1 inhibitor treatment
- Prior platinum-based chemotherapy*

R† 1:1

EV (n=301)
1.25 mg/kg 30-minute IV infusion on Days 1, 8, and 15 of a 28-day cycle

Investigator-chosen chemotherapy (n=307)**
Either of the following as an IV infusion on Day 1 of a 21-day cycle:
- Docetaxel 75 mg/m^2 over 1 hour (n=117)
- Paclitaxel 175 mg/m^2 over 3 hours (n=112)
- Vinflunine‡ 320 mg/m^2 over 20 minutes (n=78)

Until radiological disease progression or other treatment discontinuation criteria are met

Primary endpoint
- OS

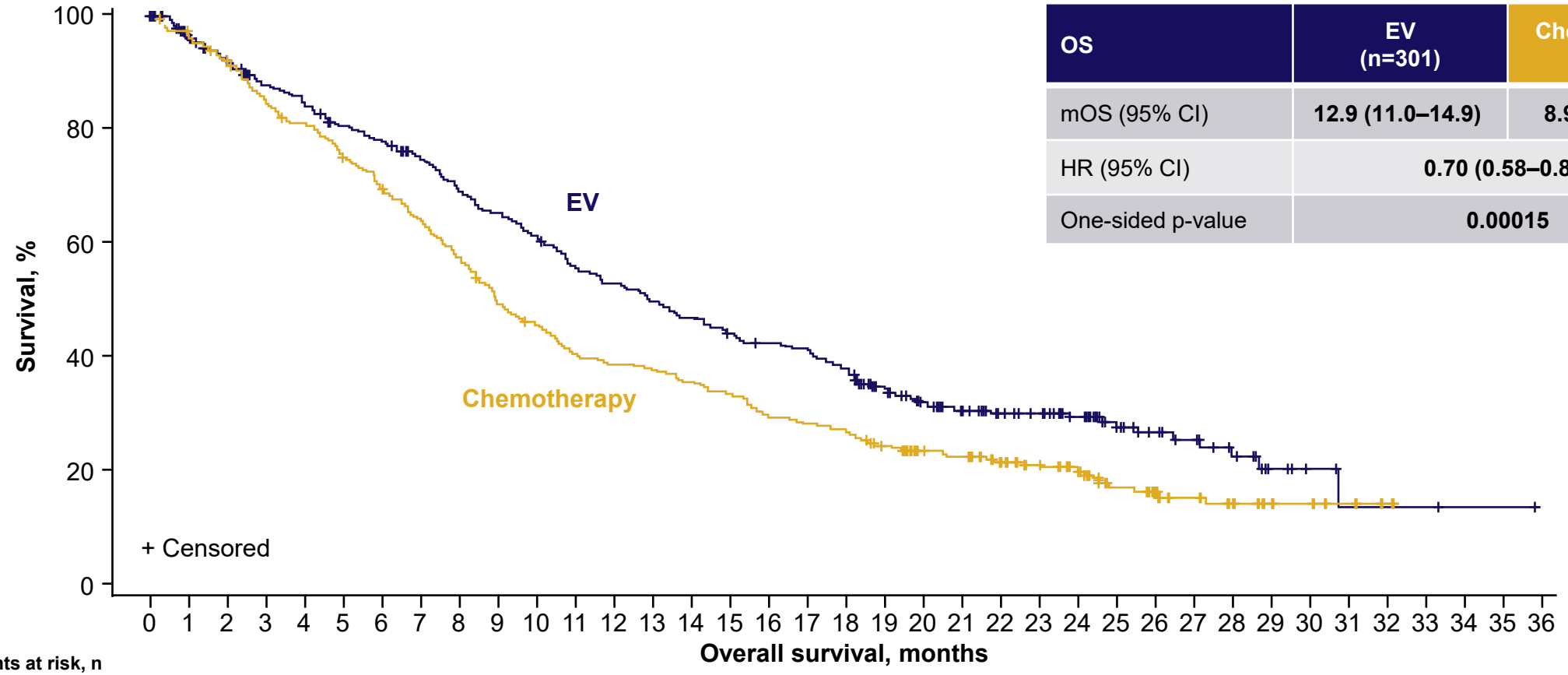
Secondary endpoints
- PFS ††
- ORR ††
- DCR ††
- CRR ††
- DOR ††
- QoL
- PROs
- Safety and tolerability

A pre-specified interim analysis was performed after 65% of patients had died. The results of the interim analysis were published in 2021 after a median follow-up of 11.1 months and are presented herein. Trial met superiority threshold at the time of interim analysis

*In EV-301 for patients who had received platinum chemotherapy as neoadjuvant or adjuvant therapy, progression must have occurred within 12 months after completion of treatment. †Stratification variables were ECOG PS (0 or 1), geographic region (USA, Western Europe, or rest of the world), and presence of liver metastasis; ‡Regimen selected by the investigator before randomisation;
**The use of vinflunine was limited to 35% of patients in the trial and was an option only in regions where it was approved for the treatment of UC; ††According to RECIST v1.1.
CRR, complete response rate; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; IV, intravenous; LA/mUC, locally advanced/metastatic urothelial carcinoma; ORR, overall response rate; OS, overall survival; PD-1/L1, programmed cell death protein 1/ligand 1; PFS, progression-free survival; PRO, patient-reported outcome; QoL, quality of life; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours.
Powles T et al. *N Engl J Med* 2021;384:1125–1135.

At a median follow-up of 24 months, the risk of death was reduced by 30% with EV vs. chemotherapy

24-month OS analysis*



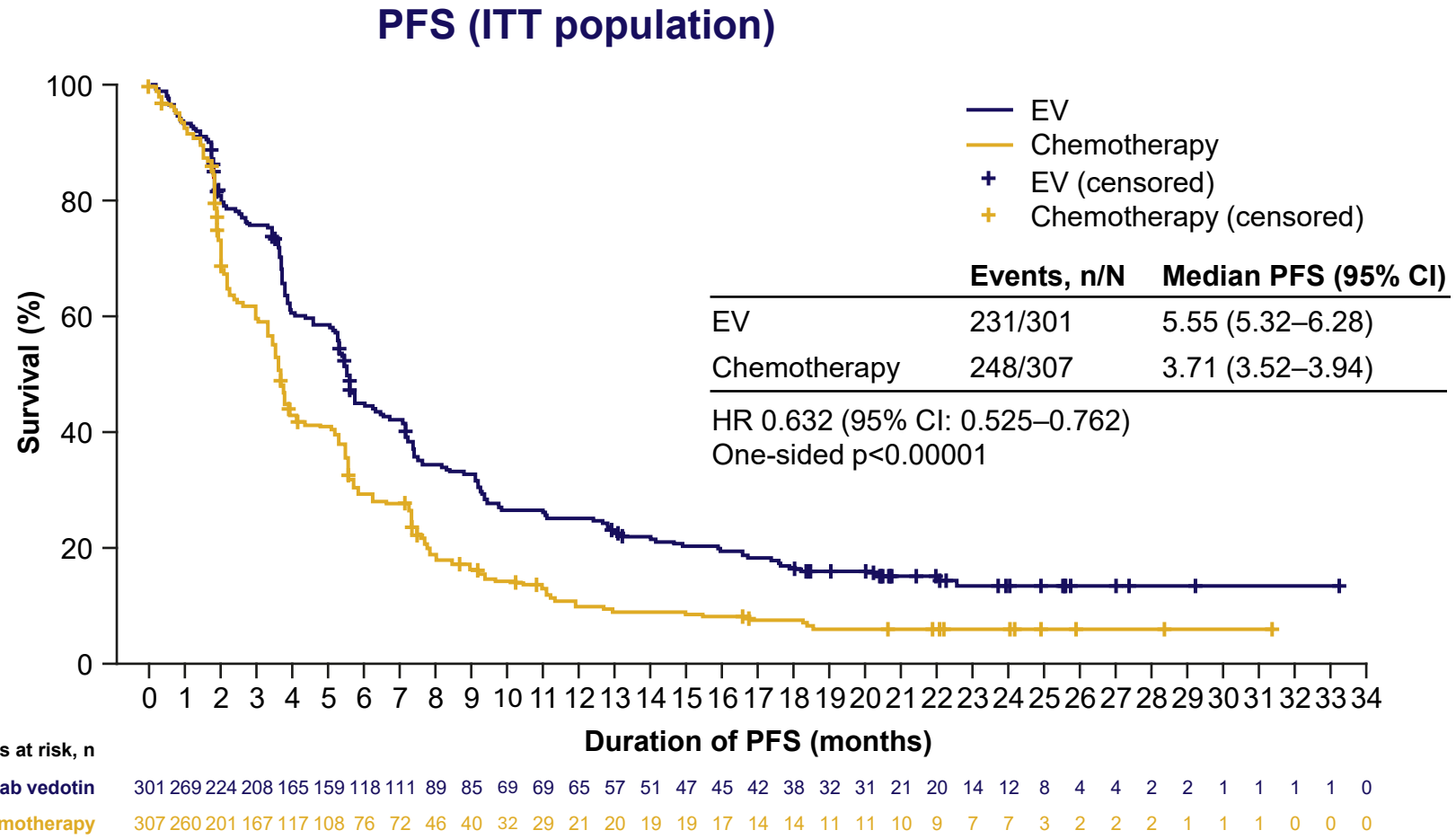
OS	EV (n=301)	Chemotherapy (n=307)
mOS (95% CI)	**12.9 (11.0–14.9)**	**8.9 (8.3–10.3)**
HR (95% CI)	**0.70 (0.58–0.85)**	
One-sided p-value	**0.00015**	

Patients at risk, n

EV	301	286	272	257	246	234	226	213	197	186	174	159	150	141	133	124	118	115	106	86	73	63	55	50	41	31	24	20	14	7	4	2	2	2	1	1	0
Chemotherapy	307	288	274	250	238	219	203	186	168	142	132	116	111	108	102	96	85	81	78	65	58	54	46	40	32	22	17	13	10	6	5	3	1	0	0	0	0

*This was an exploratory analysis. The study met threshold for superiority at time of interim analysis.
CI, confidence interval; EV, enfortumab vedotin; HR, hazard ratio; mOS, median overall survival; OS, overall survival.
Rosenberg JE et al. *Ann Oncol* 2023;13:1047–1054.

At a median follow-up of 24 months, the risk of progression or death was significantly reduced with EV by 37% compared with chemotherapy



CI, confidence interval; EV, enfortumab vedotin; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival.
Rosenberg JE et al. *Ann Oncol* 2023;13:1047–1054.

TRAE rates at 24 months in the EV and chemotherapy groups were consistent with the interim analysis

TRAEs, n (%)*	EV group (n=296)†		Chemotherapy group (n=291)†	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	278 (93.9)	155 (52.4)	267 (91.8)	147 (50.5)
Alopecia	135 (45.6)	NR	108 (37.1)	NR
Peripheral sensory neuropathy	103 (34.8)	15 (5.1)	63 (21.6)	6 (2.1)
Pruritus	96 (32.4)	4 (1.4)	14 (4.8)	1 (0.3)
Fatigue	93 (31.4)	20 (6.8)	66 (22.7)	13 (4.5)
Decreased appetite	92 (31.1)	9 (3.0)	69 (23.7)	5 (1.7)
Diarrhea	74 (25.0)	10 (3.4)	49 (16.8)	5 (1.7)
Dysgeusia	73 (24.7)	NR	22 (7.6)	NR
Nausea	71 (24.0)	3 (1.0)	64 (22.0)	4 (1.4)
Maculopapular rash	50 (16.9)	22 (7.4)	5 (1.7)	0
Anemia	34 (11.5)	8 (2.7)	63 (21.6)	23 (7.9)
Decreased neutrophil count	31 (10.5)	18 (6.1)	51 (17.5)	41 (14.1)
Neutropenia	20 (6.8)	14 (4.7)	25 (8.6)	18 (6.2)
Decreased white cell count	15 (5.1)	4 (1.4)	32 (11.0)	21 (7.2)
Febrile neutropenia	2 (0.7)	2 (0.7)	16 (5.5)	16 (5.5)

Disclaimer: PADCEV (enfortumab vedotin) can cause severe skin reactions, including Stevens–Johnson syndrome and toxic epidermal necrolysis (predominantly during the first cycle of treatment).

*Occurring in ≥20% of patients in either treatment group or Grade ≥3 TRAEs occurring in ≥5% of patients in either treatment group; †Safety population.

AE, adverse event; EV, enfortumab vedotin; NR, not reported; TRAE, treatment-related adverse event.

Rosenberg JE et al. *Ann Oncol* 2023;13:1047–1054.

Summary

ADCs are an **exciting new class of treatment** for solid tumors[1,2]

ADCs have both **cytotoxic** and **immunomodulatory** effects[3]

Many ADCs are being investigated both in **monotherapy** and **combination** for the treatment of UC[1]

EV was the **first ADC to be approved** for the treatment of LA/mUC, based on efficacy and safety vs. platinum-based ChT as demonstrated in Phase III clinical trials, and is now used globally[4–6]

ADC, antibody–drug conjugate; ChT, chemotherapy; EV, enfortumab vedotin; LA/mUC, locally advanced/metastatic urothelial carcinoma; UC, urothelial carcinoma.

1. Fuentes-Antrás J et al. *Trends Cancer* 2023;9:339–354; 2. Speaker's own opinion; 3. Nicolò E et al. *Cancer Treat Rev* 2022;106:102395; 4. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics; 5. Powles T et al. *N Engl J Med* 2021;384:1125–1135; 6. Powles T et al. *N Engl J Med* 2024;390:875–888.

Genitourinary Masterclass

astellas

Please refer to the Korean PI for PADCEV® (enfortumab vedotin) via the following link or QR Code:

<PADCEV 20mg>

<PADCEV 30mg>

Astellas Pharma Korea., Inc.
(7F Parnas tower, 521, Teheran-ro, Gangnam-gu, Seoul, Republic of Korea)

PI, Prescribing Information

Genitourinary Masterclass

What is the optimal sequence of treatment for metastatic urothelial carcinoma

Professor Daniel Petrylak

Director of Genitourinary Oncology, Yale University Cancer Center, New Haven, USA

EV as first-line therapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer. Combination therapy with pembrolizumab.

EV as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 or programmed death-ligand 1 inhibitor, and have received a platinum-containing chemotherapy

EV, enfortumab vedotin.
PADCEV® (enfortumab vedotin). Prescribing Information

Adverse events should be reported.
For Korea, healthcare professionals are asked to report any suspected adverse reactions to Astellas Pharma Korea. Inc
(Telephone: +82 10 5254 3389; Email: safety-kr@kr.astellas.com)

PADCEV®
enfortumab vedotin
Injection for IV infusion 20 mg & 30 mg vials

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Prescribing information is available at the end of this presentation. This promotional meeting is fully sponsored and supported by Astellas, including speaker-related honoraria and production of materials. It is intended for healthcare professionals only.

July 2025 | MAT-KR-PAD-2025-00062

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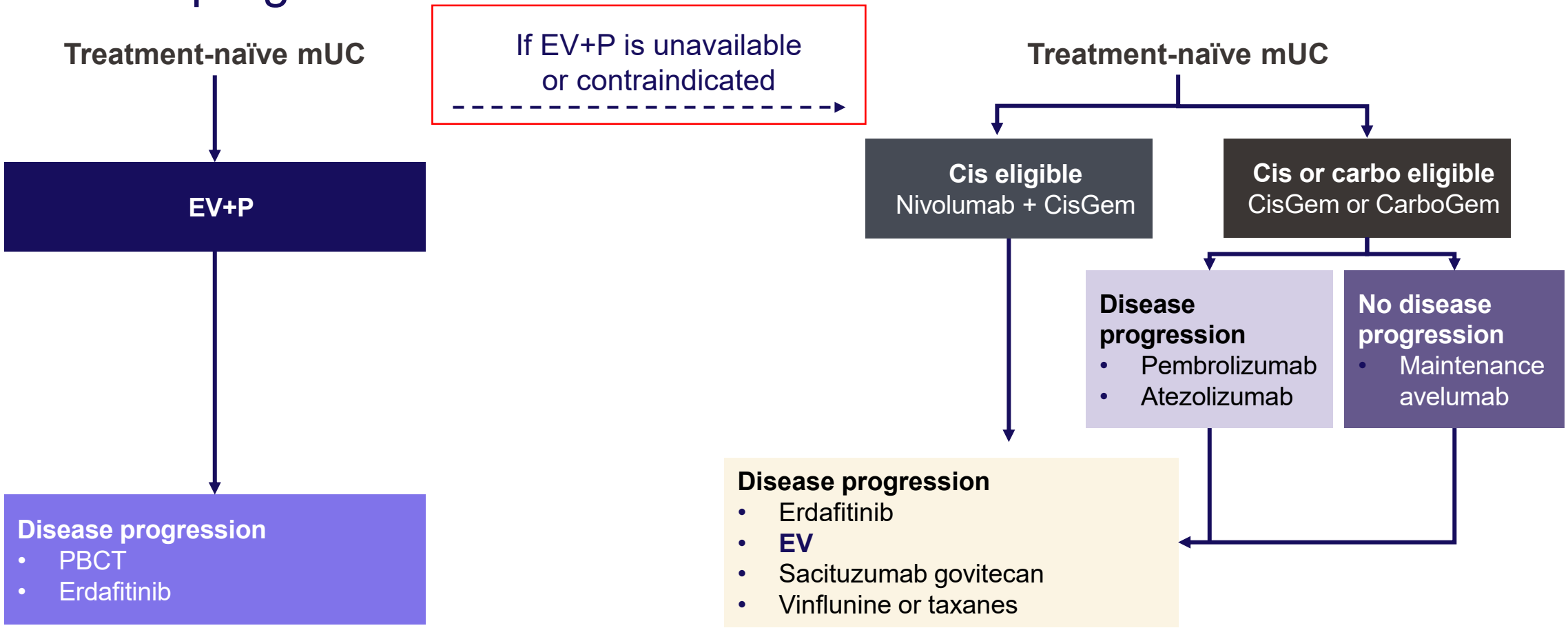
Such information, views and opinions of the presenter do not necessarily reflect the information, views and opinions of Astellas Pharma Ltd. Astellas Pharma Ltd does not recommend the use of any product in any different manner than as described in the local approval information, and complies with all applicable laws, regulations, and company policies.

Disclosures

Consulting Fees: Abbie vie, Exelixis, Corbus, Bicycle Therapeutics, Merck, Astellas, Bristol Myers, Jonhson and Jonhson, Pfizer, Novartis, Gilead, Flare Therapeutics

Research Support: Novartis, Bicycle Therapeutics, Amgen, Corbus, Arvinas, Gilead, Bioexcel, Genetech, Flare Therapeutics

In 2L, EV monotherapy is recommended by the ESMO clinical guidelines treatment of unresectable/mUC following disease progression



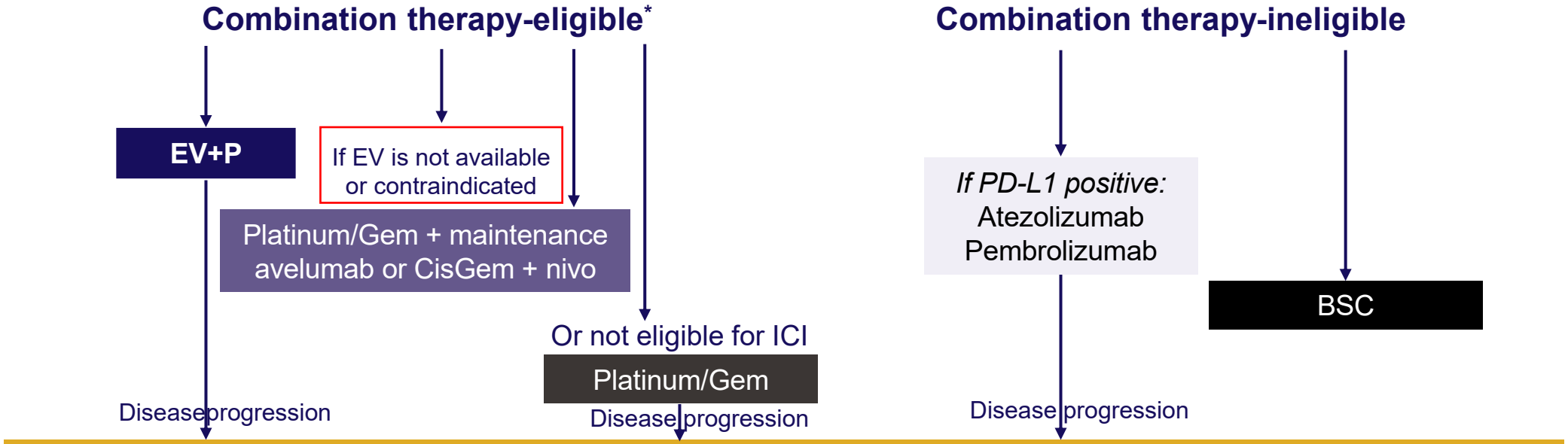
Disclaimer: EV+P is not approved for the 1L treatment of unresectable or mUC in adults in some countries/regions. All HCPs should refer to their own country's specific Prescribing Information.

Figure adapted from Powles T et al. 2024.

1L, first line; Carbo; carboplatin; Cis, cisplatin; ESMO, European Society for Medical Oncology; EV, enfortumab vedotin; Gem, gemcitabine; HCP, healthcare professional; m, metastatic; P, pembrolizumab; PBCT, platinum-based chemotherapy; UC, urothelial carcinoma.

Powles T et al. *Ann Oncol* 2024;35:485–490.

In 2L, EV monotherapy is recommended by the EAU clinical guidelines for the treatment of unresectable/mUC



Later-line therapy options

Pretreated with EV and ICI
- PBCT
- Erdafitinib if FGFR positive
- Sacituzumab govitecan
- Single agent chemotherapy
- Trials

Pretreated with platinum +/- ICI
- EV
- Erdafitinib if FGFR positive
- ICI
- Platinum/Gem
- Sacituzumab govitecan
- Single agent chemotherapy
- Trials

Pretreated with single agent
- EV†
- Erdafitinib if FGFR positive
- ICI
- Sacituzumab govitecan
- Chemotherapy
- Trials

Disclaimer: EV+P is not approved for the 1L treatment of unresectable or metastatic UC in adults in some countries/regions. All HCPs should refer to their own country's specific Prescribing Information.

Figure adapted from 2024 EAU Muscle-invasive and metastatic bladder cancer Guidelines.

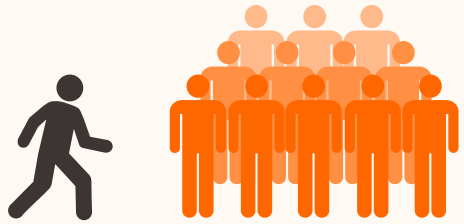
*PS 0-2, GFR > 30 ml/min, adequate rogan functions, for cisplatin: GFR > 50 ml/min; †The indication for enfortumab vedotin monotherapy as per the SmPC requires patients to have previously received a platinum-containing chemotherapy and a PD-1/-L1 inhibitor.

1L, first line; BSC, best supportive care; Carbo; carboplatin; Cis, cisplatin; EAU, European Association of Urology; EV, enfortumab vedotin; HCP, healthcare professional; ICI, immune checkpoint inhibitor; Gem, gemcitabine; m, metastatic; P, pembrolizumab; PBCT, platinum-based chemotherapy; PD-L1, programmed death-ligand 1; UC, urothelial carcinoma.

EAU. Muscle-invasive and metastatic bladder cancer. Available at: https://www.uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer. Last accessed: June 2025.

Phase 3 EV-301 trial: Study design

An international, open-label, randomised Phase III study



Adult patients with unresectable LA/mUC (N=608)

- ECOG PS 0 or 1
- Disease progression during or after PD-1/L1 inhibitor treatment
- Prior platinum-based chemotherapy*

R† 1:1

EV (n=301)
1.25 mg/kg 30-minute IV infusion on Days 1, 8, and 15 of a 28-day cycle

Investigator-chosen chemotherapy (n=307)**
Either of the following as an IV infusion on Day 1 of a 21-day cycle:
- Docetaxel 75 mg/m^2 over 1 hour (n=117)
- Paclitaxel 175 mg/m^2 over 3 hours (n=112)
- Vinflunine‡ 320 mg/m^2 over 20 minutes (n=78)

Until radiological disease progression or other treatment discontinuation criteria are met

Radiologic assessment of tumor response status was performed at baseline and every 8 weeks

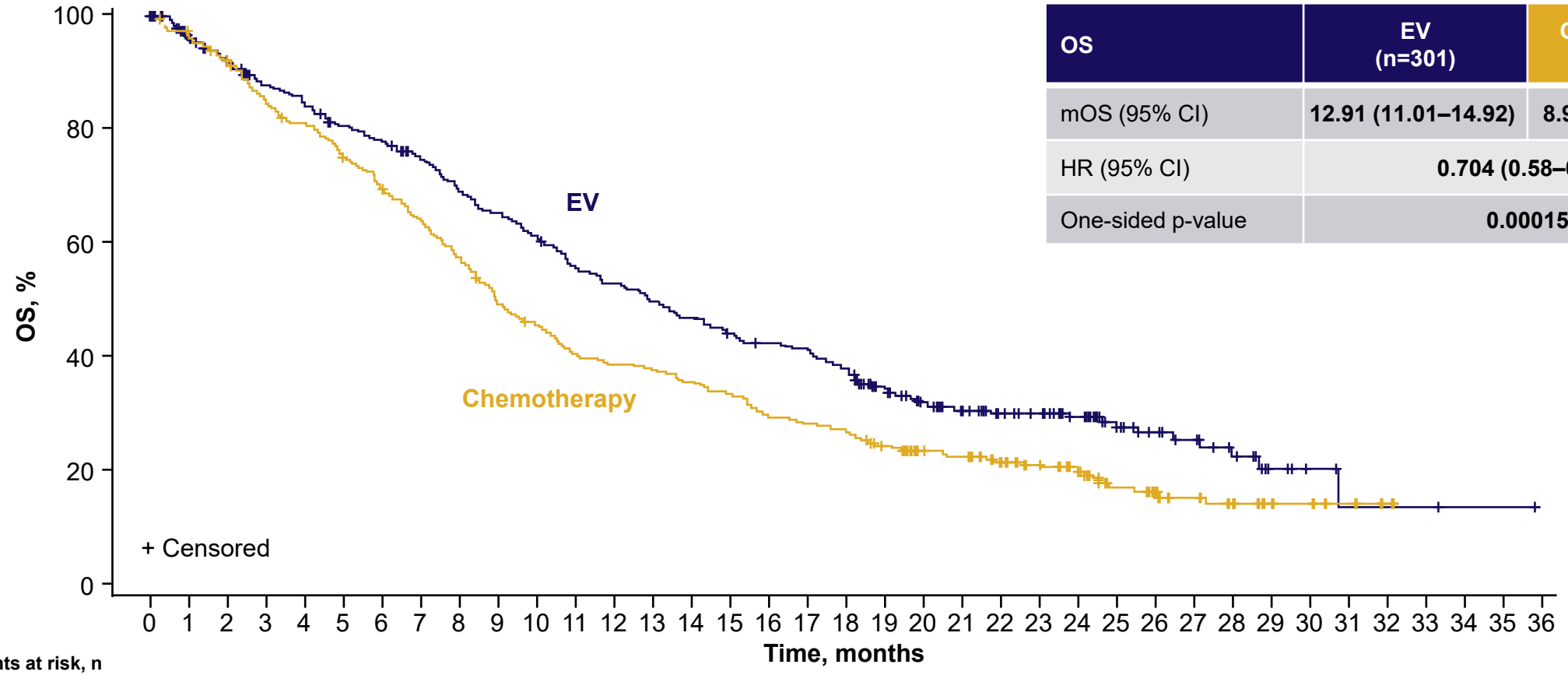
Primary endpoint
- OS

Secondary endpoints
- PFS ††
- ORR ††
- DCR ††
- CRR ††
- DOR ††
- QoL
- PROs
- Safety and tolerability

*In EV-301 for patients who had received platinum chemotherapy as neoadjuvant or adjuvant therapy, progression must have occurred within 12 months after completion of treatment. †Stratification variables were ECOG PS (0 or 1), geographic region (USA, Western Europe, or rest of the world), and presence of liver metastasis; ‡Regimen selected by the investigator before randomisation;
**The use of vinflunine was limited to 35% of patients in the trial and was an option only in regions where it was approved for the treatment of UC; ††According to RECIST v1.1.
CRR, complete response rate; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; IV, intravenous; LA/mUC, locally advanced/metastatic urothelial carcinoma; ORR, overall response rate; OS, overall survival; PD-1/L1, programmed cell death protein 1/ligand 1; PFS, progression-free survival; PRO, patient-reported outcome; QoL, quality of life; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours. Powles T et al. N Engl J Med 2021;384:1125–1135.

EV-301: Overall survival (primary endpoint)

24-month OS analysis*



OS	EV (n=301)	Chemotherapy (n=307)
mOS (95% CI)	**12.91 (11.01–14.92)**	**8.94 (8.25–10.325)**
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Patients at risk, n

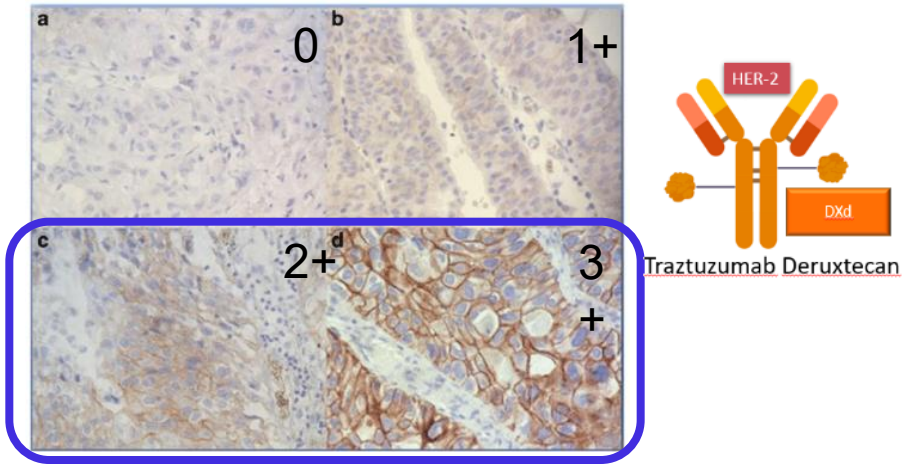
EV	301	286	272	257	246	234	226	213	197	186	174	159	150	141	133	124	118	115	106	86	73	63	55	50	41	31	24	20	14	7	4	2	2	2	1	1	0
Chemotherapy	307	288	274	250	238	219	203	186	168	142	132	116	111	108	102	96	85	81	78	65	58	54	46	40	32	22	17	13	10	6	5	3	1	0	0	0	0

*This was an exploratory analysis. The study met threshold for superiority at time of interim analysis.
CI, confidence interval; EV, enfortumab vedotin; HR, hazard ratio; mOS, median overall survival; OS, overall survival.
Rosenberg JE et al. *Ann Oncol* 2023;13:1047–1054.

Biomarker-directed options

HER2: Trastuzumab deruxtecan[1,2]

- Requires IHC testing (2+/3+)
- IHC 3+: 12% incidence in UC



Traztuzumab Deruxtecan

FGFR3: Erdafitinib[3]

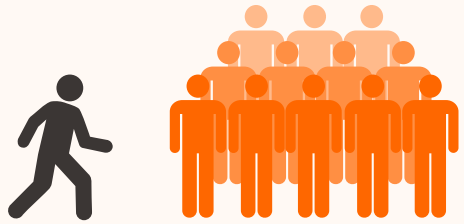
- Must have a susceptible FGFR3 mutation (R248C, S249C, G370C, or Y373C) or fusion (TACC3_V1, TACC3_V3, or BAIAP2L1)
- ~20% incidence in advanced UC

Images reproduced from 'Expression of human epidermal growth factor receptor 2 in bladder urothelial carcinoma' El Ochi MR, et al. *BMC Clin Pathol*. 2017;17:3. Available at: https://bmcclinpathol.biomedcentral.com/articles/10.1186/s12907-017-0046-z. By CC: https://creativecommons.org/licenses/by-nc/4.0/

DXd, deruxtecan; FGFR, fibroblast growth factor receptor; IHC, immunohistochemistry; UC, urothelial carcinoma.

1. El Ochi MR, et al. *BMC Clin Pathol.* 2017;17:3; 2. Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42:47–58; 3. Loriot Y, et al. *N Engl J Med*. 2023;389(21):1961-1971.

DESTINY-PanTumor02: Study Design



- Advanced solid tumors not eligible for curative therapy
- 2L patient population
- HER2 (IHC 3+ or 2+)
- Receipt of prior HER2-targeting agents allowed
- ECOG PS 0–1

T-DXd
5.4 mg/kg Q3W

n≈40
per cohort planned

- Cervical cancer
- Endometrial cancer
- Ovarian cancer
- Biliary tract cancer
- Pancreatic cancer
- Bladder cancer
- Other tumors

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

Primary endpoint

- Confirmed ORR (investigator)

Secondary endpoints

- DOR
- DCR
- PFS
- OS
- Safety

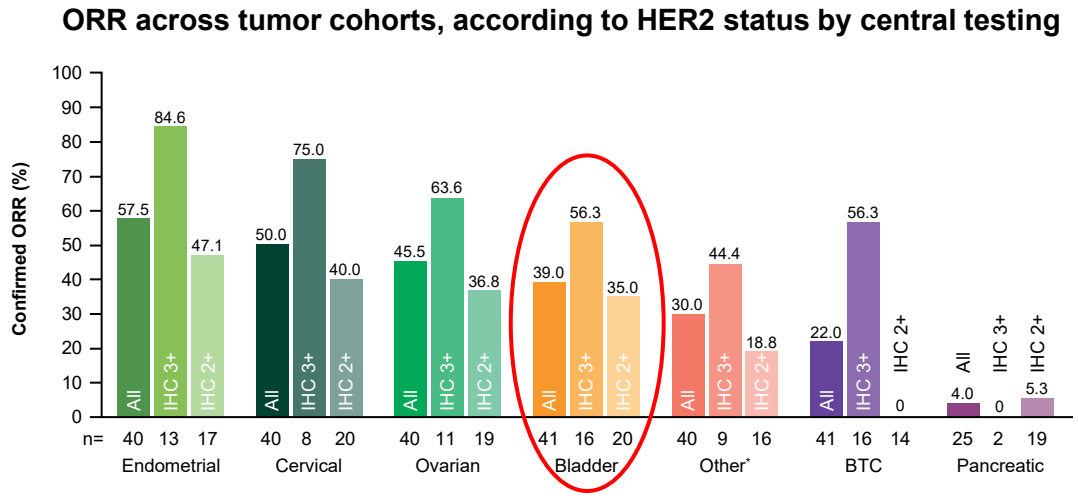
Data cut-off for analysis:

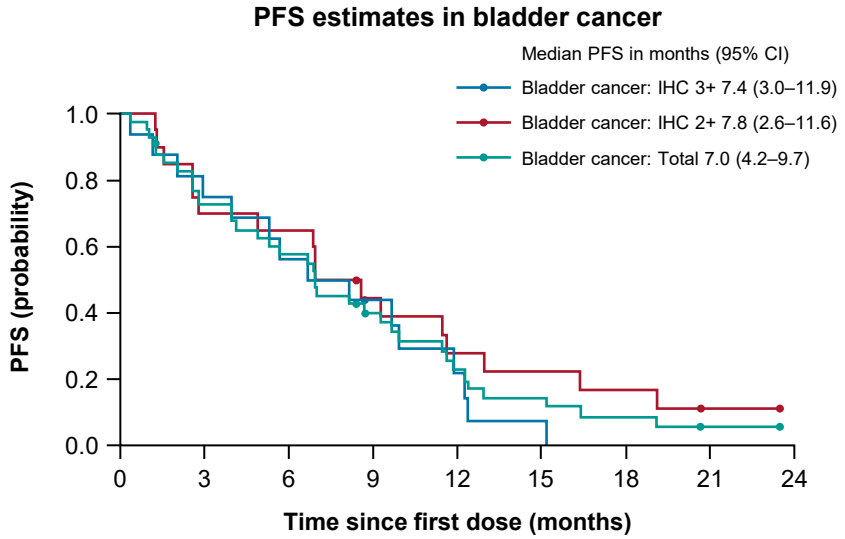
- June 8, 2023

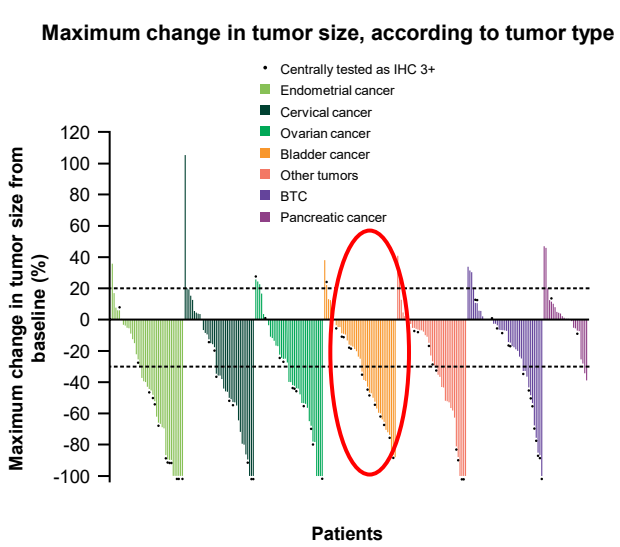
2L, second-line; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.

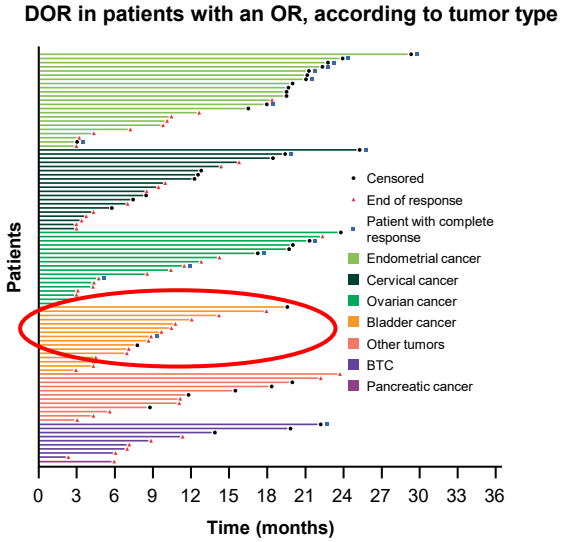
Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42(1):47-58.

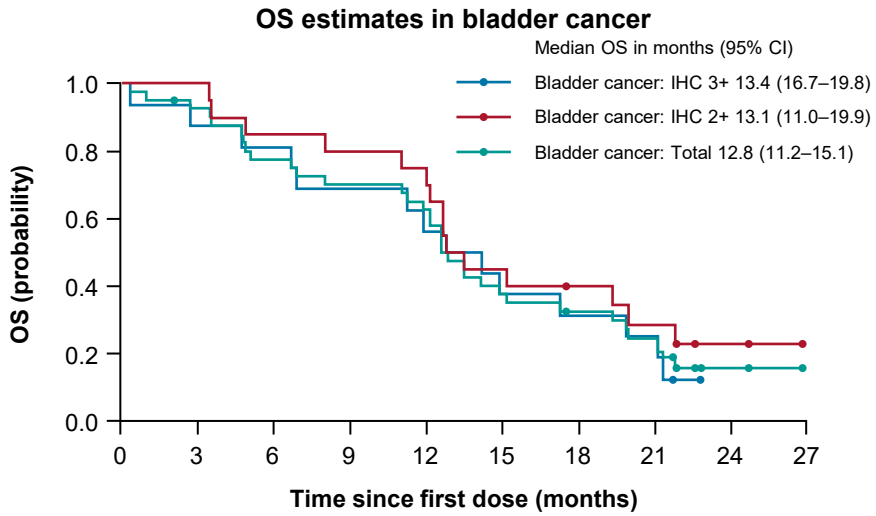
DESTINY-PanTumor02: Efficacy in bladder cancer







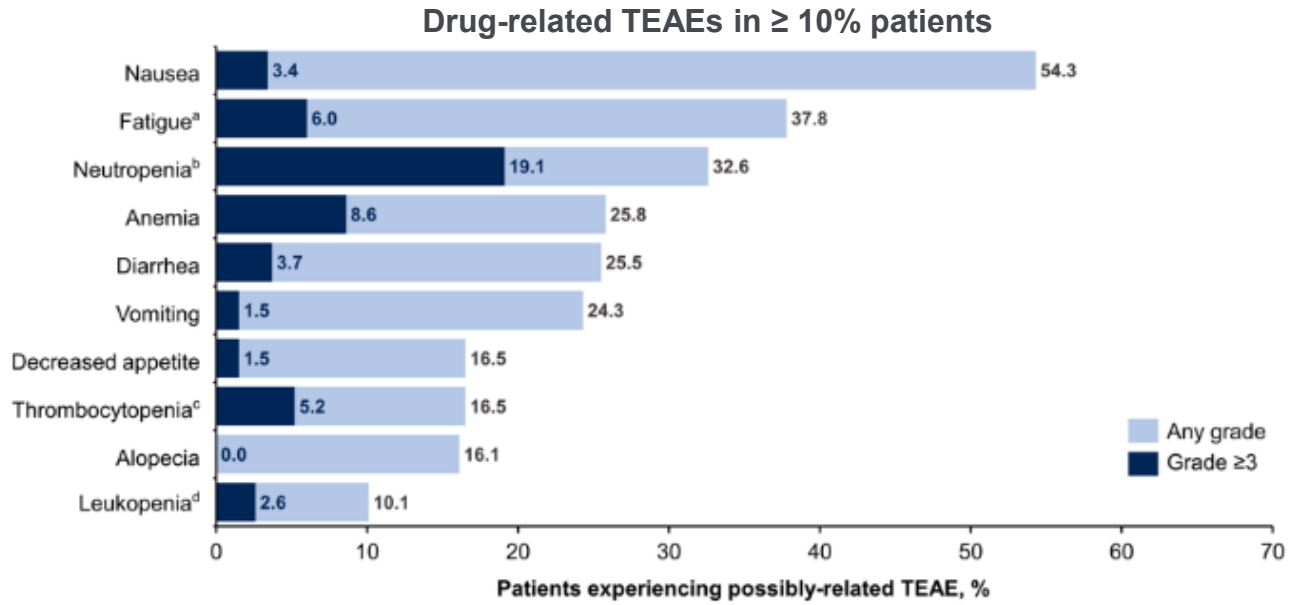




*Responses in the other tumors cohort include responses in extramammary Paget disease, oropharyngeal neoplasm, head and neck cancer, and salivary gland cancer
BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; IHC, immunohistochemistry; OR, objective response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42(1):47-58.

DESTINY-PanTumor02: Safety

Overall safety summary	All patients, n (%) N=267
Any drug-related TEAEs	225 (84.3)
Drug-related TEAEs Grade ≥3	103 (38.6)
Serious drug-related TEAEs	32 (12.0)
Drug-related TEAEs associated with dose discontinuations	22 (8.2)
Drug-related TEAEs associated with dose interruptions	49 (18.4)
Drug-related TEAEs associated with dose reductions	50 (18.7)
Drug-related TEAEs associated with deaths	2 (0.7)*



ILD/pneumonitis adjudicated as T-DXd related	
Grade	All patients, n (%) n = 267
1	6 (2.2)
2	12 (4.5)
3	1 (0.4)
4	0
5	1 (0.4)
Any	20 (7.5)

Left ventricular dysfunction	
Grade	All patients, n (%) n = 267
1	1 (0.4)
2	4 (4.5)
3	1 (0.4)
4	0
5	0
Any	7 (2.6)

*Occurred in one patient.
TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan
Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42(1):47-58.

DESTINY-PanTumor01: ORR

- Phase 2 global basket study
- Patients with advanced solid tumors harboring prespecified HER2 mutations
- Progressed on previous systemic therapy
- Trastuzumab deruxtecan 5.4 mg/kg Q3W
- Primary endpoint: ORR by central review

	N	ORR by IQR	
		N	%
All patients	102	30	29.4
Tumor type			
Breast	20	10	50.0
Colorectal	20	4	20.0
Biliary tract	19	2	10.5
Esophageal/esophagogastric	11	1	9.1
Urothelial	7	2	28.6
Salivary gland/head and neck AC	6	4	66.7
Small intestinal AC	5	0	-
Cervical	3	2	66.7
Endometrial	2	2	100
Other neuroendocrine	2	1	50.0
Pancreatic	2	0	-
AC of unknown primary origin	1	1	100
Extramammary Paget's disease	1	1	100
Melanoma	1	0	0
Ovarian	1	0	0
Urachal	1	0	0
***HER2*m domain**			
Tyrosine kinase	52	19	36.5
Extracellular	34	10	29.4
Transmembrane/juxtamembrane	17	1	5.9

HER2, human epidermal growth factor receptor; IQR, interquartile range; ORR, overall response rate; Q3W, every 3 weeks.

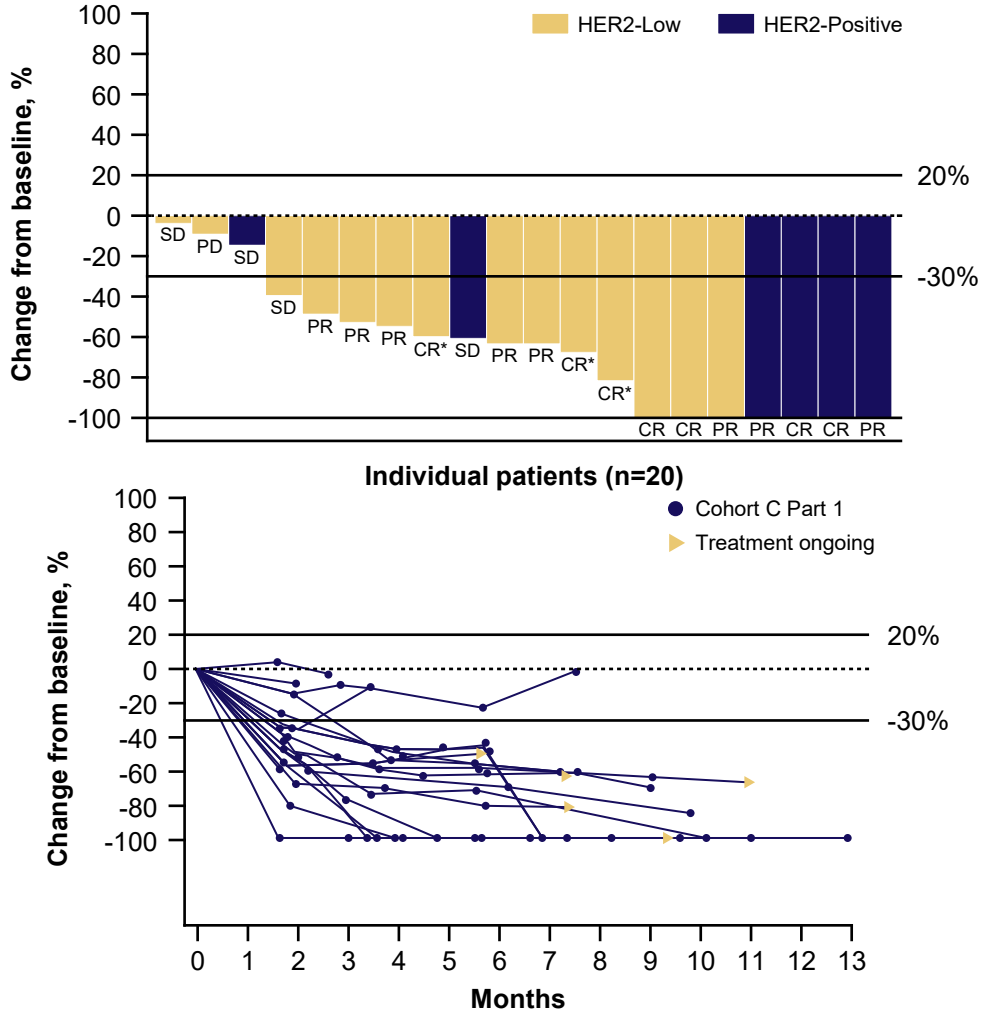
Li BT, et al. *Lancet Oncol*. 2024;25:707–719.

Phase 2 trial of disitamab vedotin + pembrolizumab in treatment-naïve HER2-expressing aUC: Cohort C

Baseline characteristic	Cohort C N=20
Male, n %)	15 (75.0)
Age (years), median (range)	75.0 (58–86)
White, n (%)	17 (85.0)
ECOG PS, n (%) 0 1	 8 (40.0) 12 (60.0)
HER2 status, n (%) HER2-positive (IHC 3+ or IHC 2+ and ISH-positive) HER2-low (IHC 2+and ISH-negative or IHC 1+)	 6 (30.0) 14 (70.0)
PD-L1 status, n (%) CPS ≥10 CPS <10	18 (90.0) 8 (40.0) 10 (50.0)
Primary tumour location, n (%) Bladder Renal pelvis Ureter	 12 (60.0) 6 (30.0) 2 (10.0)
Metastatic disease sites, n (%) Visceral disease Liver Lymph-node only disease	 15 (75.0) 4 (20.0) 4 (20.0)

Patient disposition and exposure	Cohort C N=20
Median follow up (months), median (range)	9.0 (4–16)
Median number of doses for DV (Q2W), range	7.5 (3–18)
Median number of doses for P (Q2W), range	3.5 (1–11)
Patients on treatment, n (%)	6 (30.0)
Patients off treatment, n (%)	14 (70.0)
Patients off study, n (%)	5 (25.0)

Overall population	Cohort C N=20
Confirmed ORR, n (%)	15 (75.0) [95% CI: 50.9–91.3]
Best overall response, n (%) Complete response Partial response Stable disease Progressive disease	 7 (35.0) 8 (40.0) 4 (20.0) 1 (5.0)
HER2 positive group	**n=6**
Confirmed ORR, n (%)	4 (66.7) [95% CI: 22.3–95.7]
HER2 positive group	**n=14**
Confirmed ORR, n (%)	11 (78.6) [95% CI: 49.2–95.3]



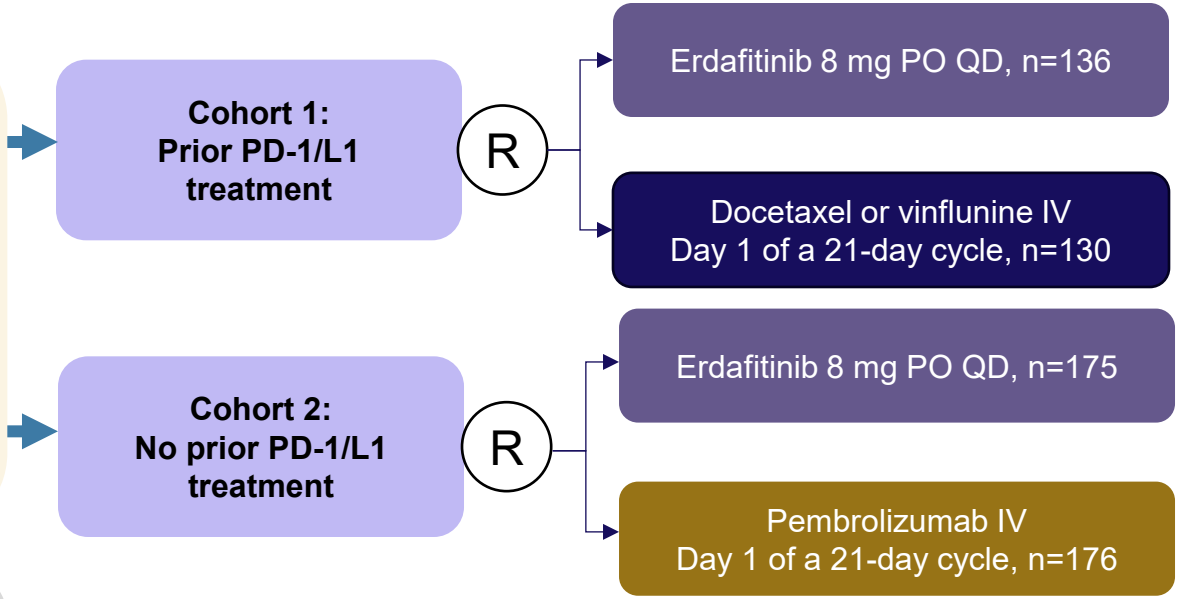
a, advanced; CPS, combined positive score; CR, complete response; DV, disitamab vedotin; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridization; ORR, overall response rate; P, pembrolizumab; PD-L1, programmed death-ligand 1; PR, partial response; Q2W, every 2 weeks; Q6W, every 6 weeks; SD, stable disease; UC, urothelial carcinoma.

Galsky MD, et al. ESMO 2024. Abstract 1967MO.

Phase III THOR trial: Study design[1–3]

Key inclusion criteria

- Unresectable or metastatic UC (minority component histologies permitted)
- FGFR inhibitor clinical trial assay to determine molecular eligibility
- One or two lines of prior systemic therapy
- ECOG PS 0–2



Primary endpoint: Overall survival

Secondary endpoints: PFS, ORR, duration of response, safety, PROs, pharmacokinetics

ECOG PS, Eastern Cooperative Group Performance Status; FGFR, fibroblast growth factor receptor; IV, intravenous; PD-1/L1, programmed cell death protein 1/ligand 1; PFS, progression-free survival; PO, by mouth; PRO, patient-reported outcome; QD, daily; R, randomization; UC, urothelial carcinoma.

1. Loriot Y et al. *N Engl J Med* 2023;389:1961–1971; 2. ClinicalTrials.gov. NCT03390504. Available at: https://clinicaltrials.gov/study/NCT03390504. Last accessed July 2025; 3. Siefker-Radtke AO et al. *Ann Oncol* 2024;35:107–117.

Phase III THOR trial (Cohort 1): Overall survival

Overview

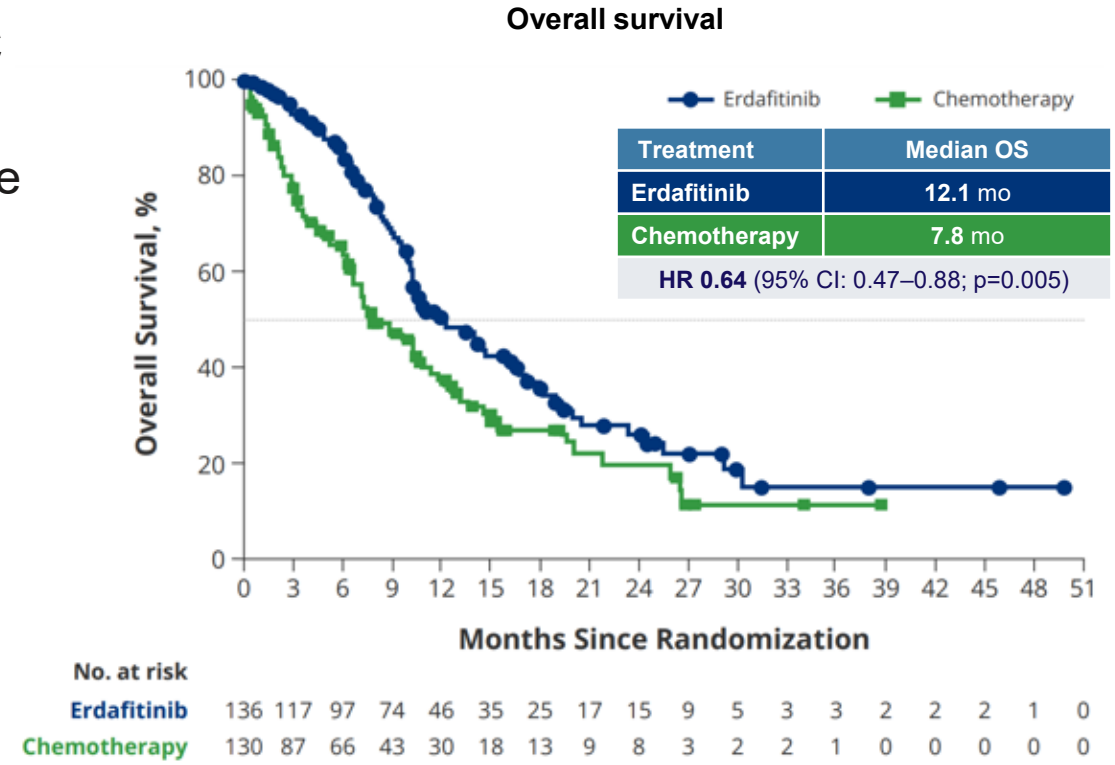
- Approximately 20% of patients with advanced UC have FGFR alterations
- Erdafitinib is an oral, selective, pan-FGFR tyrosine kinase inhibitor

Key eligibility criteria

- Unresectable or metastatic UC
- Progressed on or after ≥1 prior treatment that included an anti–PD-(L)1
- Select *FGFR3/2alt* (mutation/fusion)
- ECOG PS 0–2
- No more than 2 prior lines of treatment

Erdafitinib (n=136)
8 mg PO once daily; up-titration to 9 mg

Chemo (n=130)
Docetaxel or vinflunine every 3 weeks



CI, confidence interval; FGFR, fibroblast growth factor receptor; HR, hazard ratio; mo, months; OS, overall survival; PD-(L)1, programmed death (ligand) 1; PO, by mouth; UC, urothelial carcinoma.

Loriot Y et al. *N Engl J Med* 2023;389:1961–1971.

Phase III THOR trial (Cohort 1): Safety

AEs occurring in ≥30% (any grade) or ≥5% (Grade 3/4) of patients, n (%)	Erdafitinib (n=135)		Chemotherapy (n=112)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hyperphosphatemia	108 (80.0)	7 (5.2)	0	0
Diarrhea	84 (62.2)	4 (3.0)	19 (17.0)	3 (2.7)
Stomatitis	65 (48.1)	11 (8.1)	14 (12.5)	2 (1.8)
Dry mouth	53 (39.3)	0	4 (3.6)	0
PPE syndrome	41 (30.4)	13 (9.6)	1 (0.9)	0
Onycholysis	31 (23.0)	8 (5.9)	1 (0.9)	0

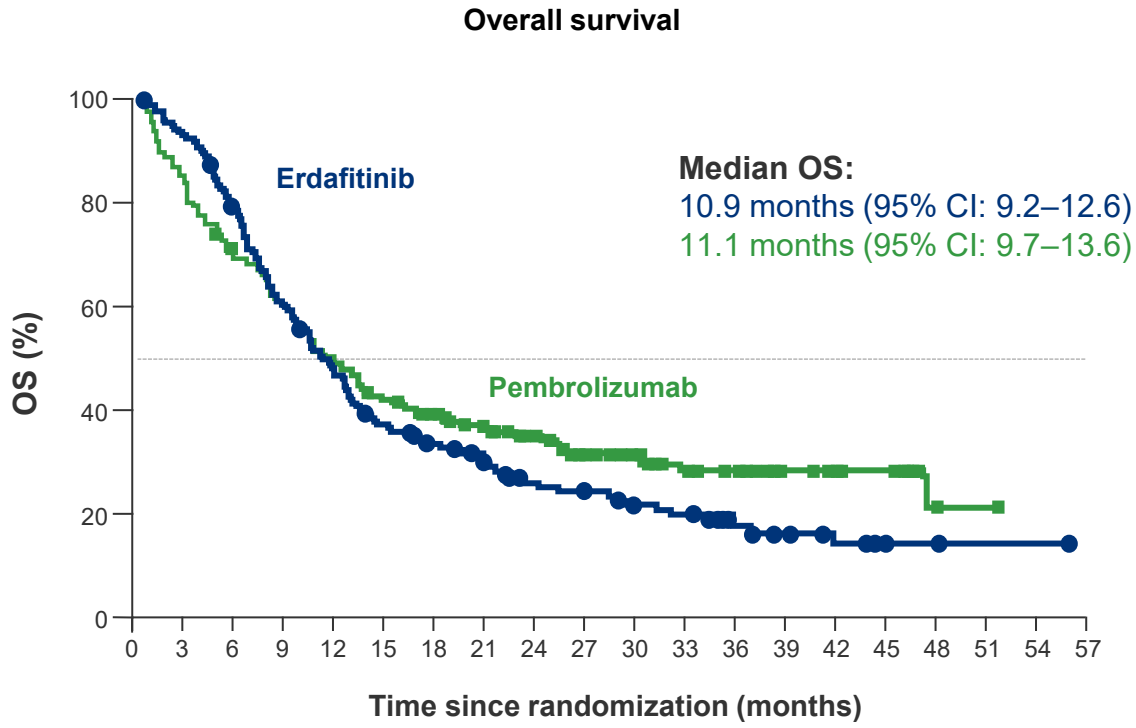
AEs of interest, n (%)	Erdafitinib (n=135)		Chemotherapy (n=112)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Nail disorders	90 (66.7)	15 (11.1)	6 (5.4)	0
Skin disorders	74 (54.8)	16 (11.9)	14 (12.5)	0
Eye disorders (excluding central serous retinopathy)	57 (42.2)	3 (2.2)	6 (5.4)	0
Central serous retinopathy	23 (17.0)	3 (2.2)	0	0

- One treatment-related death occurred in the erdafitinib group (sudden death)
- In total, 11 patients (8.1%) discontinued study treatment with erdafitinib due to treatment-related AEs

AE, adverse event; PPE, palmar-plantar erythrodysesthesia.
Loriot Y et al. *N Engl J Med* 2023;389:1961–1971.

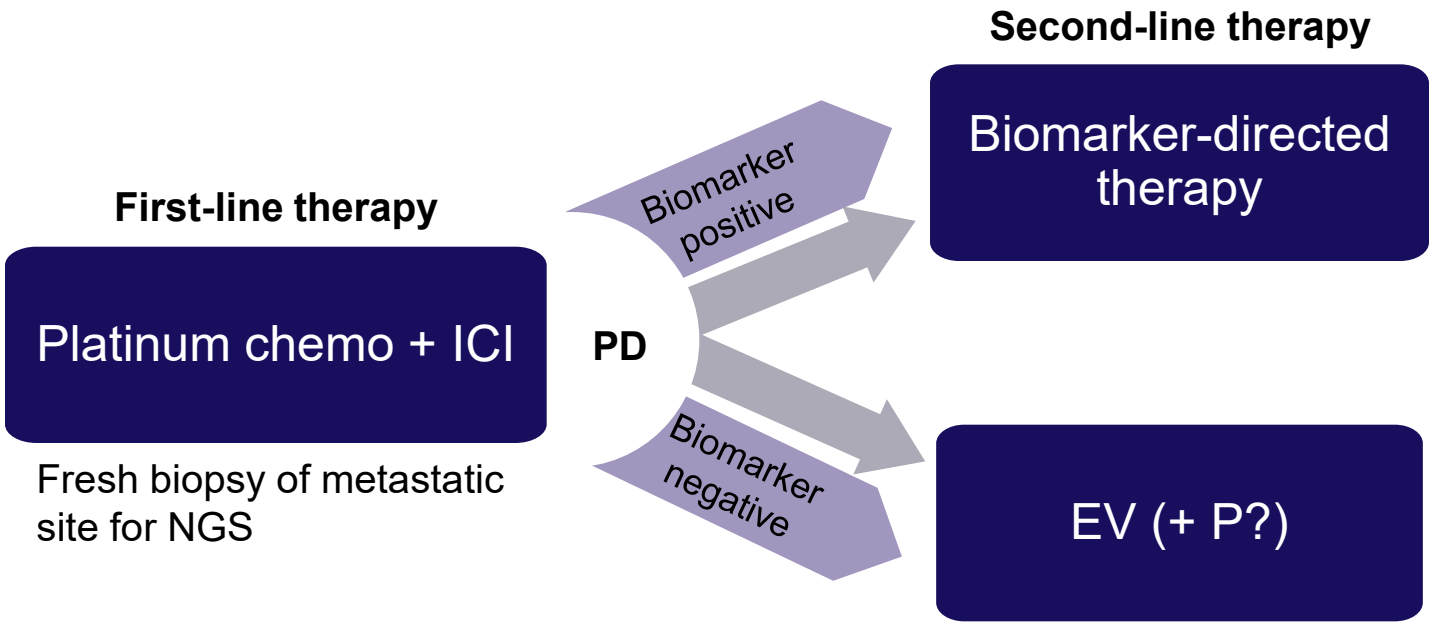
Phase III THOR (Cohort 2): Overall survival

- The primary endpoint was not met
- Median OS was 10.9 months (95% CI: 9.2–12.6) with erdafitinib and 11.1 months (95% CI: 9.7–13.6) with pembrolizumab
  - HR 1.18 (95% CI: 0.92–1.51; p=0.18)



CI, confidence interval; HR, hazard ratio; OS, overall survival.
Siefker-Radtke AO et al. *Ann Oncol* 2024;35:107–117.

Sequencing therapies when EV+P is NOT used in the first line



EV, enfortumab vedotin; ICI, immune checkpoint inhibitor; NGS, next-generation sequencing; P, pembrolizumab; PD, progressive disease.
Speaker's expert opinion.

First-line standard of care is EV+P for almost all patients; second-line therapy is now a data-free zone…

- EV+P is now the standard of care first-line therapy for advanced UC[1]
  - Many patients experience durable responses[2]
  - However, most still eventually develop resistance[2]
- To date, there are no prospective clinical trials reporting efficacy in the second-line setting after disease progression on EV+P[2]

Second-line options include:[2]

- Platinum-based chemotherapy
- Biomarker-directed therapy (HER2, FGFR3)
- Taxane chemotherapy
- Clinical trial

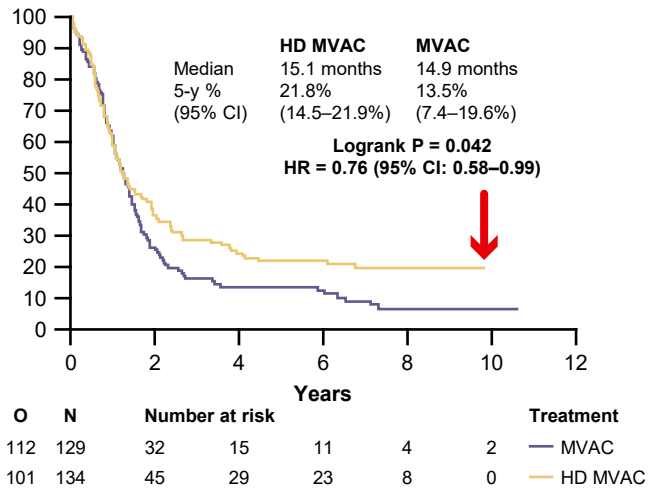
EV, enfortumab vedotin; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; P, pembrolizumab; UC, urothelial carcinoma.

1. Powles T et al. *Ann Oncol* 2024;35:485–490; 2. Speaker's expert opinion.

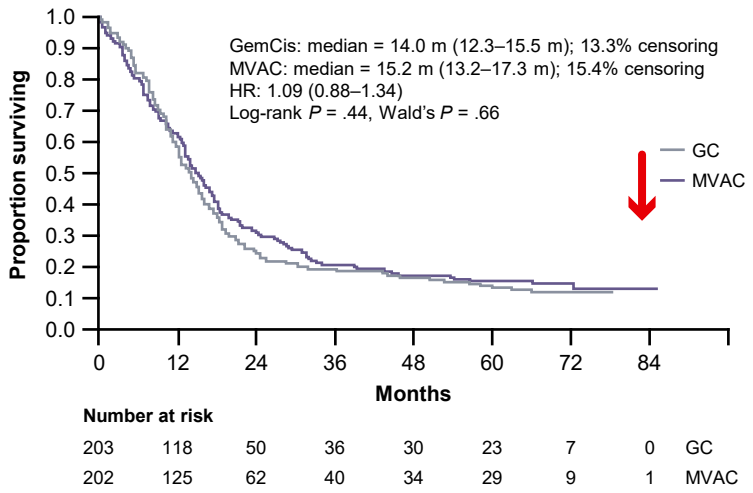
Platinum may still be active: Extrapolating from prior first-line datasets (before the era of ICIs)

Cisplatin eligible

ddMVAC[1]
ORR: 72%
CR: 25%
mOS: 15.1 mo

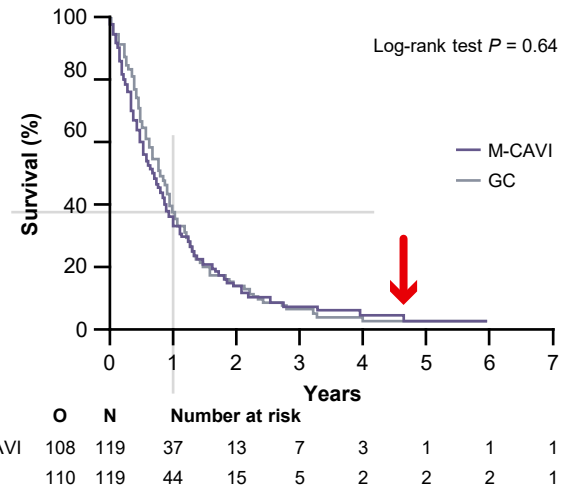


Gemcitabine/cisplatin[2]
ORR: 49%
CR: 12%
mOS: 14 mo



Cisplatin ineligible

Gemcitabine/carboplatin[3]
ORR: 36%
CR: 3%
mOS: 9.3 mo

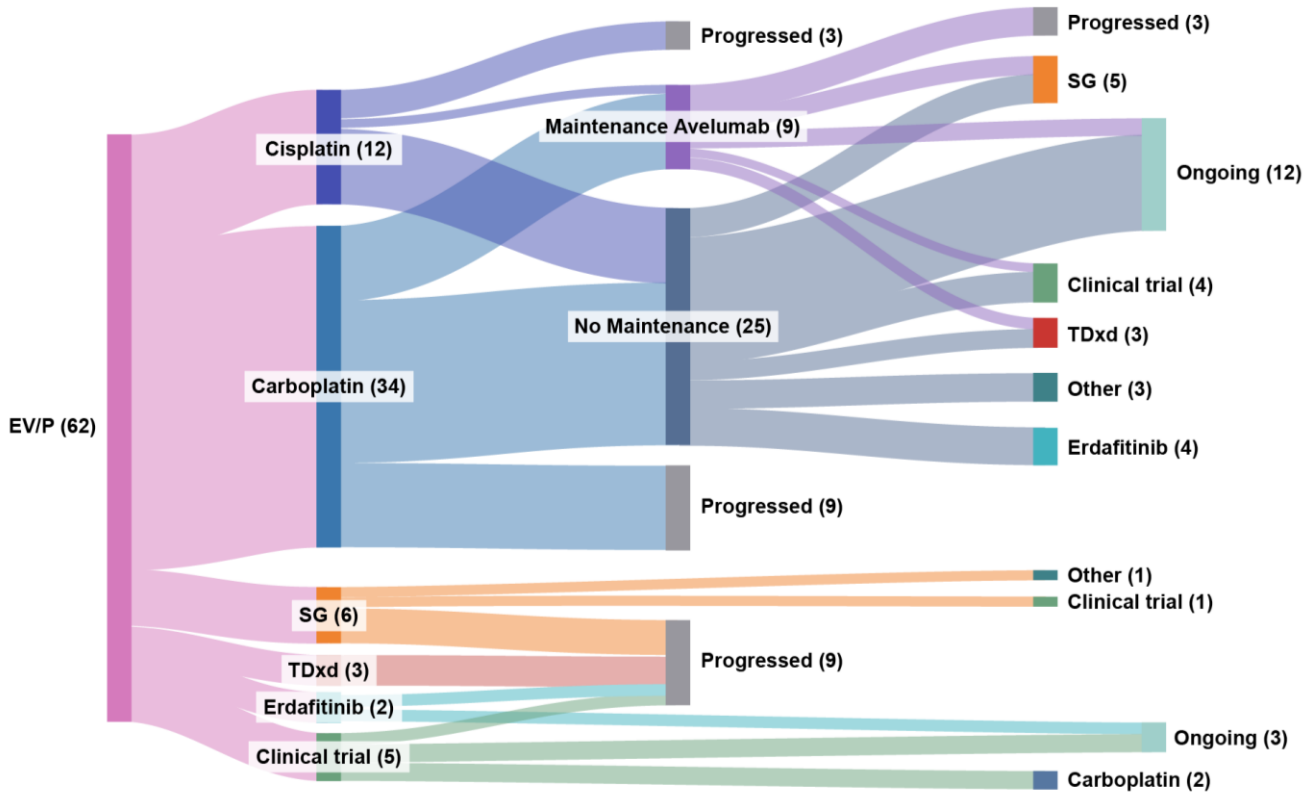


CI, confidence interval; Cis, cisplatin; CR, complete response; (dd)MVAC, (dose-dense) methotrexate, vinblastine, doxorubicin + cisplatin; Gem, gemcitabine; HD, high-dose; HR, hazard ratio; ICI, immune checkpoint inhibitor; M-CAVI, carboplatin, methotrexate, and vinblastine; m/mo, months; mOS, median overall survival; ORR, overall response rate; y, years.

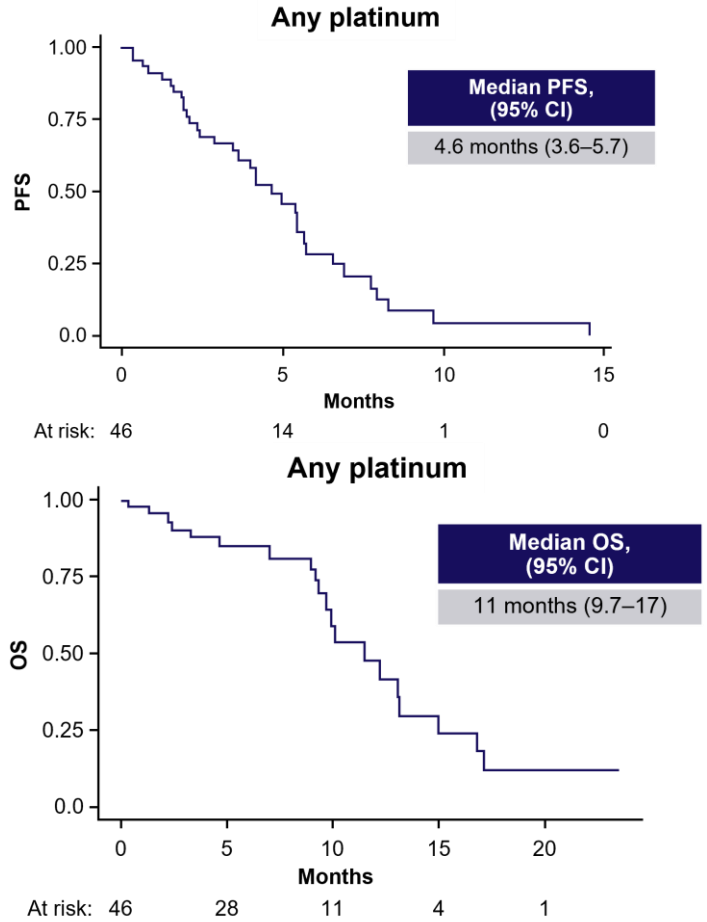
1. Sternberg C et al. *Eur J Cancer* 2006;42:50–54; 2. von der Maase H et al. *J Clin Oncol* 2005;23:4602–4608; 3. de Santis M et al. *J Clin Oncol* 2012;30:191–199.

Treatment after EV+P for first-line UC

Treatment patterns after EV+P



OS and PFS in patients who received PBCT following progression on EV+P (n=46)



CI, confidence interval; EV, enfortumab vedotin; OS, overall survival; P, pembrolizumab; PBCT, platinum-based chemotherapy; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; SG, Sacituzumab govitecan; UC, urothelial carcinoma.

Sternschuss M et al. Presented at ASCO 2025. Abstract 4573.

EV-302: Subsequent therapy

Parameters	EV+P (n=442)	Chemotherapy (n=444)
Number of patients (%)		
Patients who remained on treatment	144 (32.6)	0
Patients who received subsequent anticancer therapies	140 (31.7)	313 (70.5)
First subsequent systemic therapy	128 (29.0)	294 (66.2)
PBCT	110 (24.9)	17 (3.8)
PD-1/L1 inhibitor-containing treatment	7 (1.6)	260 (58.6)
Maintenance therapy*†	0	143 (32.2)
Avelumab	0	135 (30.4)
Other therapy	7 (1.6)	117 (26.4)

Of those who progressed on EV+P and received subsequent therapy, 79% received platinum-based therapy

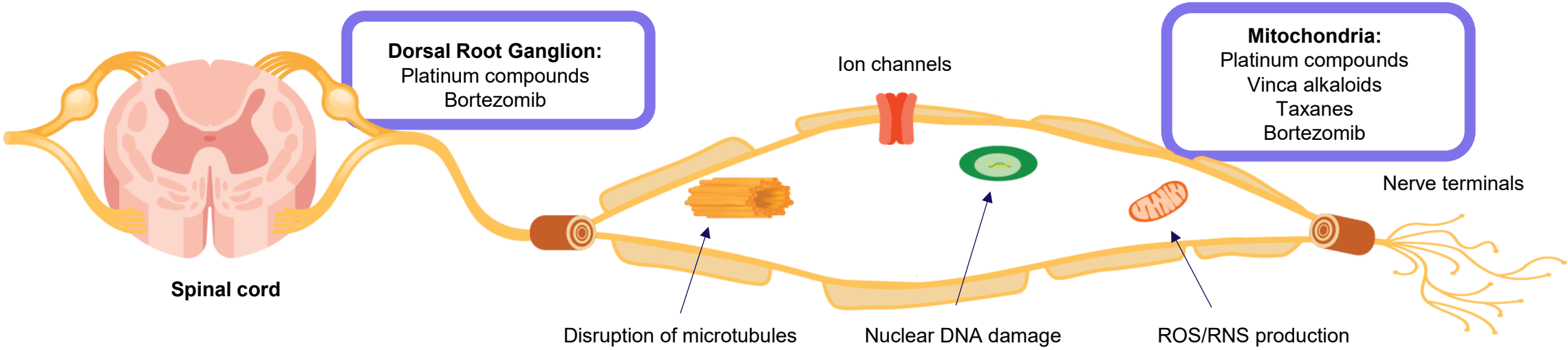
*Included atezolizumab, avelumab, ipilimumab, M6223, nivolumab, NKTR-255, and pembrolizumab; †Maintenance therapy was permitted in the trial after PBCT.
EV, enfortumab vedotin; P, pembrolizumab; PBCT, platinum-based chemotherapy; PD-1/L1, programmed cell death protein 1/ligand 1.
Powles T et al. *N Engl J Med* 2024;390:875–888 (Supplementary data).

Practical considerations for PBCT

Does the patient have residual neuropathy due to EV treatment?

- Cisplatin induces long-term peripheral neuropathy in 30–40% of patients[1]
- The incidence of long-term peripheral neuropathy is the same with carboplatin, but severity of symptoms is milder and onset is later[1,2]
- Both treatments are subject to “coasting” phenomenon: worsening neuropathy after treatment cessation[1]

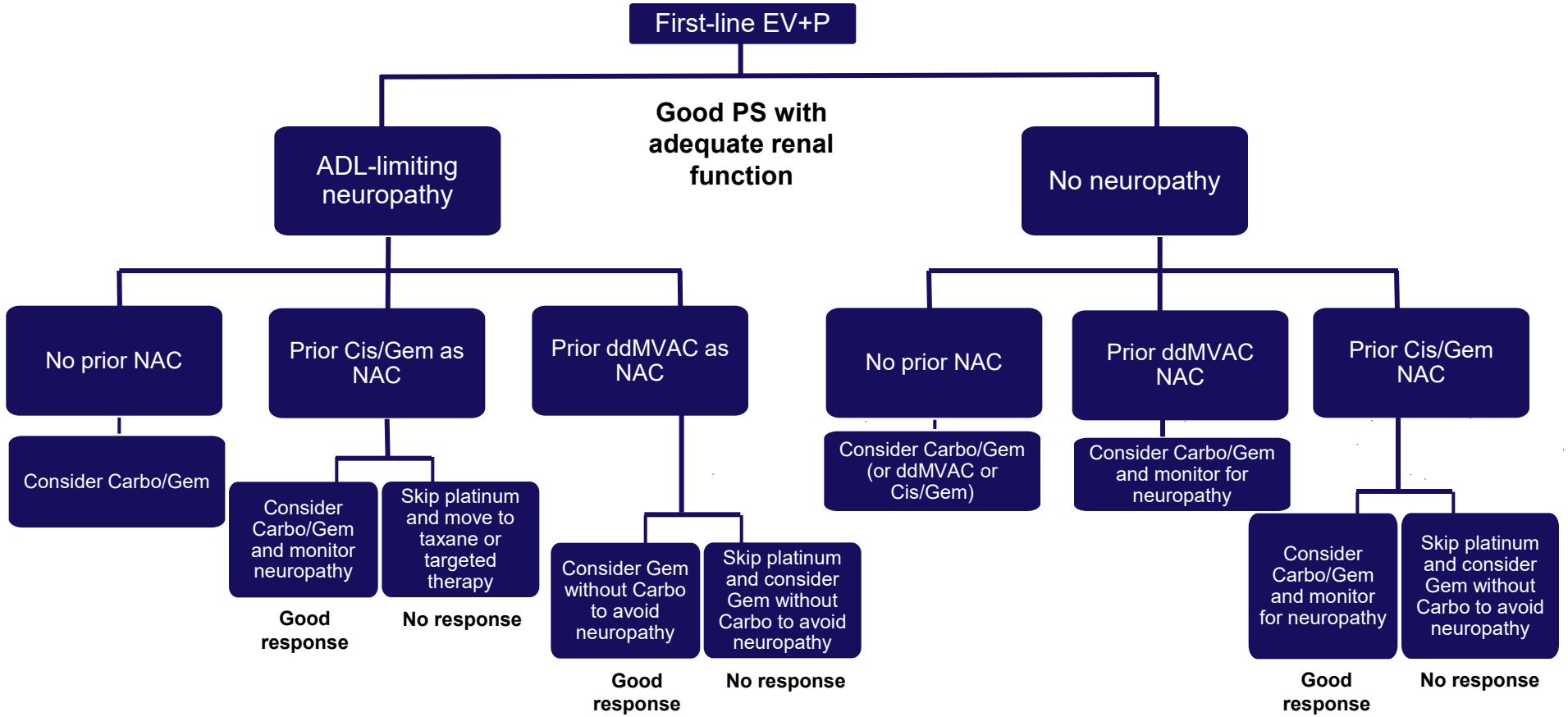
Chemotherapy toxicity and putative sites of peripheral neuropathy in the peripheral nervous system[1,3]



DNA, deoxyribonucleic acid; EV, enfortumab vedotin; PBCT, platinum-based chemotherapy; PD-1, programmed cell death protein 1; RNS, reactive nitrogen species; ROS, reactive oxygen species.

1. Staff NP et al. *Ann Neurol* 2017;81:772–781; 2. Speaker’s expert opinion; 3. Zhou L et al. *Neurotherapeutics* 2023;20:339–358.

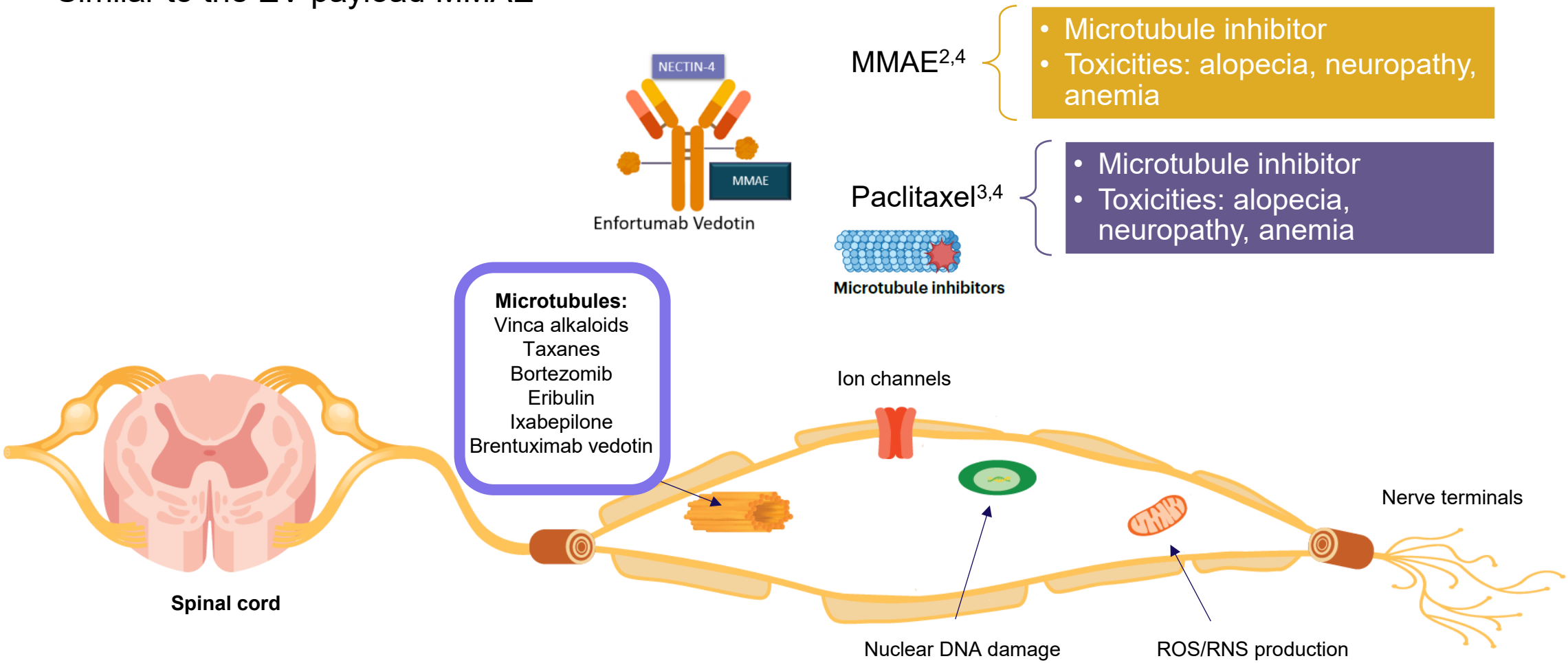
First step: Pathways for consideration of PBCT



ADL, activities of daily living; Carbo, carboplatin; Cis, cisplatin; ddMVAC, dose-dense methotrexate, vinblastine, doxorubicin + cisplatin; EV, enfortumab vedotin; Gem, gemcitabine; NAC, N-acetylcysteine; P, pembrolizumab; PBCT, platinum-based chemotherapy; PS, performance status.
Speaker's expert opinion.

Practical considerations for taxanes

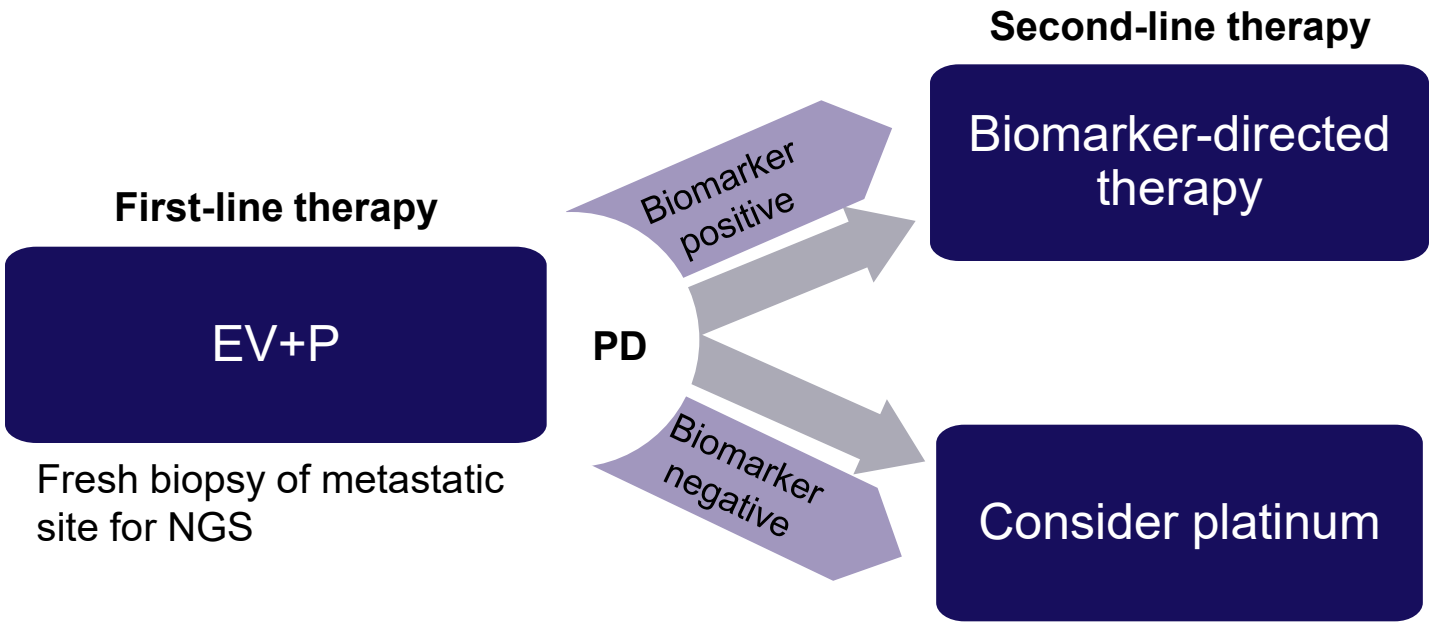
- Similar to the EV payload MMAE[1–3]



EV, enfortumab vedotin; MMAE, monomethyl auristatin E; PD-1, programmed cell death protein 1.

1. Zhou L et al. *Neurotherapeutics* 2023;20:339–358; 2. Staff NP et al. *Ann Neurol* 2017;81:772-781; 3. Ungaro A et al. *Cells* 2022;11:803; 4. Tarantino P et al. *Nat Rev Clin Oncol* 2023;20:558–576.

Sequencing therapies when first-line EV+P is used



EV, enfortumab vedotin; NGS, next-generation sequencing; P, pembrolizumab; PD, progressive disease.
Speaker's expert opinion.

Summary

- The optimal sequence of treatment after EV+P is yet to be defined[1]
- PBCT retains activity after EV+P[2]
- Targeted therapy is appropriate in patients expressing HER2/neu or FGFR2/3[3,4]
- The patient's prior treatment-related toxicity should be considered during treatment selection[1]

EV, enfortumab vedotin; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; P, pembrolizumab; PBCT, platinum-based chemotherapy.

1. Speaker's expert opinion; 2. Sternschuss M et al. Presented at ASCO 2025. Abstract 4573.; 3. Galsky MD, et al. ESMO 2024. Abstract 1967MO; 4. Loriot Y et al. *N Engl J Med* 2023;389:1961–1971.

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PI, Prescribing Information

Genitourinary Masterclass

Changes in clinical practice since the approval of EV monotherapy

Dr Kaiwei Yang

Deputy Chief Physician, Department of Urology,
Peking University First Hospital, China

EV as first-line therapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer. Combination therapy with pembrolizumab.

EV as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 or programmed death-ligand 1 inhibitor, and have received a platinum-containing chemotherapy

1L, first line; EV, enfortumab vedotin; P, pembrolizumab;

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July 2025 | MAT-KR-PAD-2025-00064

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Speaker disclosures

No disclosures.

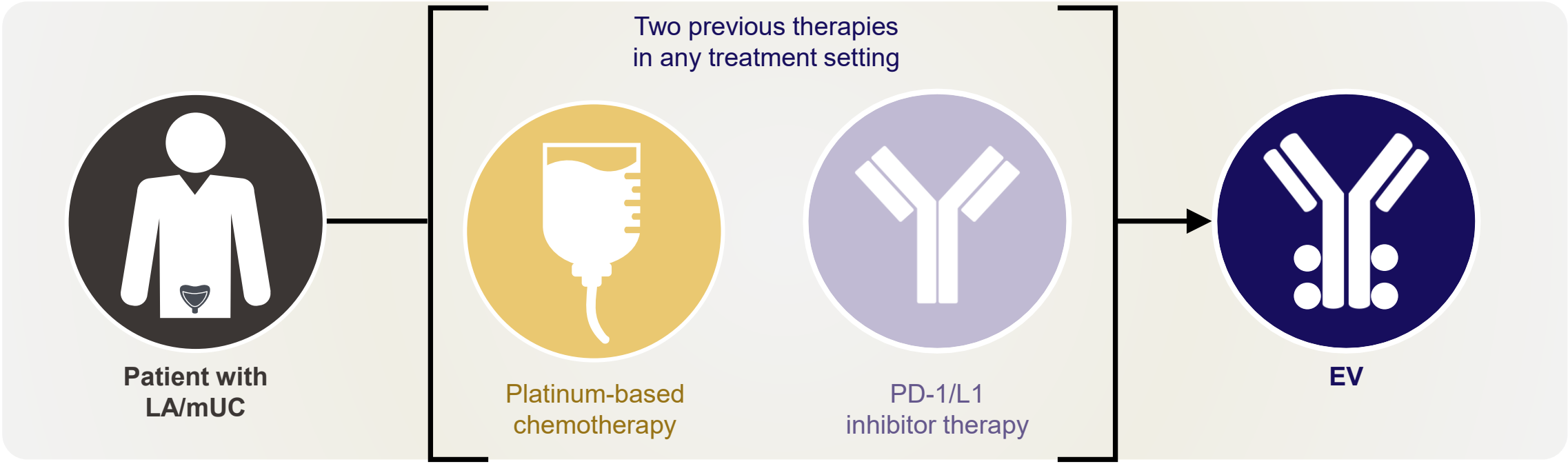
Footnotes

Contents

EV, enfortumab vedotin; LA/mUC, locally advanced/metastatic urothelial carcinoma.

EV monotherapy is a treatment for patients with LA/mUC who have received previous platinum-based chemotherapy and a PD-1/L1 inhibitor

Based on the efficacy and safety data from the pivotal Phase III EV-301 study, EV as monotherapy is indicated for the treatment of adult patients with LA/mUC who have previously received a platinum-containing chemotherapy and a PD-1/L1 inhibitor[1]



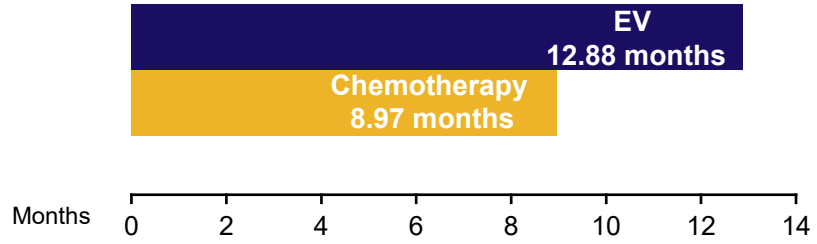
EV, enfortumab vedotin; LA/mUC, locally advanced/metastatic urothelial carcinoma; PD-1/L1, programmed cell death protein 1/ligand.
1. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics.

Reshaping the treatment landscape for patients who have progressed with chemotherapy or PD-1/L1 inhibitors

EV-301 study data demonstrated the superior efficacy of EV over chemotherapy in patients with aUC who had previously received treatment with platinum-based chemotherapy and PD-1/L1 inhibitors[1]

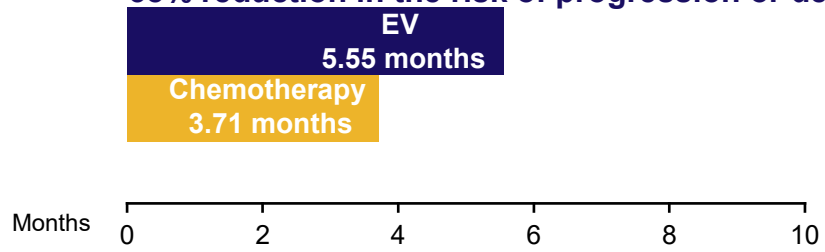
mOS[1]

EV: 30% reduction in the risk of death (p=0.001)



mPFS[1]

EV:
38% reduction in the risk of progression or death (p<0.001)



Based on the positive results of the EV-301 study, major guidelines list EV monotherapy as a preferred regimen for patients with LA/mUC post-chemotherapy immunotherapy (no previous EV)[2–4]

EV now plays an important role in the evolving treatment paradigm of LA/mUC,[5] but does real-world clinical practice reflect the clinical trial data?

aUC, advanced urothelial carcinoma; EV, enfortumab vedotin; LA/mUC, locally advanced/metastatic urothelial carcinoma; mOS, median overall survival; mPFS, median progression-free survival; PD-1/L1, programmed cell death protein 1/ligand.

1. Powles T et al. *N Engl J Med* 2021;384:1125–1135; 2.Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Bladder Cancer V.1.2025. © 2025 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available.; 3. EAU. Muscle-invasive and metastatic bladder cancer. Available at: https://www.uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer. Last accessed: March 2025; 4. Powles T et al. *Ann Oncol* 2024;35:485–490; 5. Nakamura Y et al. *Clin Genitourin Cancer* 2025;23:102301.

Contents

EV, enfortumab vedotin; LA/mUC, locally advanced/metastatic urothelial carcinoma.

Does real-world clinical practice reflect the clinical trial data?

RCT results need validation in diverse real-world clinical settings[1]

- In contrast to the highly selected patient population included in clinical trials, RWE bridges the gap between results in the RCT setting and real-world clinical practice[2]
- Strict trial criteria limit the generalizability of RCT data, but RWE extends findings to broader populations[1]

RCT vs. RWE[1]

	RCT	RWE
Setting	Experimental or interventional setting	Real-world setting or observational or noninterventional setting
Study conduct	Protocol-based, GCP-compliant	Real-life clinical practice
Treatment	Fixed pattern	Variable pattern
Participant population	Strict and many inclusion and exclusion criteria	Very few inclusion and exclusion criteria
Attending physician	Investigator	Practitioner
Comparator	Placebo/selective alternative interventions	Either no control arm or standard treatment or care
Outcome	Efficacy	Effectiveness
Randomization and blinding	Yes	No

RCT, randomized controlled trial; RWE, real-world evidence; GCP, good clinical practice.

1. Chodankar D. *Perspect Clin Res* 2021;12:171–174; 2. Niedersuess-Beke D et al. *Clin Genitourin Cancer* 2025;23:102278.

Real-world evidence for EV monotherapy in patients with LA/mUC

Real-world analyses have further confirmed the efficacy and safety profile of EV monotherapy, providing support for its use in a broad patient population

UNITE study[1]

Patients:
N=304 aUC

Median follow-up (from the start of EV):
7.2 months

Results:
- mOS: 14.4 months
- mPFS: 6.8 months
- ORR (investigator-assessed): 52%

European multicenter RWE[2]

Patients:
N=188 mUC

Median follow-up:
11 months

Results:
- mOS: 12.0 months
- mPFS: 7.0 months
- ORR: 46.3%

YUSHIMA Study-04[3]

Patients:
N=115 mUC

Median follow-up:
7.1 months

Results:
- mOS: 12.9 months
- mPFS: 6.7 months
- ORR: 49%

Japan multicenter retrospective study[4]

Patients:
N=419 LA/mUC

Methods:
Chemo-alone;
chemo-ICI;
chemo-ICI-EV

Results:
- mOS: Significantly longer in the chemo-ICI-EV group vs. other chemo or chemo-ICI

Studies are show for illustrative purposes and should not be directly compared.
aUC, advanced urothelial carcinoma; chemo, chemotherapy; EV, enfortumab vedotin; ICI, immune checkpoint inhibitor; LA/mUC, locally advanced/metastatic urothelial carcinoma; RWE, real-world evidence; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate.
1. Koshkin VS et al. *Cancer* 2022;128:1194–1205; 2. Zschaebitz S et al. *J Clin Oncol* 2024;42:suppl 553; 3. Nakamura Y et al. *Clin Genitourin Cancer* 2025;23:102301; 4. Hatakeyama S et al. *J Clin Oncol* 2025;43:suppl 712.

Baseline characteristics of patients included in real-world studies

Real-world studies evaluated the effectiveness of EV in broad patient populations, including older patients, those with comorbidities, and patients with poorer performance status compared with the EV-301 study[1–3]

Baseline characteristic	UNITE study[1] (EV, n=260)	European multicenter RWE (n=188)[2]	YUSHIMA Study-04 (EV, n=115)[3]	Japan multicenter retrospective study (chemo-ICI-EV, n=115)[4]	EV-301 (EV, n=301)[5]
Median age (range), years	71*	66 (31–89)	74 (34–85)	74 (23–89)	68.0 (34.0–85.0)
Sex, n (%)					
Female	55 (21)	61 (32.4)	30 (26)	–	63 (20.9)
Male	205 (79)	127 (76.6)	85 (74)	83 (72)	238 (75.6)
ECOG PS, %					
0–1	79	75	84	–	100
≥2	20.4	14	16	10	*Excluded*
Location of primary tumor, n (%)					
Bladder/other site	190 (73.4)	–	56 (49)	–	203 (67.4)
Upper tract	65 (25)	–	59 (51)	52 (45)	98 (32.6)
Metastasis, n (%)					
Lymph node	52 (20)	–	93 (80)	54 (47)	34 (11.3)
Liver metastasis	84 (32)	–	24 (21)	15 (13)	93 (30.9)
≥3 previous lines of systemic therapy, n (%)	64 (25)	–	115 (100)	–	39 (13.0)
Histology, n (%)					
Pure urothelial	177 (68)	–	97 (84)	–	–
UC with variant histology	8 (3)	–	14 (12)	–	–

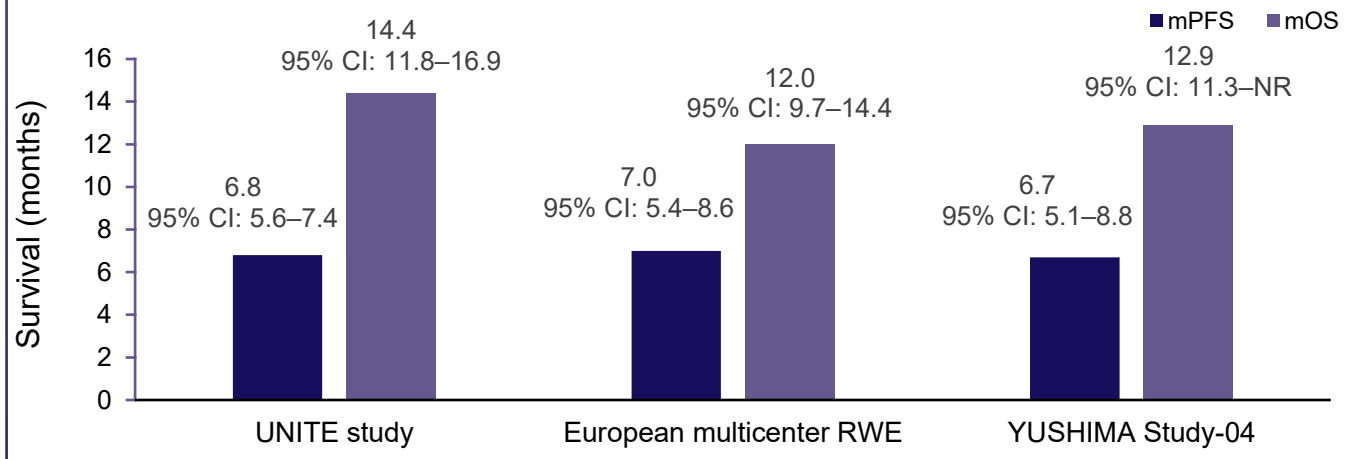
Studies are show for illustrative purposes and should not be directly compared.

*Range not available. chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; ICI, immune checkpoint inhibitor; RWE, real-world evidence; UC, urothelial carcinoma.

1. Koshkin VS et al. *Cancer* 2022;128:1194–1205; 2. Zschaebitz S et al. *J Clin Oncol* 2024;42:suppl 553; 3. Nakamura Y et al. *Clin Genitourin Cancer* 2025;23:102301; 4. Hatakeyama S et al. *J Clin Oncol* 2025;43:suppl 712; 5. Powles T et al. *N Engl J Med* 2021;384:1125–1135.

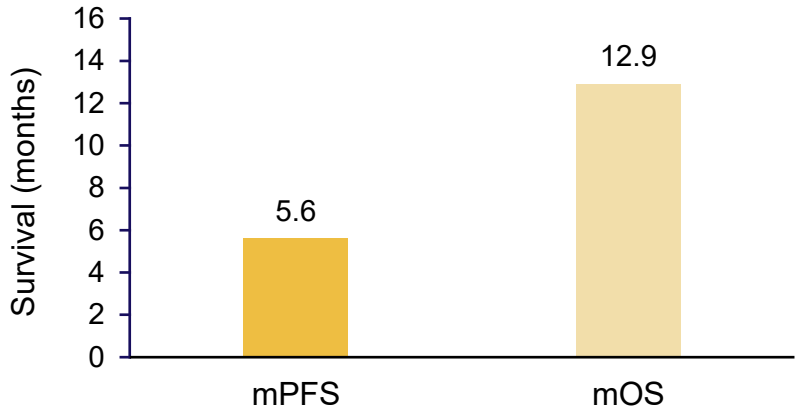
Real-world outcomes for OS, PFS, and ORR are comparable with those from the EV-301 trial

Efficacy outcomes for patients receiving EV in real-world studies[1–3]



	UNITE (n=260)	European (n=188)	YUSHIMA (n=115)
ORR	52%	46%	49%
CR	7%	4%	5%
PR	45%	42%	43%

EV-301 (EV group)[4]



	n=288
ORR	40.6%
CR	4.9%
PR	35.8%

Studies are show for illustrative purposes and should not be directly compared.

CI, confidence interval; CR, complete response; EV, enfortumab vedotin; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RWE, real-world evidence.

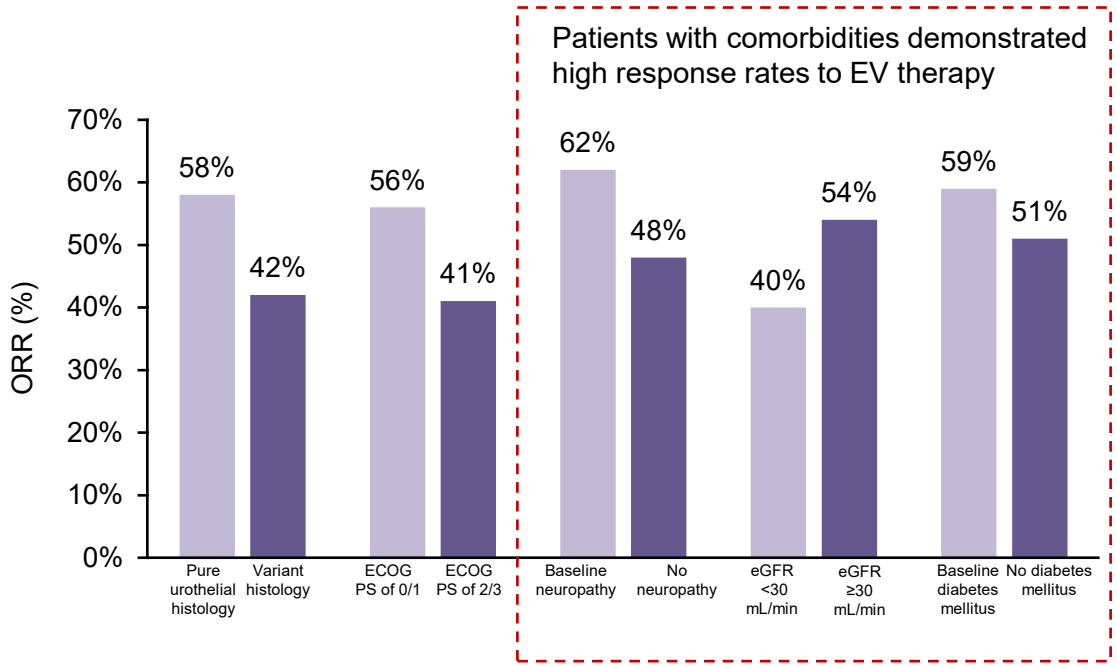
1. Koshkin VS et al. *Cancer* 2022;128:1194–1205; 2. Zschaebitz S et al. *J Clin Oncol* 2024;42:suppl 553; 3. Nakamura Y et al. *Clin Genitourin Cancer* 2025;23:102301; 4. Powles T et al. *N Engl J Med* 2021;384:1125–1135.

The UNITE study results showed that EV has robust activity in clinically relevant patient subgroups

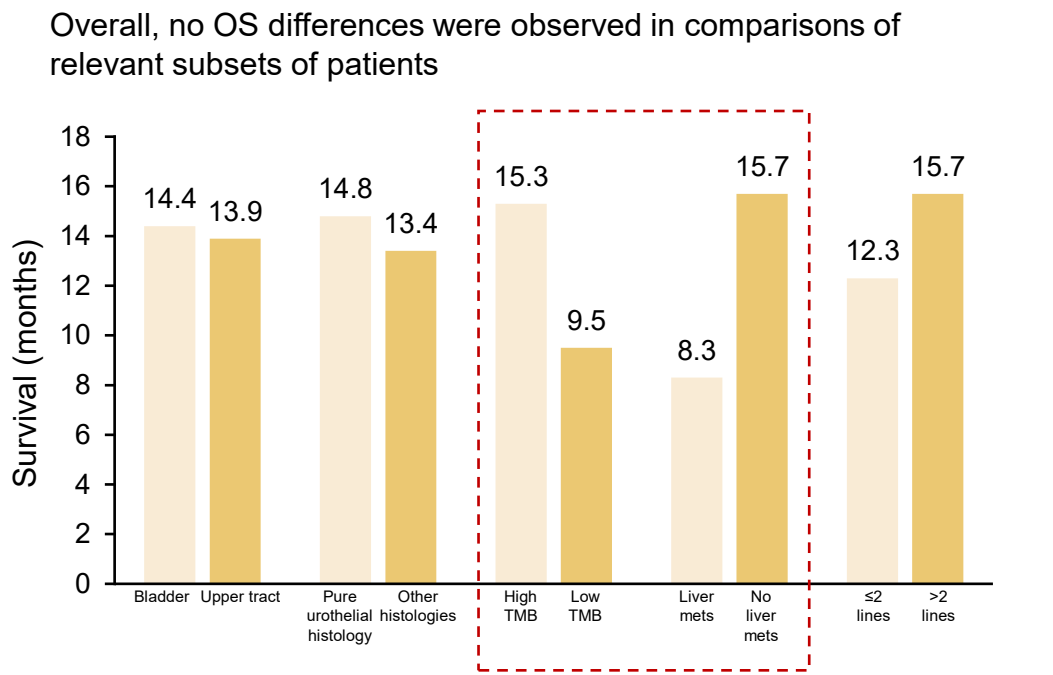
In clinically relevant patient subgroups, EV demonstrated robust activity, including for patients with variant histology, those with a poor performance status (ECOG PS >1), and those with relevant medical comorbidities (e.g., peripheral neuropathy and diabetes mellitus), among others[1]

Given variations in completeness of subgroup efficacy disclosure across studies, we conducted a focused analysis of the UNITE study's subgroup outcomes.

UNITE study: ORR of the relevant subgroups[1]



UNITE study: mOS of the subgroups[1]

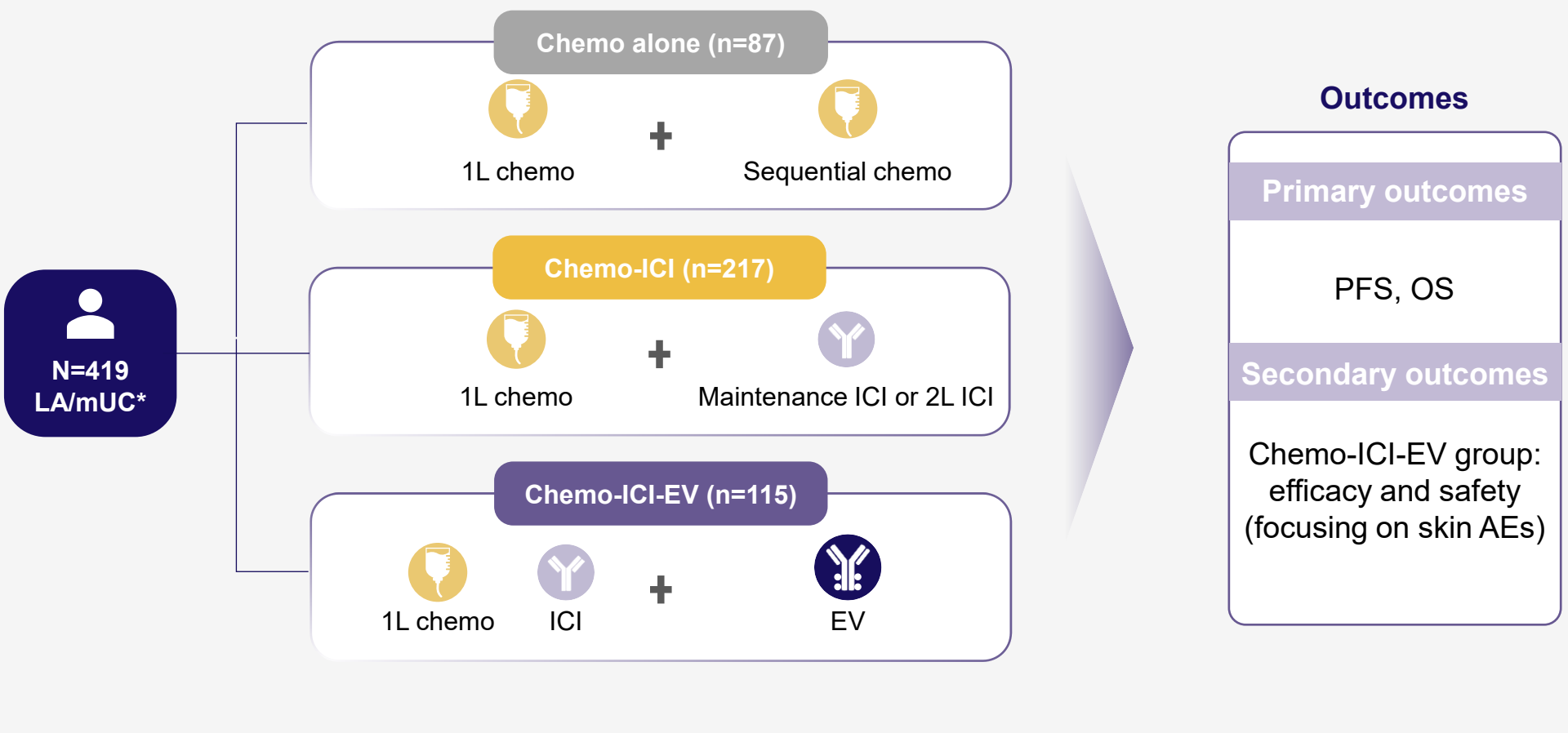


ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; EV, enfortumab vedotin; met, metastasis; mOS, median overall survival; ORR, objective response rate; OS, overall survival; TMB, tumor mutational burden.

1. Koshkin VS et al. *Cancer* 2022;128:1194–1205.

Asian patient population: Japan multicenter retrospective study design

- The aim was to evaluate the efficacy and safety profile of EV in patients with LA/mUC in a real-world clinical practice setting[1]

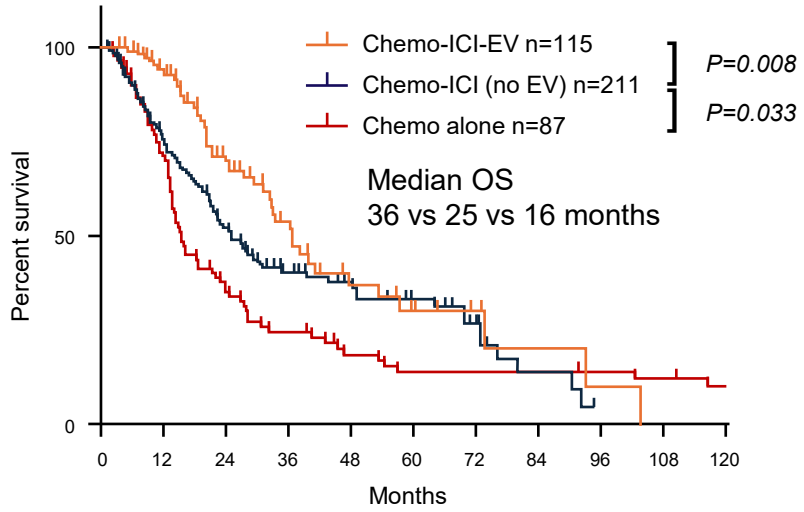


*Included 419 patients treated for LA/mUC between April 2004 to April 2024.
1L, first line; 2L, second line; AE, adverse event; chemo, chemotherapy; EV, enfortumab vedotin; ICI, immune checkpoint inhibitor; LA/mUC, locally advanced/metastatic urothelial carcinoma; OS, overall survival; PFS, progression-free survival.
1. Hatakeyama S et al. *J Clin Oncol* 2025;43:suppl 712.

Asian patient population: Japan multicenter retrospective study OS

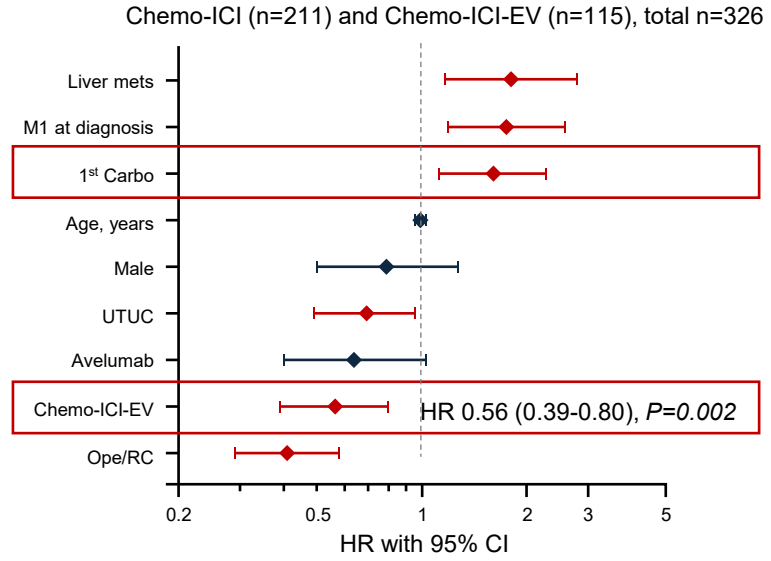
The outcomes further confirmed the efficacy of EV monotherapy in patients with LA/mUC who had received prior chemo and ICI treatment[1]*

OS from 1L therapy (unadjusted)[2]



The OS from 1L therapy was **significantly longer in the chemo-ICI-EV group than in the other groups[2]**

Cox regression analysis for OS from 1L therapy[2]



The administration of EV **was significantly associated with prolonged OS[2]**

*Included 419 patients treated for LA/mUC between April 2004 to April 2024.

1L, first line; carbo, carboplatin; chemo, chemotherapy; CI, confidence interval; EV, enfortumab vedotin; HR, hazard ratio; ICI, immune checkpoint inhibitor; LA/mUC, locally advanced/metastatic urothelial carcinoma; met, metastasis; Ope/RC, open radical cystectomy; OS, overall survival; UTUC, upper-tract urothelial carcinoma.

1. Hatakeyama S et al. *J Clin Oncol* 2025;43:suppl 712; 2. Ozaki K et al. *J Urol* 2025;213:e1281.

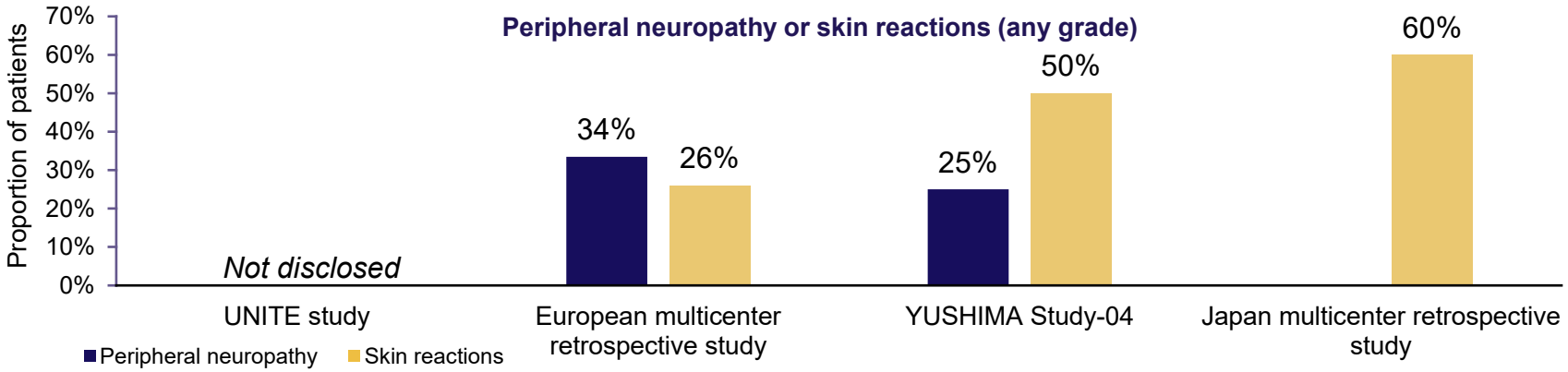
Safety: No new safety signals were identified in the real-world setting

In the real-world study analysis:[1–4]

- No new safety signals were observed
- The incidence rates of any grade or Grade ≥3 TRAEs observed in the real-world studies were numerically lower than those reported in the EV-301 study
- Skin reactions and peripheral neuropathy were the most common TRAEs

Real-world studies: TRAE

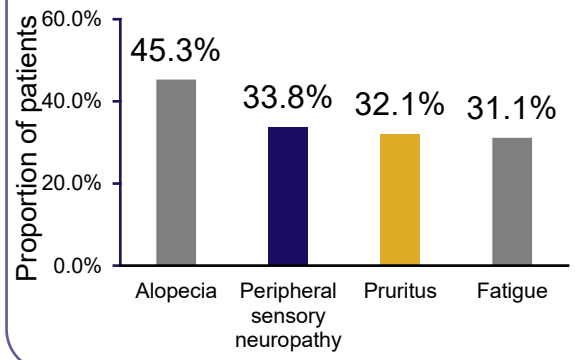
	UNITE study[5] (EV, n=260)	European multicenter RWE[1] (n=188)	YUSHIMA Study-04[2] (n=115)	Japan multicenter retrospective study[4] (chemo-ICI-EV, n=115)
Any grade	–	71%	77%	–
Grade ≥3	–	32%	25%	–



EV-301: TRAE (EV, n=296)[6]

Any grade: 93.9%
Grade ≥3: 51.4%

The most common TRAEs (any grade)



Studies are show for illustrative purposes and should not be directly compared.

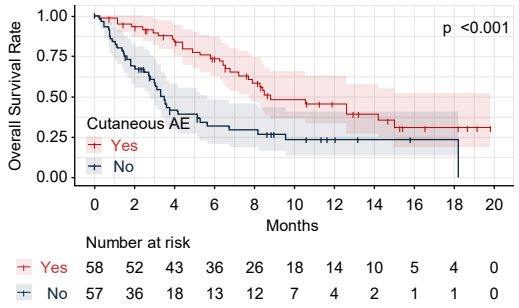
chemo, chemotherapy; EV, enfortumab vedotin; ICI, immune checkpoint inhibitor; RWE, real-world evidence; TRAE, treatment-related adverse event.

1. Zschaebitz S et al. *J Clin Oncol* 2024;42:suppl 553; 2. Nakamura Y et al. *Clin Genitourin Cancer* 2025;23:102301; 3. Niedersuess-Beke D et al. *Clin Genitourin Cancer* 2025;23:102278; 4. Hatakeyama S et al. *J Clin Oncol* 2025;43:suppl 712; 5. Koshkin VS et al. *Cancer* 2022;128:1194–1205; 6. Powles T et al. *N Engl J Med* 2021;384:1125–1135.

Asian patient population: Outcomes and occurrence of skin reactions*

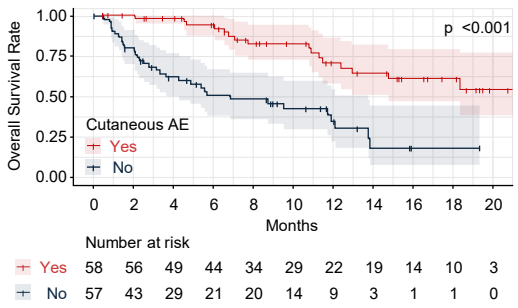
YUSHIMA Study-04[1]

PFS



mPFS: **skin AEs(+) 8.8 months**
mPFS: skin AEs(-) 3.3 months
(P < 0.001)

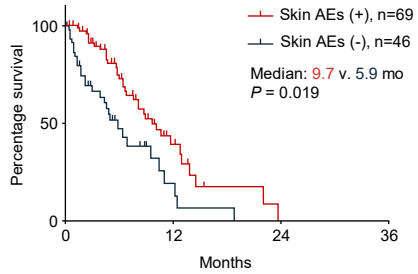
OS



mOS: **skin AEs(+) NR**
mOS: skin AEs(-) 6.8 months
(P < 0.001)

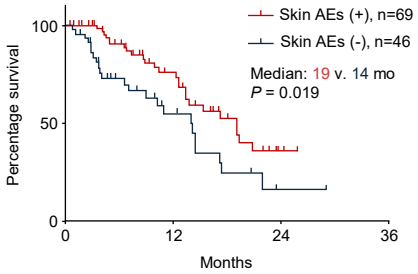
Japan multicenter retrospective study[2]

PFS



mPFS: **skin AEs(+) 9.7 months**
mPFS: skin AEs(-) 5.9 months
(P = 0.001)

OS



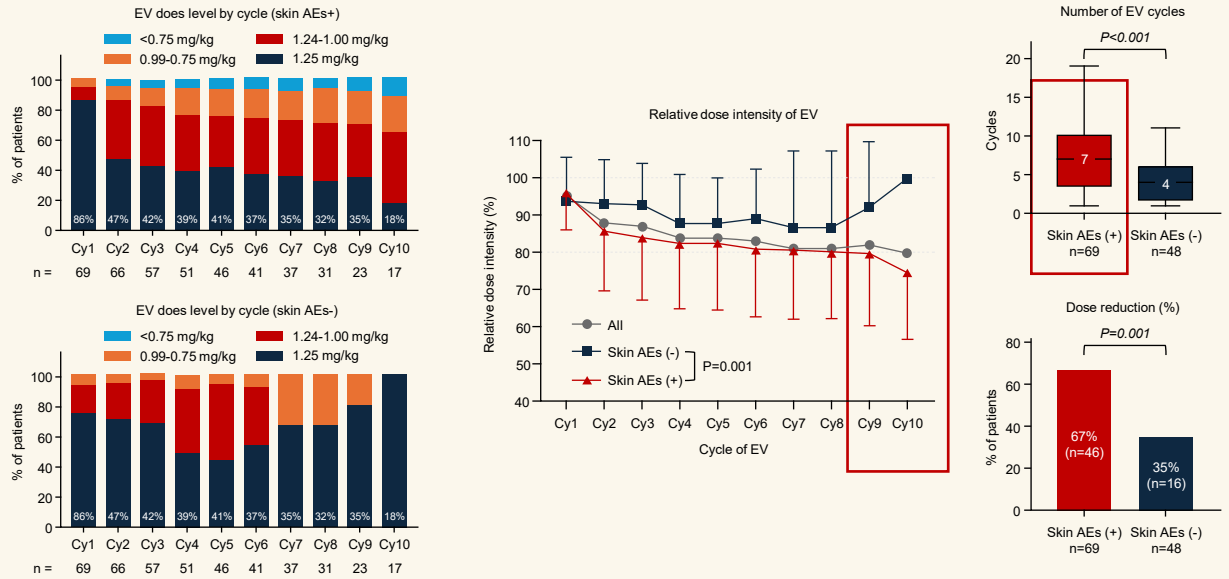
mOS: **skin AEs(+) 19 months**
mOS: skin AEs(-) 14 months
(P = 0.019)

This information has not been validated through pivotal or large-scale studies. This multivariable Cox regression analysis indicates that patients experiencing skin AEs may have prolonged PFS and OS compared with those without*[1,2]

***Disclaimer: This information has not been validated through pivotal or large-scale studies. Data are included here as part of the speaker's personal scientific opinion.**
AE, adverse event; EV, enfortumab vedotin; mo, month; mOS, median overall survival; mPFS, median progression-free survival; NR, not reported; OS, overall survival; PFS, progression-free survival.
1. Nakamura Y et al. *Clin Genitourin Cancer* 2025;23:10230; 2. Ozaki K et al. *J Urol* 2025;213:e1281.

Appropriate monitoring and management of AEs can minimize the impact of TRAEs, helping to optimize EV outcomes in clinical practice

Japan multicenter retrospective study:[1,2]
The impact of skin AEs on dose reduction*



- Patients with skin AEs experienced reduced dose stability across treatment cycles, compared with those without[1]
- Dose reduction in patients with skin AEs enabled prolonged treatment duration while maintaining clinical benefits[1]

Clinical implication

The occurrence of cutaneous AEs does not equate to inferior therapeutic efficacy

Effective monitoring and management of AEs, including dose adjustments, may support long-term administration of EV, helping to optimize treatment outcomes for patients[2]

***Disclaimer: This information has not been validated through pivotal or large-scale studies. Data are included here as part of the speaker's personal scientific opinion. Treatment with EV should always be initiated at the recommended dosage. Always refer to local guidance.**

AE, adverse event; EV, enfortumab vedotin; TRAE, treatment-related adverse event.

1. Hatakeyama S et al. *J Clin Oncol* 2025;43:suppl 712; 2. Nakamura Y et al. *Clin Genitourin Cancer* 2025;23:102301.

Contents

EV, enfortumab vedotin; LA/mUC, locally advanced/metastatic urothelial carcinoma.

Summary

EV has become a preferred treatment option for subsequent line therapies[1,2]

The emergence of ADCs has inaugurated the precision oncology era in UC therapeutics. EV, the first Nectin-4–directed ADC, has established its therapeutic position in aUC through the pivotal Phase III EV-301 trial[3]

Treatment efficacy and TRAEs in real-world studies were consistent with results of the EV-301 study[4–6]

- Patients receiving EV after 1L chemotherapy +/or ICI demonstrated better treatment outcomes vs those who did not[4]
- EV maintains clinically meaningful efficacy across clinically relevant subgroups of patients with aUC, including patients with a poor performance status, patients with a low eGFR, and patients with relevant medical comorbidities (e.g., peripheral neuropathy and diabetes mellitus)[5]
- Interruption or dose reduction of EV is unlikely to compromise its efficacy; early identification of TRAEs and appropriate dose adjustments may enhance the safe long-term administration of EV and maximize its effectiveness in clinical practice[6]
- The presence of cutaneous AEs was independently and significantly associated with prolonged PFS and OS,[4,6*] and may be useful for risk stratification and tailored treatment strategies[6†]

Large-scale reports of real-world treatment efficacy, AEs, and prognostic factors for EV monotherapy are limited[6]

Real-world studies may have some limitations, including reporting and documentation bias and missing data, but these results provide important insights and provide a basis for the use of EV in a broad patient population

***Disclaimer: This information has not been validated through pivotal or large-scale studies. Data are included here as part of the speaker's personal scientific opinion. Treatment with EV should always be initiated at the recommended dosage. Always refer to local guidance.** †Speakers expert opinion.

1L, first line; ADC, antibody–drug conjugate; AE, adverse event; aUC, advanced urothelial carcinoma; eGFR, estimated glomerular filtration rate; EV, enfortumab vedotin; ICI, immune checkpoint inhibitor; OS, overall survival; PFS, progression-free survival; TRAE, treatment-related adverse event; UC, urothelial carcinoma.

 2. Powles T et al. *Ann Oncol* 2024;35:485–490.

3. Powles T et al. *N Engl J Med* 2021;384:1125–1135; 4. Hatakeyama S et al. *J Clin Oncol* 2025;43:suppl 712; 5. Koshkin VS et al. *Cancer* 2022;128:1194–1205; 6. Nakamura Y et al. *Clin Genitourin Cancer* 2025;23:102301.

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PI, Prescribing Information