Genitourinary Masterclass

Unmet needs and the evolution of 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

EV, enfortumab vedotin.
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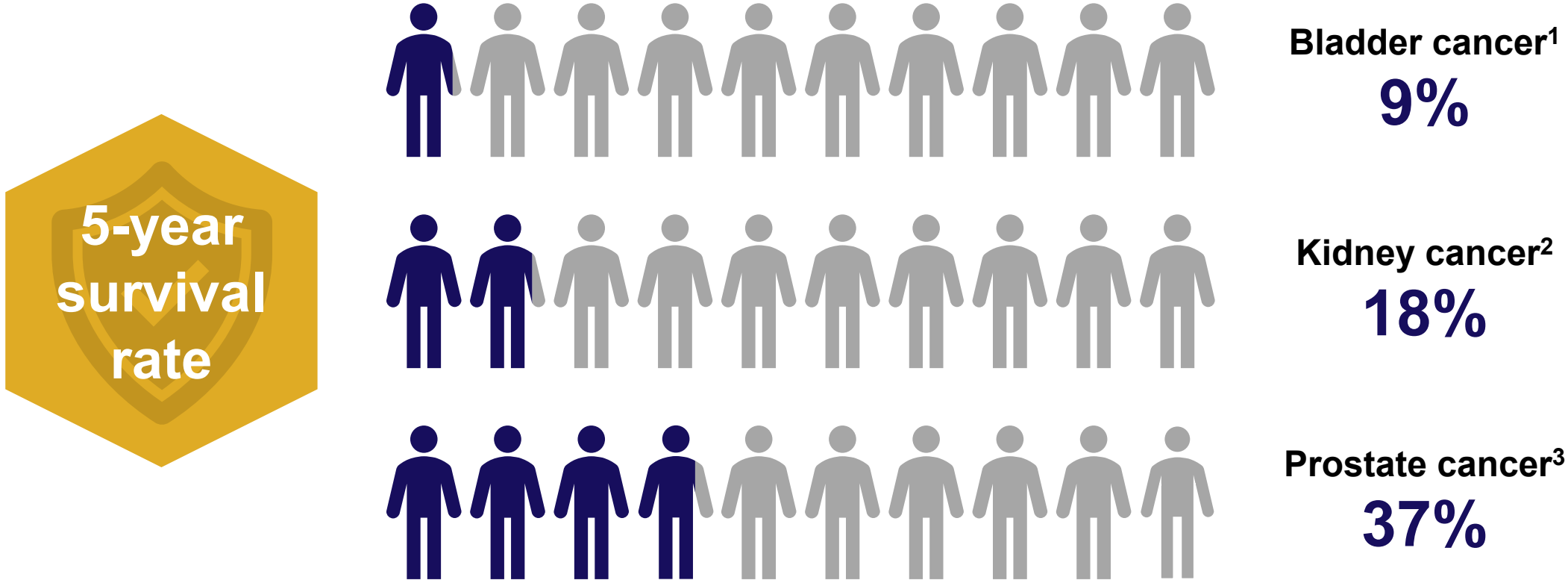
Speaker disclosures

- I have provided scientific advice to: Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Johnson & Johnson Global Services, Merck KGaA, Merck Sharp & Dohme, Pfizer & Roche
- I have participated in medical meetings organised by: Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Johnson & Johnson Global Services, Merck KGaA, Merck Sharp & Dohme, Pfizer & Roche

Survival rates for patients with mUC are poorer, compared with other urological cancers[1–3]

Survival rates after diagnosis of metastatic disease:*

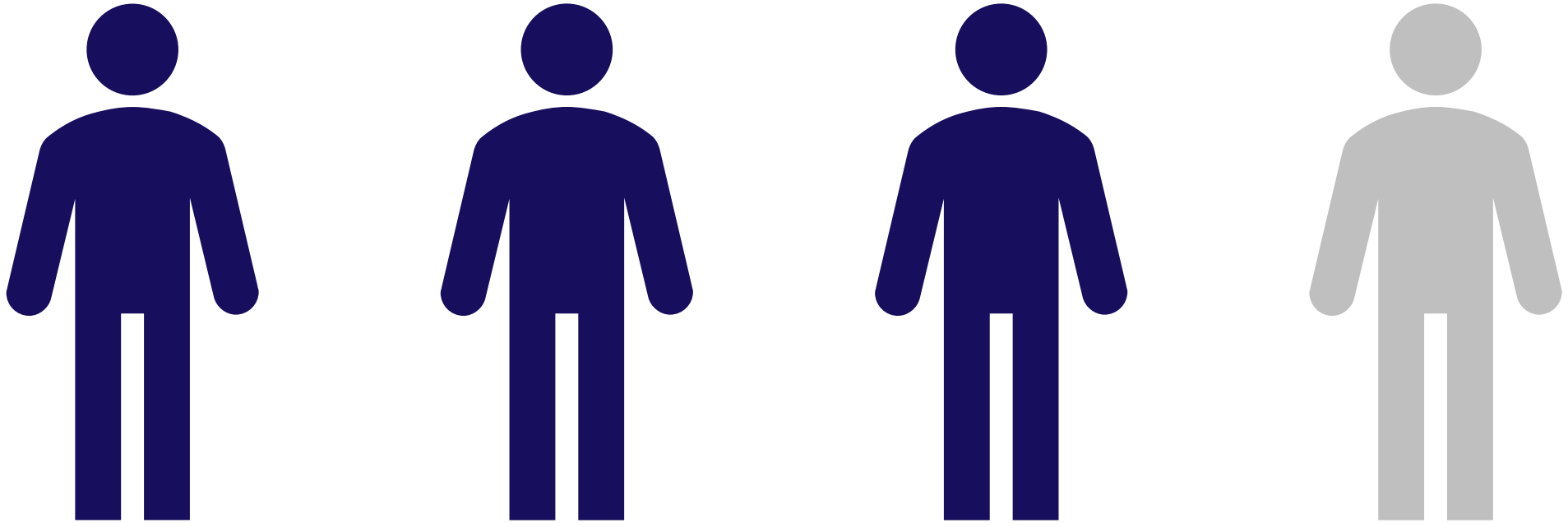


*Disease has spread to distant parts of the body such as the lungs, liver, brain, or bones.[1–3]
mUC, metastatic urothelial carcinoma.

1. American Cancer Society. Survival rates for bladder cancer. Available at: cancer.org/cancer/types/bladder-cancer/detection-diagnosis-staging/survival-rates.html. Last accessed: March 2025;
2. American Cancer Society. Survival rates for kidney cancer. Available at: cancer.org/cancer/types/kidney-cancer/detection-diagnosis-staging/survival-rates.html. Last accessed: March 2025;
3. American Cancer Society. Survival rates for prostate cancer. Available at: cancer.org/cancer/types/prostate-cancer/detection-diagnosis-staging/survival-rates.html. Last accessed: March 2025.

Advanced UC is a high-burden disease with a proportion of patients often not receiving any 1L treatment

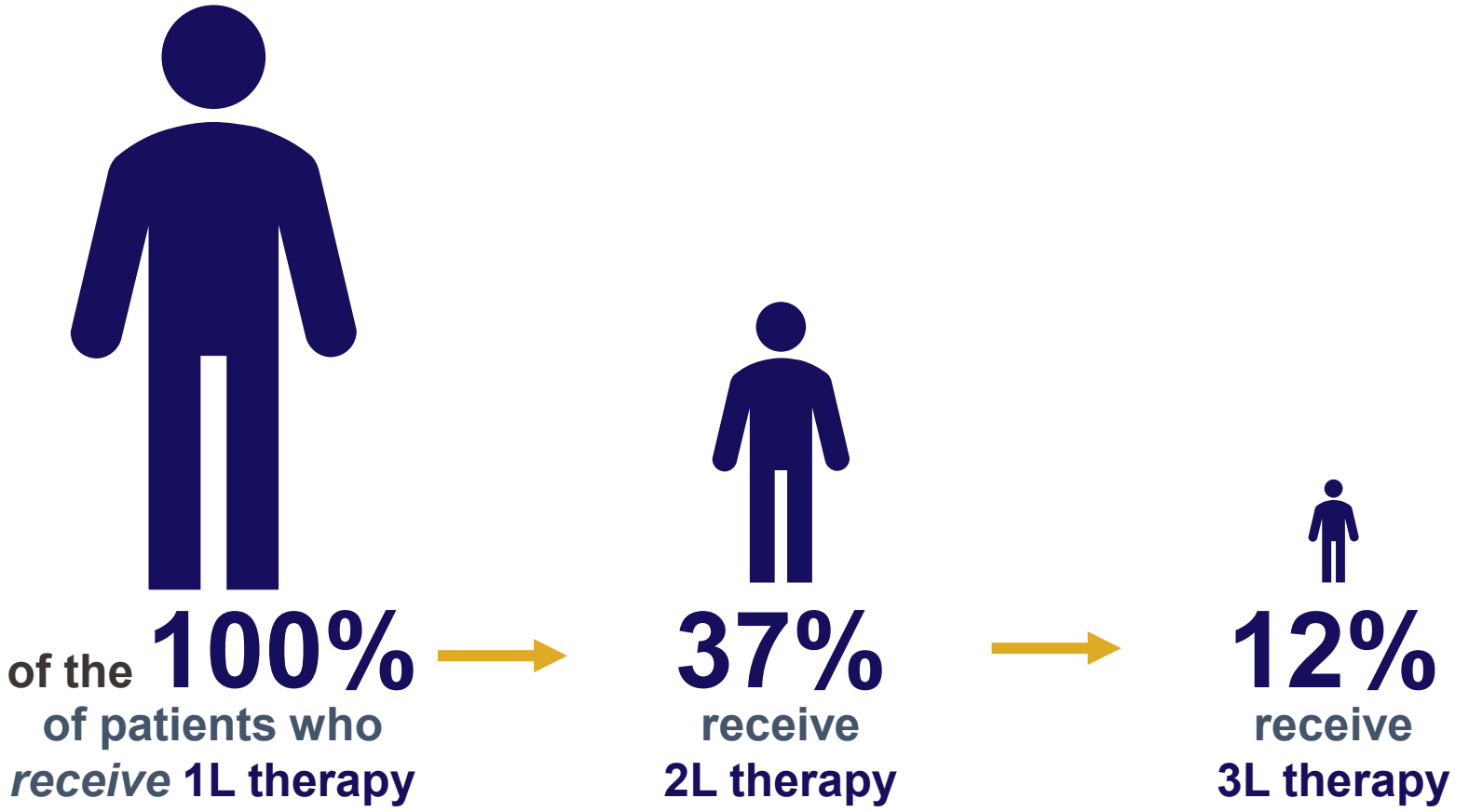
Of patients with LA/mUC who are eligible for treatment…



…nearly 1 in 4 do not receive 1L treatment

1L, first-line; LA/mUC, locally advanced or metastatic urothelial carcinoma; UC, urothelial carcinoma.
Morgans AK, et al. *Uro Oncol* 2023;41:357.e11–357.e21.

Of patients who do receive 1L treatment, many do not receive 2L or 3L therapy



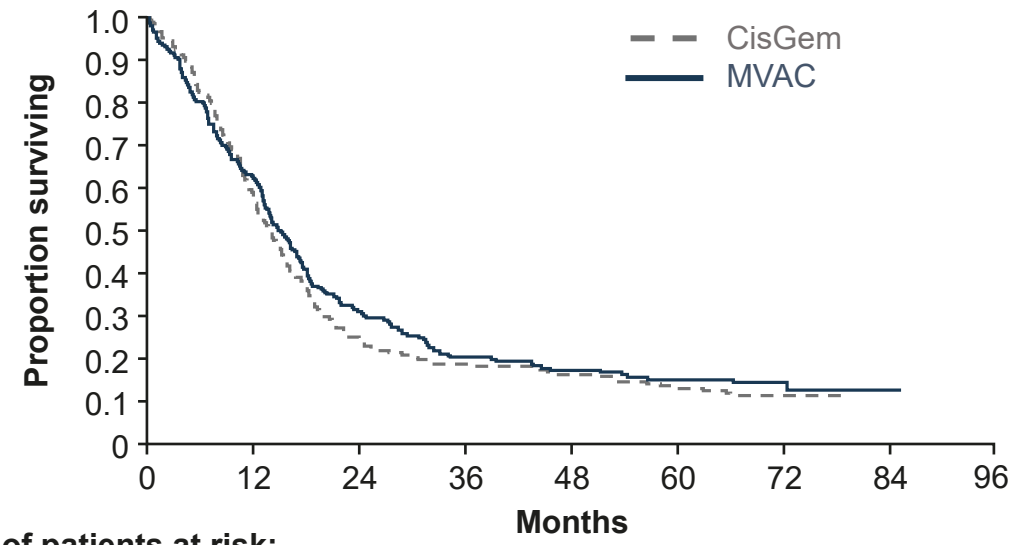
As few patients receive 2L+ treatment, 1L treatment choice is crucial

1/2/3L, first-/second-/third-line; UC, urothelial carcinoma.
Thomas VM et al. *JAMA Netw Open* 2024;7:e249417.

Platinum-based CT was the SOC in the 1L setting for decades[1]

	CisGem[3]	CarboGem[4]
Patient population	KPS ≥70, adequate bone marrow reserve, GFR ≥60 ml/min	Ineligible for Cis, WHO PS of 2, and/or impaired renal function (GFR >30 and <60 ml/min)
Comparator	MVAC	M-CAVI
mOS, months	13.8	9.3
mPFS, months	7.4	5.8
ORR, %	49.4	41.2
CR, %	12.2	3.4
AE Grade 3/4, % (top 5 most common toxicities)	• **Neutropenia, 71.1** • **Thrombocytopenia, 57.0** • Anaemia, 27.0 • Nausea/vomiting, 22.0 • Alopecia, 10.5	• **Neutropenia, 52.5** • **Thrombocytopenia, 48.3** • **Leukopenia, 44.9** • Infection, 11.8 • Febrile neutropenia, 4.2
QoL EORTC QLQ-C30	No difference (vs. MVAC)	No difference (vs. M-CAVI) (low compliance)
LoE, GoR[5]	I, A	I, A

OS CisGem vs. MVAC[2]



No. of patients at risk:

CisGem	203	118	50	36	30	23	7	0
MVAC	202	125	62	40	34	29	9	1

Data shown are for illustrative purposes only; direct comparisons should not be drawn

Platinum-based CT has limited efficacy in patients with advanced UC, with various Grade 3/4 AEs reported[2–4]

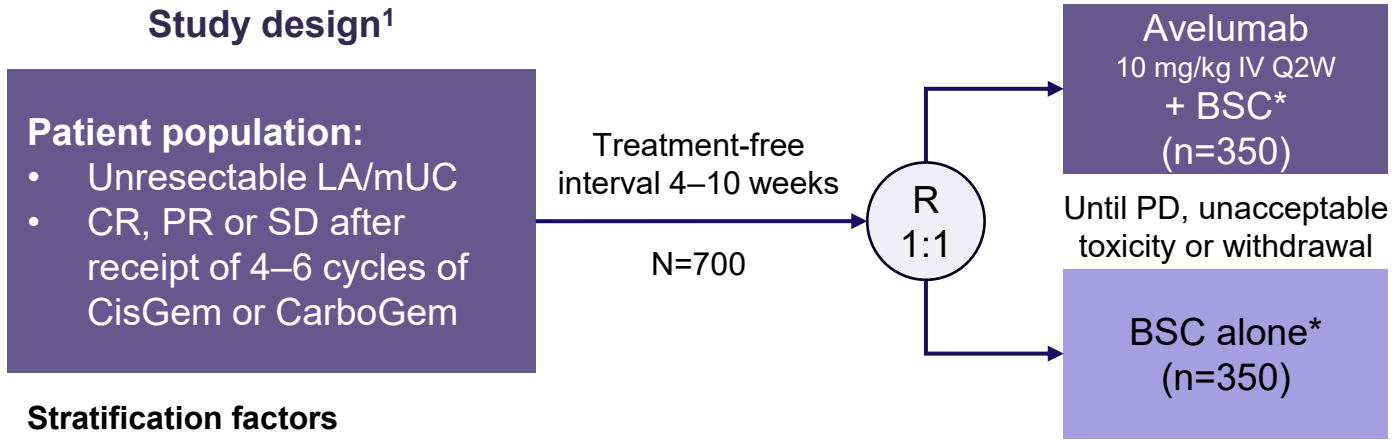
Table adapted from respective references.

AE, adverse event; Carbo, carboplatin; Cis, cisplatin; CR, complete response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; Gem, gemcitabine; GFR, glomerular filtration rate; GoR, grade of recommendation; KPS, Karnofsky performance status; LoE, level of evidence; M-CAVI, carboplatin, methotrexate and vinblastine; (m)OS, (median) overall survival; mPFS, median progression-free survival; MVAC, methotrexate, vinblastine, doxorubicin and cisplatin; ORR, overall response rate; CT, chemotherapy; PS, performance status; QoL, quality of life; SOC, standard of care; UC, urothelial carcinoma; WHO, World Health Organization.

1. Galluzzi L et al. *Oncogene* 2012;31:1869–1883; 2. von der Maase H et al. *J Clin Oncol* 2005;23:4602–4608; 3. von der Maase H et al. *J Clin Oncol* 2000;17:3068–3077; 4. De Santis M et al. *J Clin Oncol* 2012;30:191–199; 5. Powles T et al. *Ann Oncol* 2024;35:485–490.

Addition of maintenance avelumab to platinum-based CT was assessed in the JAVELIN Bladder 100 trial

Study design[1]



Stratification factors
- Best response to 1L platinum-based CT (CR or PR vs. SD)
- Metastatic site (visceral vs. non-visceral)

Primary endpoint
- OS

Primary analysis populations
- All randomised patients
- PD-L1+ population

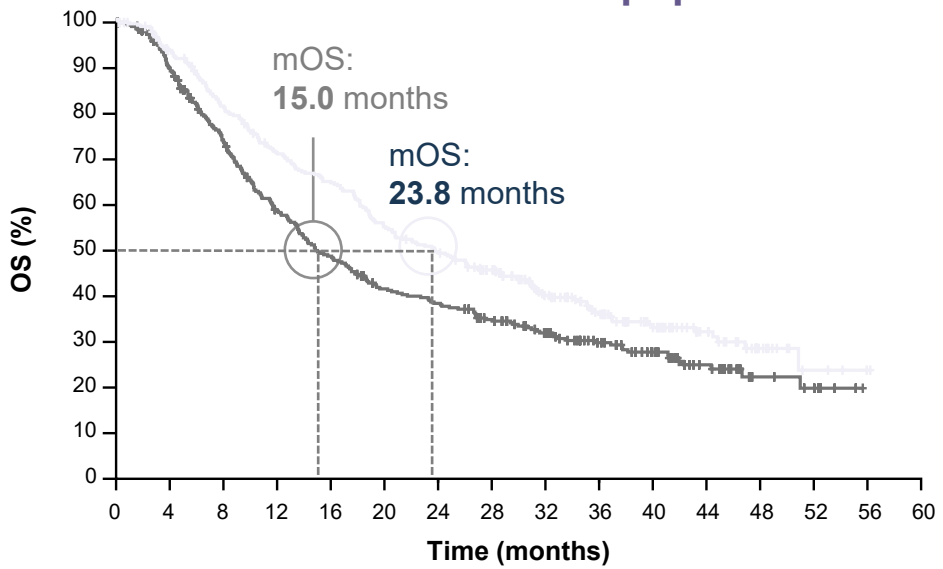
Secondary endpoints
- PFS and objective response per RECIST 1.1
- Time to response, DOR, and disease control
- Safety and tolerability

Select baseline characteristics† (avelumab arm)[2]	
Type of Platinum-based CT, %	**CisGem:** 52.3; **CarboGem:** 42
ECOG PS, %	**0:** 60.9; **≥1:** 39.1
Best response to 1L Platinum-based CT, %	**CR:** 25.7; **PR:** 46.6; **SD:** 27.7
Visceral metastases, %	54.6
PD-L1 positivity, %	54.0

*Administered according to local practice based on clinical judgment and the patient's condition. BSC included antibiotic agents, nutritional support, hydration and pain management; other systemic anti-tumour therapy was not permitted, but palliative local radiotherapy for isolated lesions was permitted;[1] †From ≥2 years of follow-up.[2]
1L, first-line; BSC, best supportive care; Carbo, carboplatin; Cis, cisplatin; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Gem, gemcitabine; IV, intravenous; LA, locally advanced; m, metastatic; OS, overall survival; CT, chemotherapy; PD, progressive disease; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PR, partial response; Q2W, every 2 weeks; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease; UC, urothelial carcinoma.
1. Powles T et al. *N Engl J Med* 2020;383:1218–1230; 2. Powles T et al. *J Clin Oncol* 2023;41:3486–3492.

Avelumab maintenance became the next 1L SOC and demonstrated an improvement in OS vs BSC

JAVELIN Bladder 100: OS in the overall trial population[1]



No. at risk:

Avelumab + BSC	350	318	274	237	216	183	164	140	99	74	53	31	13	4	1	0
BSC alone	350	304	243	190	158	131	121	103	82	62	46	27	10	7	0	

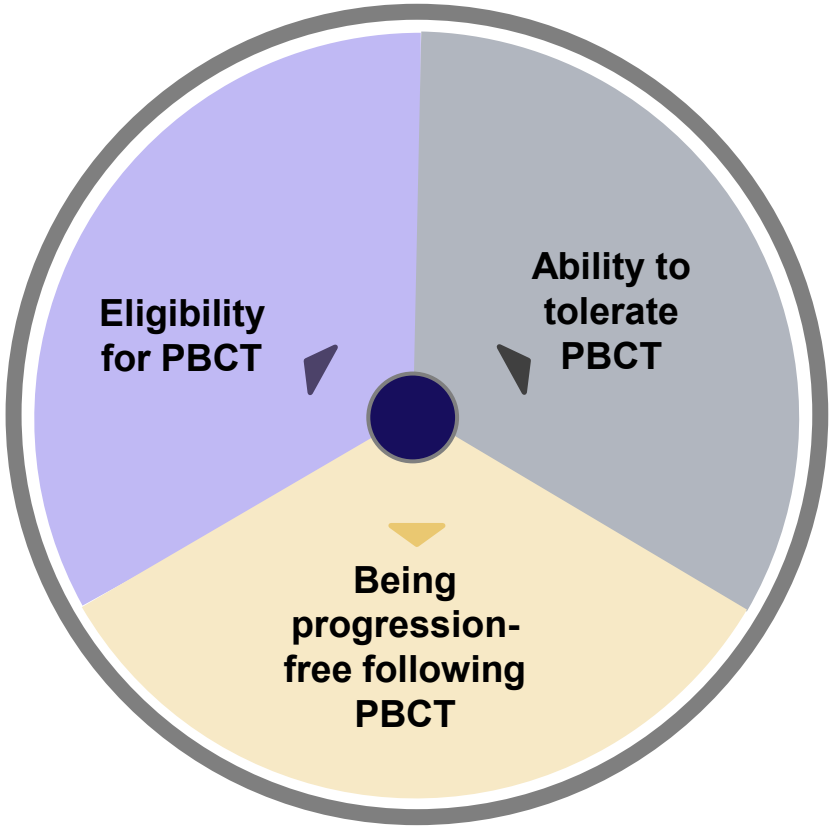
	Avelumab + BSC	BSC	HR (95% CI) p-value
mOS,[1] months	23.8	15	0.76 (0.63–0.91) 0.0036
mPFS,[1] months	5.5	2.1	0.54 (0.46–0.64) <0.0001
ORR,[2] %	9.7	1.4	–
CR,[2] %	6.0	0.9	–
AE/TRAE[1]* Any grade, % Grade 3 or 4, %	98.3/78.2 53.8/19.5	NA†	–
TRAE leading to discontinuation,[4] %	11.6	NA‡	–
QOL[5] (FBISI-18, EQ-5D-5L, TTD)	Results were similar between both arms		

An improvement in OS was seen for platinum-based CT + maintenance avelumab, however this was only seen in a highly selective patient population[1,2]

Because the trial met its objective in the initial analysis (data cut-off: October 21, 2019),[1] updated analysis are considered exploratory, and all p-values are descriptive.
*In patients with ≥12 months of avelumab treatment.[1] †Safety data from the primary analysis were 77.7% for any grade AE or 25.5% for ≥ Grade 3 AEs.[2] ‡TRAEs leading to discontinuation in the primary analysis were 0.6% in BSC arm.[2]
Avelumab + BSC median follow-up: 38.0 months; BSC median follow-up: 39.6 months.[1]
AE, adverse event; BSC, best supportive care; CI, confidence interval; CR, complete response; EQ-5D-5L, European Quality of Life 5-Dimension 5-Level Questionnaire; FBISI-18, National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Bladder Symptom Index-18; HR, hazard ratio; (m)OS, (median) overall survival; mPFS, median progression-free survival; NA, not available; ORR, overall response rate; QOL, quality of life; TRAE, treatment-related adverse event; TTD, time to deterioration.
1. Powles T et al. *J Clin Oncol* 2023;41:3486–3492; 2. Powles T et al. *N Engl J Med* 2020;383:1218–1230; 3. Powles T et al. *N Engl J Med* 2020;383:1218–1230 (supplementary appendix);
4. Powles T et al. *J Clin Oncol* 2023;41:3486–3492 (supplementary appendix); 5. Grivas P et al. *Eur Urol* 2023;83:320–328.

Despite becoming the SOC, specific factors determined whether patients could receive avelumab maintenance

Avelumab maintenance is dependent on:



PBCT, platinum-based chemotherapy.
BAVENCIO (avelumab). Summary of Product Characteristics.

Real-world 1L treatment patterns show that not all patients eligible to receive avelumab receive it

~20–40%

of patients with unresectable/mUC who receive 1L platinum-based CT will go on to receive avelumab maintenance[1]

RWE in the US[2]

- US Oncology Network
- 30 April 2020–30 June 2021

32%

of the population receiving 1L platinum-based CT received avelumab maintenance

RWE in the US[3]

- US Flatiron Health longitudinal EHR-derived database
- 01 April 2019–31 January 2022

19.9%

of the overall population receiving 1L platinum-based CT received avelumab maintenance

RWE in France[4]

- French national database for hospitalisation records
- 01 January 2020–30 June 2022

17.0%

of patients received avelumab maintenance

Response to platinum-based CT cannot be predicted at the time of 1L treatment selection; many patients may be unable to receive maintenance treatment[1,5]

1L, first-line; CT, chemotherapy; EHR, electronic health record; mUC, metastatic urothelial carcinoma; RWE, real-world evidence.

1. Powles T, et al. *N Engl J Med* 2024;390:875–888; 2. Li H, et al. *J Clin Oncol* 2023;41:483–483; 3. Morgans AK, et al. *Clin Genitourin Cancer* 2025;23:102270; 4. Joly F, et al. Presented at ESMO 2024. Poster 2001P; 5. BAVENCIO (avelumab). Summary of Product Characteristics.

Further improving OS outcomes with platinum-based CT with immunotherapy seemed unfeasible

Study	Study arms	Population	OS HR (95% CI)	p-value	Result
DANUBE[1]	**Durvalumab** *vs. PBCT*	PD-L1 positive	0.89 (0.71–1.11)	0.30	×
	Durvalumab + tremelimumab *vs. PBCT*	ITT	0.85 (0.72–1.02)	0.075	×
IMvigor130[2]	**Atezolizumab** *vs. PBO + PBCT*	PD-L1 positive	0.68 (0.43–1.08)	NA	×
	Atezolizumab + PBCT *vs. PBO + PBCT*	ITT	0.83 (0.69–1.00)	0.027	NA
KEYNOTE-361[3]	**Pembrolizumab** *vs. PBCT*	PD-L1 positive	1.01 (0.77–1.32)	–	×
	Pembrolizumab + PBCT *vs. PBCT*	ITT	0.86 (0.72–1.02)	0.0407	×

Immunotherapy alone or in addition to platinum-based CT did not improve OS outcomes in advanced UC[1–3]

Table for illustrative purposes; studies should not be compared.
CI, confidence interval; CT, chemotherapy; HR, hazard ratio; ITT, intention to treat; NA, not available; OS, overall survival; PBCT, platinum-based chemotherapy; PBO, placebo; PD-L1, programmed cell death ligand 1; UC, urothelial carcinoma.
1. Powles T, et al. *Lancet Oncol* 2020;21:1574–1588; 2. Galsky MD, et al. *Lancet* 2020;395:1547–1557; 3. Powles T, et al. *Lancet Oncol* 2021;22:931–945.

Summary

Today, few patients with mUC receive 2L or 3L of treatment.[1] It is therefore **crucial that patients receive the 1L treatment that is most likely to result in the greatest clinical benefit**

PBCT ± maintenance avelumab has shown efficacy benefits over former BSC for patients[2,3] but:

- Not all patients are **eligible** to receive PBCT[4]
- Not all patients **tolerate or remain progression-free** following PBCT,[2,5] making them ineligible to receive avelumab
- We cannot identify patients who are likely to respond to PBCT **before initiating 1L treatment**

Many patients in real-world studies do not receive maintenance avelumab after 1L platinum-based CT[6,7]

A treatment option **more effective** than PBCT and **suitable for a broad patient population** was required for the treatment of 1L advanced UC

1/2/3L, first-/second-/third-line; BSC, best standard of care; mUC, metastatic urothelial carcinoma; CT, chemotherapy.

1. Thomas VM et al. *JAMA Netw Open* 2024;7:e249417; 2. Von der Maase H, et al. *J Clin Oncol* 2000;18:3068–3077; 3. Powles T et al. *J Clin Oncol* 2023;41:3486–3492;
4. Azam F, et al. *Cureus* 2024 Aug 9;16(8):e66520. doi: 10.7759/cureus.66520; 5. De Santis M, et al. *J Clin Oncol* 2012:191–199; 6. Morgans AK, et al. *Clin Genitourin Cancer* 2025 Feb;23(1):102270; 7. Joly F, et al. Presented at ESMO 2024. Poster Number: 2001P.

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PI, Prescribing Information

Genitourinary Masterclass

Recent data and guidelines in LA/mUC

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

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

A more effective treatment option suitable for a broad patient population was required for the treatment of 1L advanced mUC

Nivolumab + CisGem
CheckMate 901[1]

PBCT + maintenance avelumab
JAVELIN Bladder 100[2]

EV+P
EV-302[3]

Patient populations

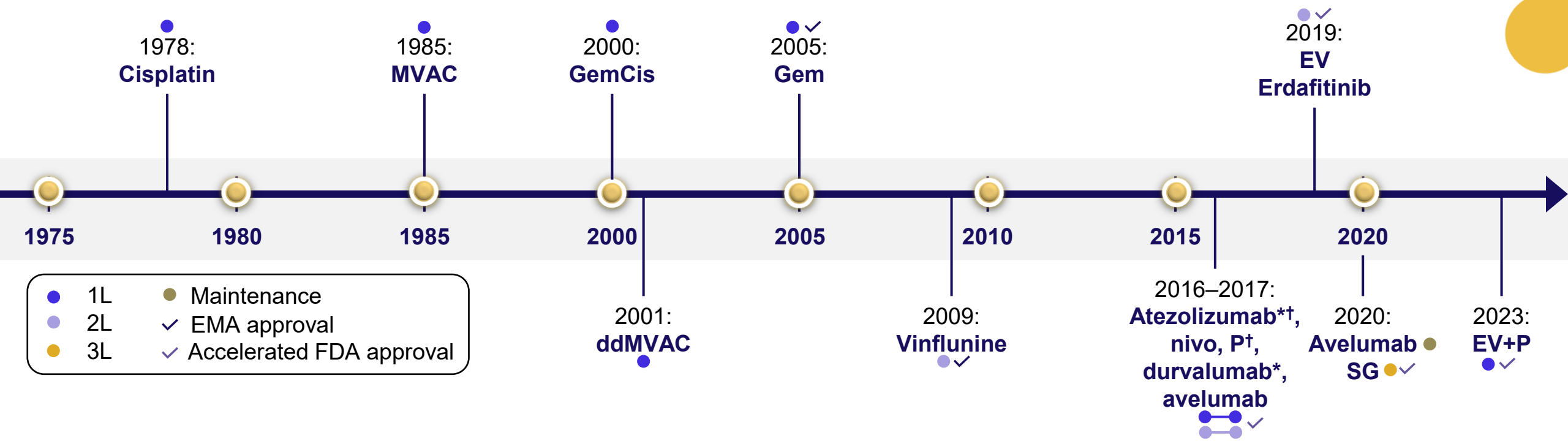
Cisplatin eligible

No disease progression* following 1L PBCT

Platinum eligible

*Complete response, partial response, or stable disease.
1L, first line; Cis, cisplatin; EV+P, enfortumab vedotin plus pembrolizumab; Gem, gemcitabine; m, metastatic; PBCT, platinum-based chemotherapy; UC, urothelial carcinoma.
1. van der Heijden MS et al. *N Engl J Med* 2023;389:1778–1789; 2. Powles T et al. *N Engl J Med* 2020;383:1218–1230; 3. Powles T et al. *N Engl J Med* 2024;390:875–888.

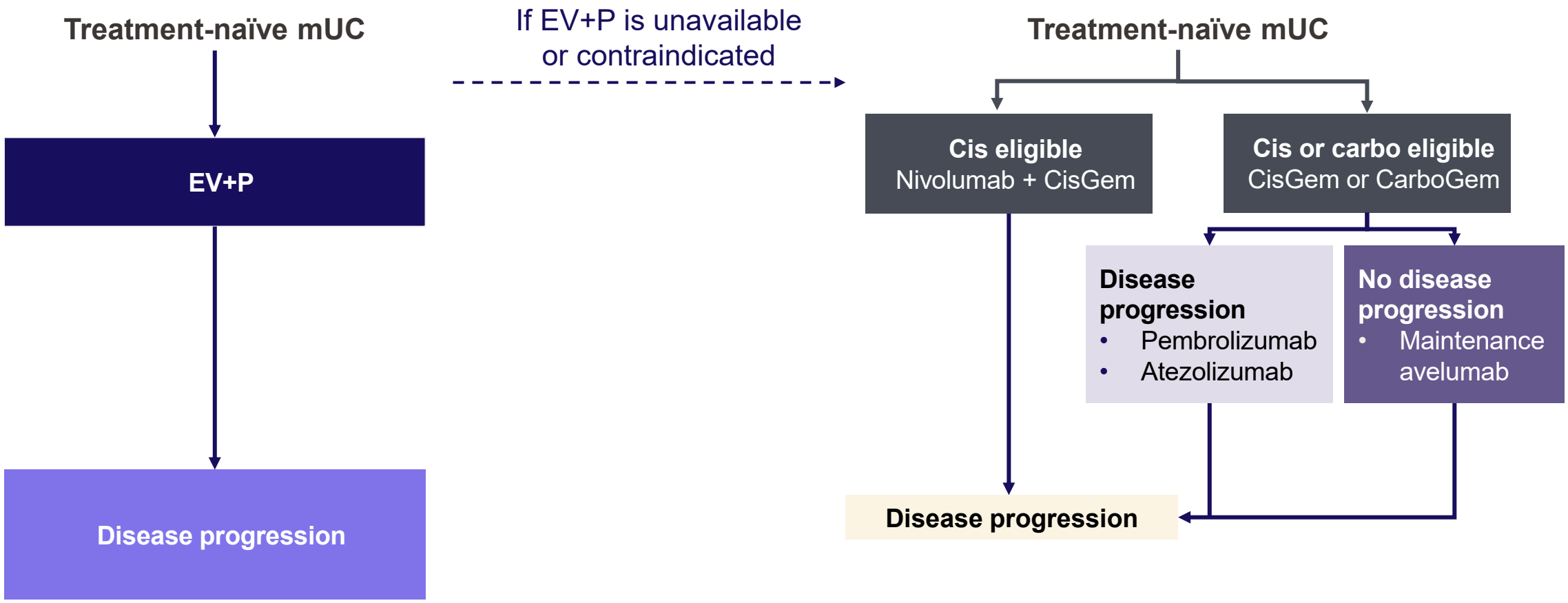
Evolution of front-line therapy in metastatic bladder cancer



- Bladder cancer affects approximately 2.4 people per 100,000 women and 9.5 people per 100,000 men worldwide per year
- Between 5–10% of people with UC have metastatic disease at diagnosis
- Groundbreaking results from EV-302 and CheckMate 901 presented at ESMO 2023 redefined the treatment landscape of previously untreated mUC

*Withdrawn for 2L indication in US; †Restricted to cisplatin-ineligible PD-L1+ or platinum-ineligible patients.
1L/2L/3L, first-/second-/third-line; Cis, cisplatin; (dd)MVAC, (dose-dense) methotrexate, vinblastine, doxorubicin, and cisplatin; EMA, European Medicines Agency; ESMO European Societyy for Medical Oncology; EV, enfortumab vedotin; FDA, U.S. Food and Drug Administration; Gem, gemcitabine; (m)UC, (metastatic) urothelial carcinoma; Nivo, nivolumab; P, pembrolizumab; PD-L1, programmed cell death ligand 1; SG, sacituzumab govitecan.
Roviello G et al. *Nat Rev Urol* 2024;21:580–592.

Recent data updates are reflected in clinical guideline updates – ESMO guidelines



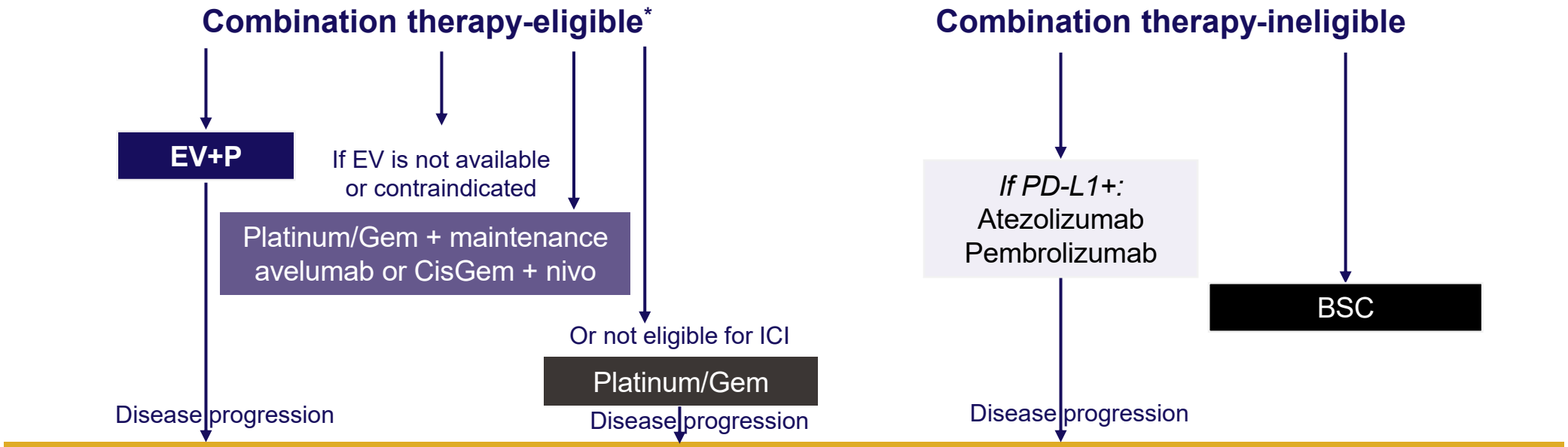
Disclaimer: The ESMO Clinical Practice Guideline aligns with the EU regulatory approval for pembrolizumab for the 1L treatment of unresectable or metastatic UC in adults. EV+P is not approved for the 1L treatment of unresectable or metastatic UC in adults in some countries/regions. All HCPs should refer to their own country's specific Prescribing Information.

Figure adapted from 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; UC, urothelial carcinoma.

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

Recent data updates are reflected in clinical guideline updates – EAU guidelines



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

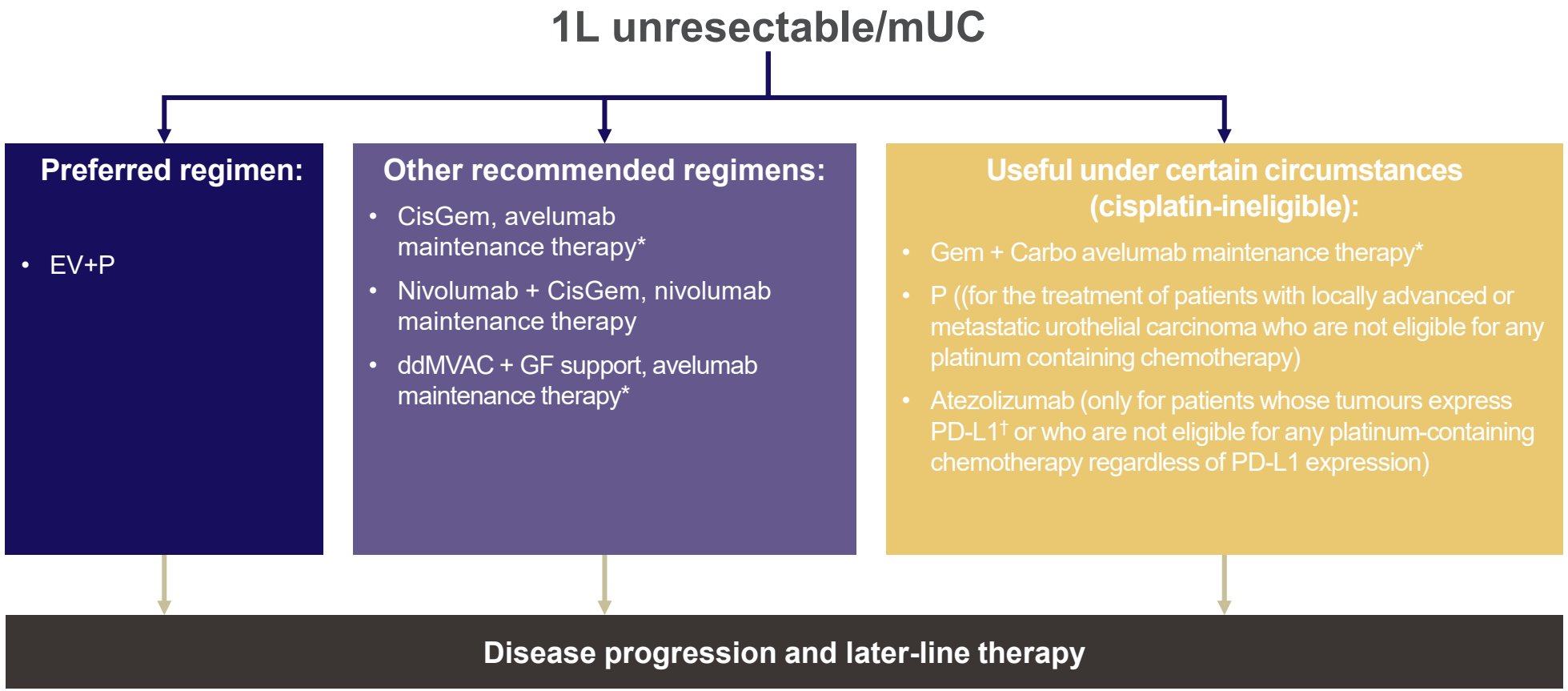
Disclaimer: EV+P is not approved for the 1L treatment of unresectable or metastatic UC in adults in some countries/regions. All HCPs should refer to their own country's specific Prescribing Information.

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; Cis, cisplatin; EAU, European Association of Urology; EV, enfortumab vedotin; ICI, immune checkpoint inhibitor; Gem, gemcitabine; GFR, glomerular filtration rate; HCP, healthcare professional; m, metastatic; nivo, nivolumab; P, pembrolizumab; PBCT, platinum-based chemotherapy; PD-L1, programmed cell death ligand 1; SmPC, Summary of Product Characteristics; 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: July 2025.

Recent data updates are reflected in clinical guideline updates – NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)



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*Maintenance therapy with avelumab only if there is no progression on first-line platinum-containing chemotherapy; †Atezolizumab: SP142 assay, PD-L1–stained tumor-infiltrating immune cells covering ≥5% of the tumor area.

1L, first line; Carbo, carboplatin; Cis, cisplatin; DDMVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; EV, enfortumab vedotin-ejfv; Gem, gemcitabine; GF, growth factor; HCP, healthcare professional; LA/mUC, locally advanced/metastatic urothelial carcinoma; NCCN, National Comprehensive Cancer Network; P, pembrolizumab; PD-L1, programmed cell death ligand 1.

CheckMate 901: Nivolumab + CisGem vs. CisGem alone

Study design[1,2]

Patient population
- Untreated, unresectable LA/mUC
- PD-1/L1 inhibitor-naïve
- Adequate renal function (GFR ≥60 ml/min)
- ECOG PS 0 or 1

N=608

R 1:1

Stratification factors
- PD-L1 expression*
- Presence of liver metastases

Combination phase

Nivolumab (360 mg on D1) + Gem (1000 mg/m² on D1/D8) + Cis (70 mg/m² on D1) Q3W up to 6 cycles†

Treatment until disease progression per BICR, clinical progression, unacceptable toxicity, or completion of maximum number of cycles

Gem (1000 mg/m² on D1/D8) + Cis (70 mg/m² on D1) Q3W†

Monotherapy phase

Nivolumab (480 mg) Q4W

Until disease progression, unacceptable toxicity, withdrawal, or up to 24 months‡

Up to 6 cycles or until disease progression, unacceptable toxicity, or withdrawal Q3W†

Primary endpoints
- OS
- PFS

Secondary endpoints
- OS and PFS by central review
- Change from baseline in EORTC QLQ-C30

Exploratory outcomes
- OR (CR and PR) per RECIST
- Safety and tolerability

CheckMate 901[1,2]	
Patient population	• ECOG PS **0, 1** • **Cis eligible**
Comparator	• CisGem (max. 6 cycles) • Subsequent therapy before PD: Avelumab maintenance (9%)/atezolizumab (2%)[2]
Primary endpoints	OS; PFS by BICR

Select baseline characteristics (nivo/cis/gem), all values in %[1,2]	
Cis eligible, %	100
Renal pelvis/other tumor type at initial diagnosis, %	10.9/11.8
Liver metastasis at initial diagnosis, %	21.1
PD-L1-positive expression, %	36.5

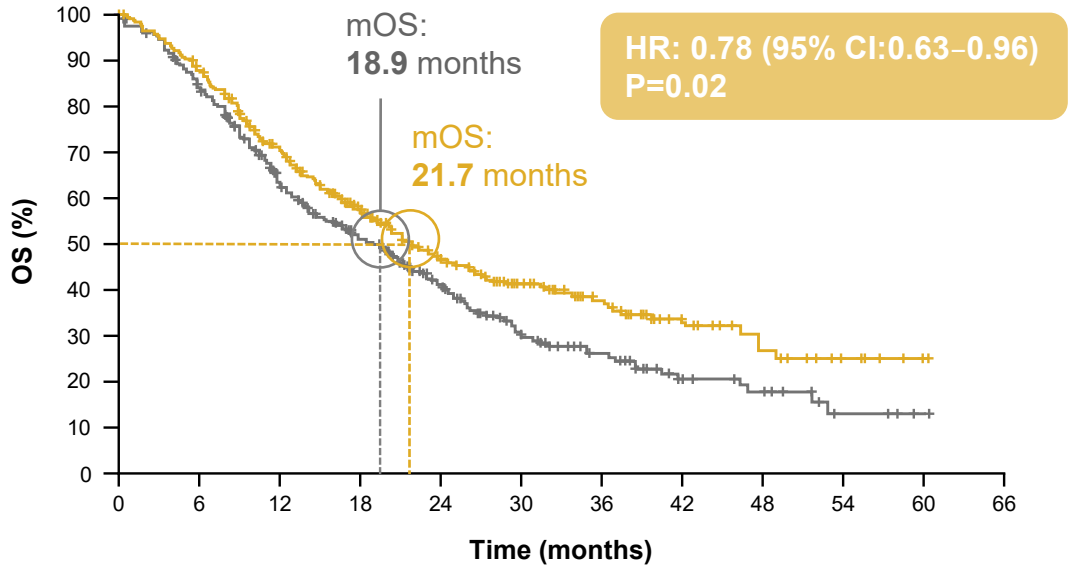
*Per PD-L1 pharmDx IHC assay.[1]†Patients who discontinued cisplatin could be switched to CarboGem for the remainder of the platinum-doublet cycles (up to six in total); ‡A maximum of 24 months from first dose of nivolumab administered as part of the nivo + CisGem combination.[1]

BICR, blinded independent central review; Carbo, carboplatin; Cis, cisplatin; CR, complete response; D, day; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ, European Ogranization of Research and Treatment of Cancer Quality of Life Questionnaire; Gem, gemcitabine; GFR, glomerular filtration rate; IHC, immunohistochemistry; LA, locally advanced; m, metastatic; Nivo, nivolumab; OR, objective response; OS, overall survival; PD-1/L1, programmed cell death ligand 1; PD, progressive disease; PFS, progression-free survival; PR, partial response; PS, performance status; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomization; UC, urothelial carcinoma.

1. van der Heijden MS et al. *N Engl J Med* 2023;389:1778–1789; 2. van der Heijden MS et al. Presented at ESMO 2023. LBA7.

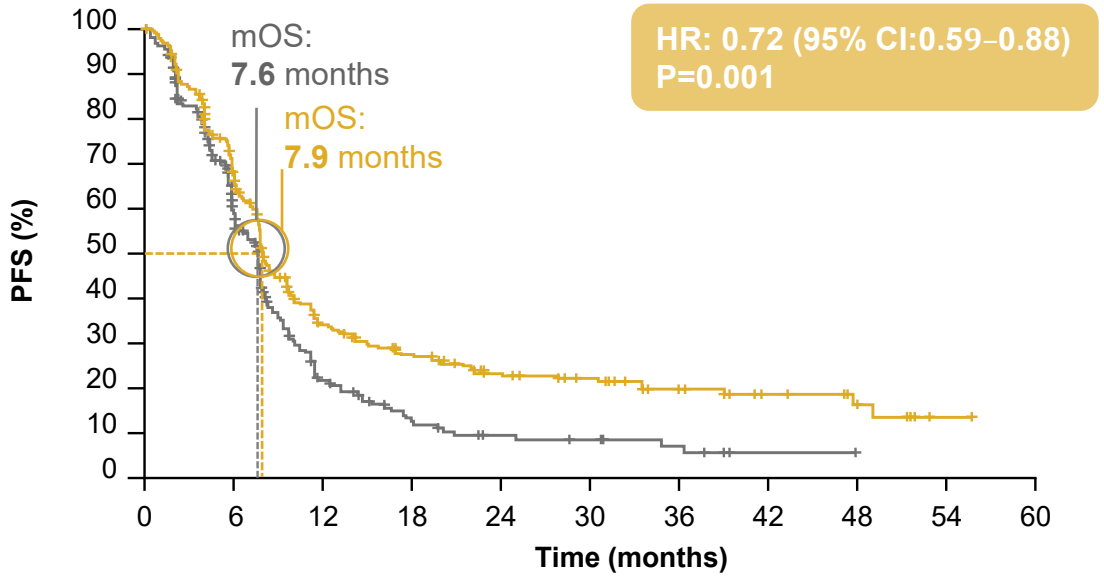
CheckMate 901: Nivolumab + CisGem was associated with significant improvements in OS vs. CisGem alone, with a consistent safety profile

OS in the ITT population



No. at risk:												
Nivo + CisGem	304	264	196	142	97	69	48	25	15	7	2	0
CisGem	304	242	166	122	82	49	33	17	13	4	1	0

PFS in the ITT population

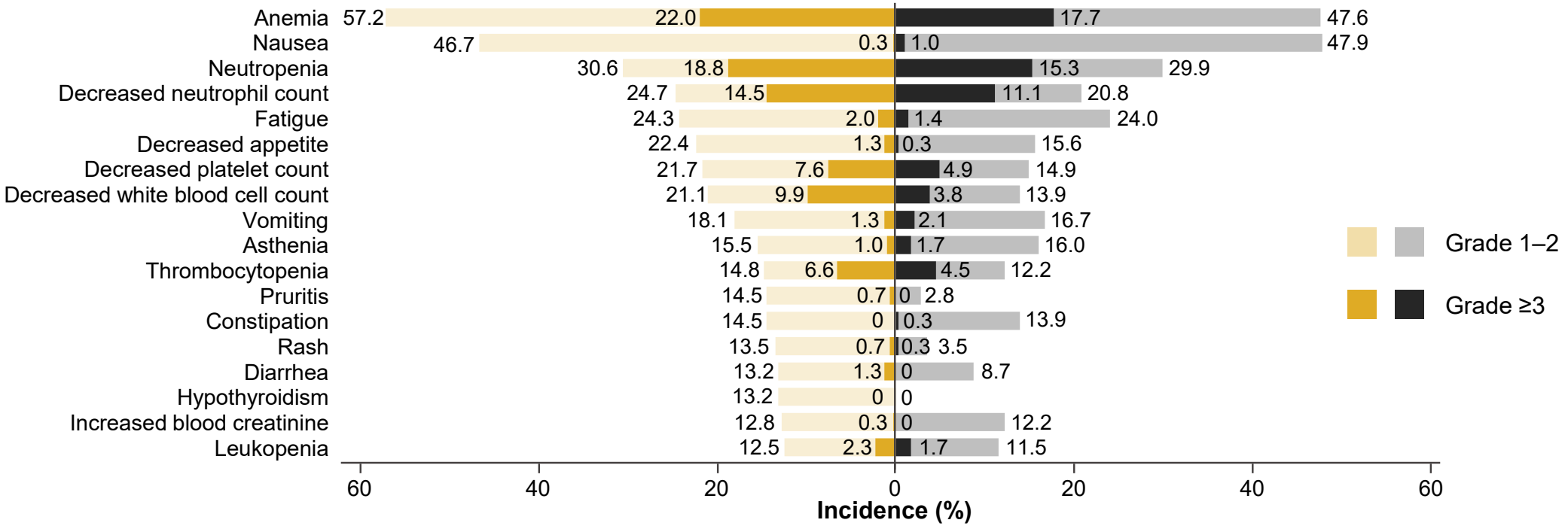


No. at risk:												
Nivo + CisGem	304	179	82	57	41	31	19	11	6	1	0	
CisGem	304	119	35	17	10	8	5	1	0	0	0	

Median follow-up: 33.6 months.
CI, confidence interval; Cis, cisplatin; Gem, gemcitabine; HR, hazard ratio; ITT, intention to treat; (m)OS, (median) overall survival; Nivo, nivolumab; No., number; PFS, progression-free survival; TRAE, treatment-related adverse event.
van der Heijden MS et al. *N Engl J Med* 2023;389:1778–1789.

CheckMate 901: The safety profile of nivolumab + CisGem was consistent with the established safety profiles of these agents in previous trials

TRAE occurrence* (any grade in ≥10% of patients)	Nivo + CisGem (n=304)		CisGem (n=288)	
	Any grade	Grade ≥3†	Any grade	Grade ≥3†
Overall, %	97.4	61.8	92.7	51.7
Leading to discontinuation, %	21.1	11.2	17.4	7.6



*Includes events that occurred in treated patients between the first dose and 30 days after the last dose of study therapy. The tornado plot displays individual, TRAEs of any grade occurring in ≥10% of treated patients in either arm; †One Grade 5 event occurred in each arm (sepsis in the Nivo+ CisGem arm and acute kidney injury in the CisGem arm).

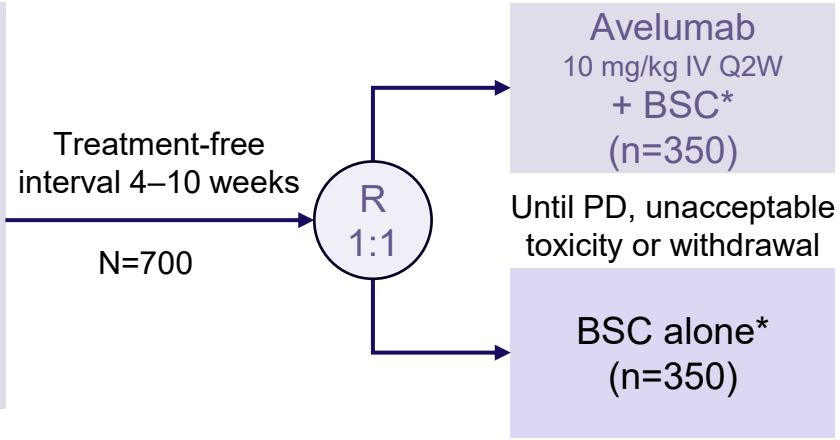
Cis, cisplatin; Gem, gemcitabine; Nivo, nivolumab; TRAE, treatment-related adverse event.

van der Heijden MS et al. *N Engl J Med* 2023;389:1778–1789.

JAVELIN Bladder 100: Avelumab maintenance vs. BSC alone[1,2]

Study design[1]

Patient population:
- Unresectable LA/mUC Immunotherapy-naïve
- Adequate renal function (CrCl ≥50 ml/min)
- ECOG PS 0 or 1
- Ongoing CR, PR, or SD after receipt of 4–6 cycles of standard 1L PBCT (GemCis or GemCarbo)



Primary endpoint
- OS

Primary analysis populations
- All randomized patients
- PD-L1+ population

Secondary endpoints
- PFS and objective response per RECIST 1.1
- Time to response, DOR, and disease control
- Safety and tolerability

Stratification factors
- Best response to 1L PBCT (CR or PR vs. SD)
- Metastatic site (visceral vs. non-visceral)

JAVELIN Bladder 100[1]	
Patient population	• ECOG PS 0/1 • Prior to initiating avelumab: received 4–6 cycles of PBCT and **did not have disease progression**
Comparator	BSC (unblinded)
Primary endpoint	OS

Select baseline characteristics† (avelumab arm)[2]	
Type of PBCT, %	**CisGem:** 52.3; **CarboGem:** 42
ECOG PS, %	**0:** 60.9; **≥1:** 39.1
Best response to 1L PBCT, %	**CR:** 25.7; **PR:** 46.6; **SD:** 27.7
Visceral metastases, %	54.6
PD-L1 positivity, %	54.0

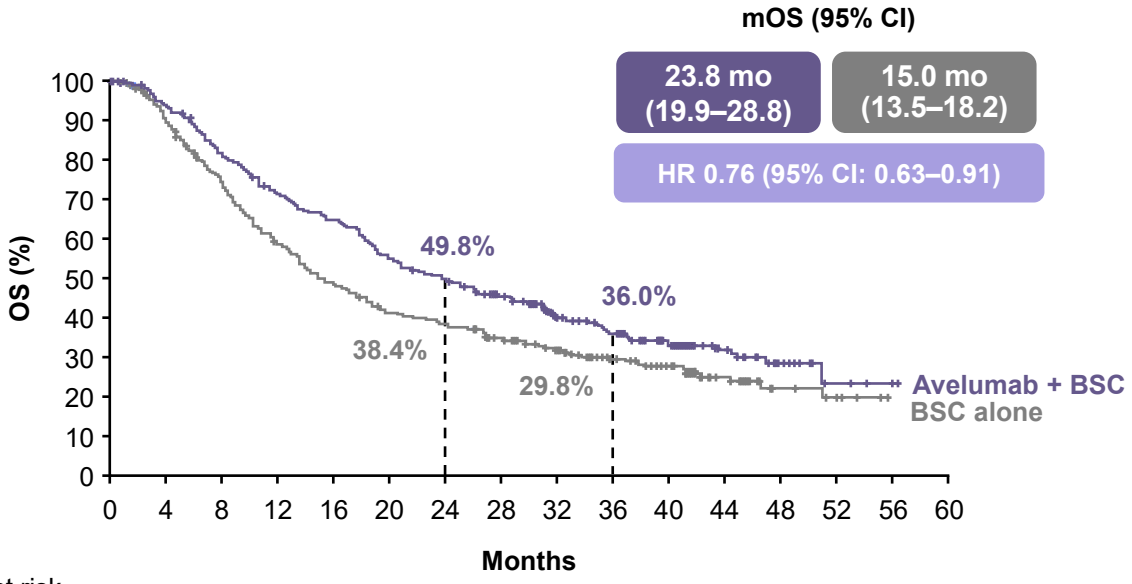
*Administered according to local practice based on clinical judgment and the patient's condition. BSC included antibiotic agents, nutritional support, hydration and pain management; other systemic anti-tumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was permitted;[1] †From ≥2 years of follow-up.[3]

1L, first line; BSC, best supportive care; Carbo, carboplatin; Cis, cisplatin; CR, complete response; CrCl, creatinine clearance; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; IV, intravenous; LA, locally advanced; m, metastatic; OS, overall survival; PBCT, platinum-based chemotherapy; PD, progressive disease; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PR, partial response; Q2W, every 2 weeks; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease; UC, urothelial carcinoma.

1. Powles T et al. *N Engl J Med* 2020;383:1218–1230; 2. Powles T et al. *J Clin Oncol* 2023;41:3486–3492.

JAVELIN Bladder 100: Long-term follow-up outcomes from start of avelumab 1L maintenance

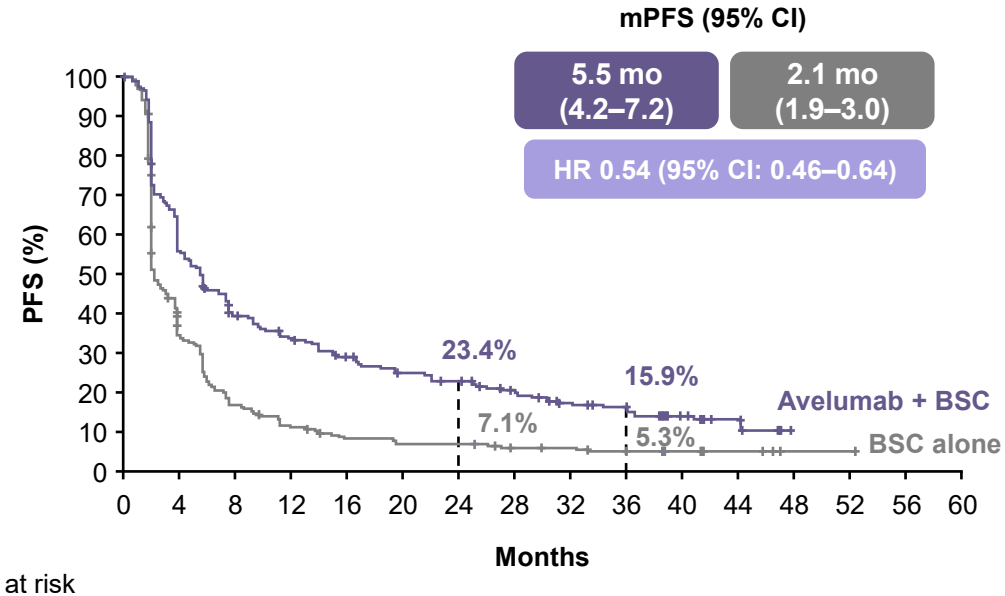
OS



No. at risk

Avelumab + BSC	350	318	274	237	216	183	164	140	99	74	53	31	13	4	1	0
BSC alone	350	304	243	190	158	131	121	103	82	62	46	27	10	7	0	

PFS



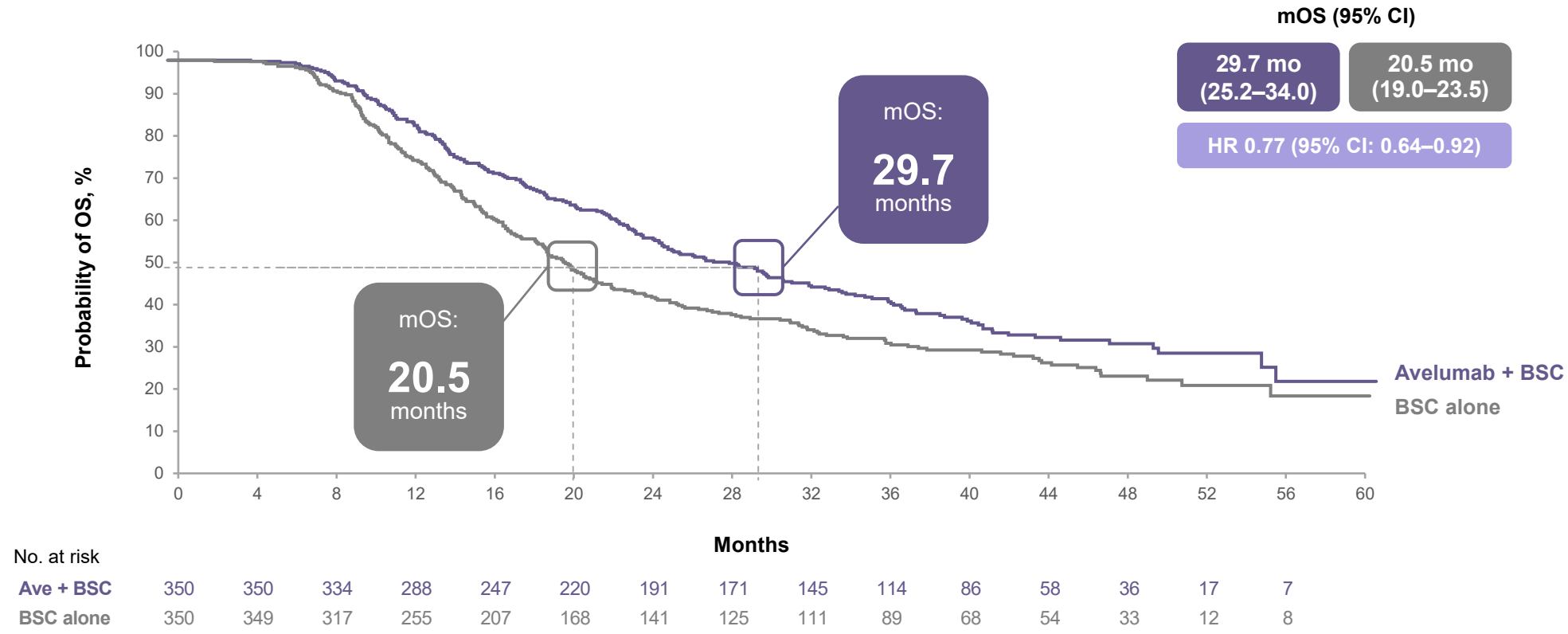
No. at risk

Avelumab + BSC	350	182	126	105	88	73	67	43	32	25	12	6	0				
BSC alone	350	101	51	33	24	19	19	14	13	9	6	4	1	1	0		

Data cutoff: June 4, 2021. Median follow-up was 38.0 months with avelumab + BSC and 39.6 months with BSC alone (≥2 years in all patients).
1L, first-line; BSC, best supportive care; CI, confidence interval; HR, hazard ratio; mo, months; (m)OS, (median) overall survival; (m)PFS, (median) progression-free survival; No., number.
Powles T, et al. *J Clin Oncol* 2023;41:3486–3492.

JAVELIN Bladder 100: mOS data from start of 1L PBCT

Exploratory *post hoc* analysis of OS from the start of 1L PBCT in select patients treated with avelumab 1L maintenance following no PD on 1L PBCT*[1]



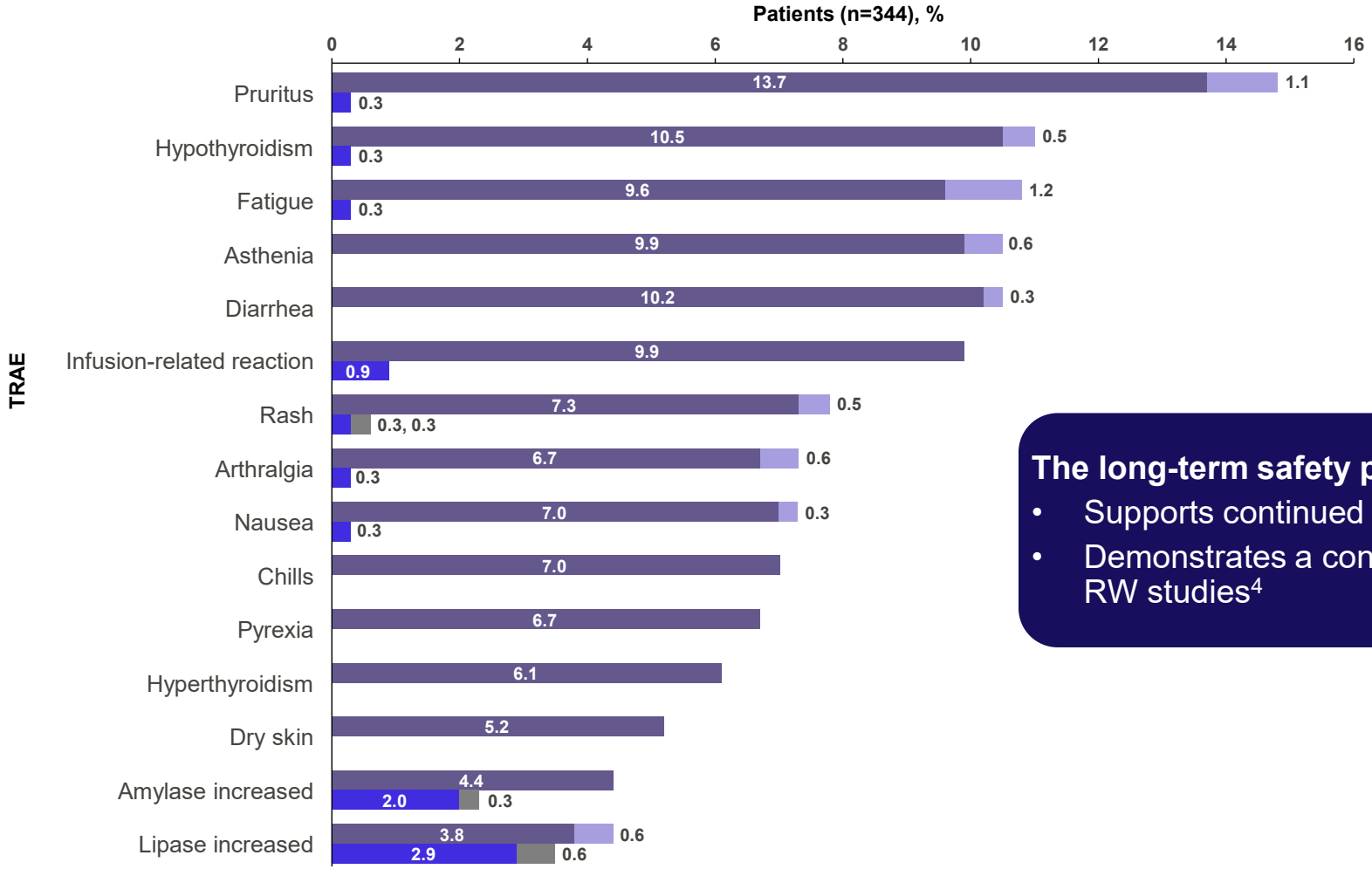
*Median follow-up of ≥38 months. OS data calculated from the start of 1L chemotherapy is inclusive of 4–6 cycles of platinum-containing chemotherapy, 4–10 weeks of treatment-free interval, randomized study treatment with avelumab + BSC or BSC alone, and subsequent therapy. This is an exploratory, *post hoc* analysis of OS data calculated from the start of chemotherapy, and there are limitations to the interpretation of these data.

1L, first-line; Ave, avelumab; BSC, best supportive care; CI, confidence interval; HR, hazard ratio; mo, months; (m)OS, (median) overall survival; PBCT, platinum-based chemotherapy; PD, progressive disease.

Grivas P et al. *ESMO Open* 2023;8:102050.

JAVELIN Bladder 100: Safety outcomes

Most common TRAEs observed with avelumab + BSC in initial analysis and ≥2-year follow-up in JAVELIN Bladder 100[1]



TRAEs of any grade (occurring in ≥5% of patients)
- Initial analysis
- Since initial analysis

TRAEs of Grade ≥3 (occurring in ≥2% of patients)
- Initial analysis
- Since initial analysis

The long-term safety profile of avelumab 1L maintenance:
- Supports continued treatment until disease progression[2,3]
- Demonstrates a consistent safety profile across clinical and RW studies[4]

1L, first-line; BSC, best supportive care; RW, real-world; TRAE, treatment-related adverse event.

1. Powles T et al. *J Clin Oncol* 2023;41:3486–3492 (suppl); 2. BAVENCIO (Avelumab). Summary of Product Characteristics; 3. EAU. Muscle-invasive and metastatic bladder cancer. Available at: https://www.uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer. Last accessed: July 2025; 4. Kearney M et al. Presented at ISPOR 2024. Poster C068.

EV-302: Enfortumab vedotin + pembrolizumab vs. PBCT

Study design[1,2]

Patient population
- Untreated, unresectable LA/mUC
- PD-1/L1 inhibitor-naïve
- Adequate renal function (≥30 ml/min)*
- ECOG PS ≤2†

N=866

R 1:1

Stratification factors
- Cis eligibility
- PD-L1 expression (high/low)
- Liver metastases (present/absent)

EV+P
No maximum treatment cycles for EV, maximum of 35 cycles for P (n=442)

CisGem or CarboGem
Maximum of 6 cycles (n=444)

Treatment until disease progression per BICR, clinical progression, unacceptable toxicity, or completion of maximum number of cycles

Maintenance therapy could be added following PBCT

Primary endpoints
- PFS (by BICR)
- OS

Select secondary endpoints
- ORR per RECIST 1.1 by BICR and investigator assessment
- Safety

EV-302/KEYNOTE-A39[1,2]	
Patient population	• ECOG PS **≤2** • GFR **≥30 ml/min**
Comparator	• CisGem or CarboGem (max. 6 cycles) • Avelumab maintenance (~30% of population)
Primary endpoint	PFS by BICR; OS

Select baseline characteristics (EV+P)[1]	
Cis eligible, %	54.3
Upper tract, %	30.5
Visceral metastases, %	71.9
Liver metastases, %	22.6
High PD-L1+ expression (CPS ≥10), %	58.0

*GFR ≥30 ml/min measured by the Cockcroft–Gault formula, modification of Diet in Renal Disease or 24-hour urine test;[2] †Patients with an ECOG PS of 2 were required to meet additional criteria: hemoglobin ≥10 g/dL, GFR ≥50 ml/min, may not have NYHA Class III heart failure.[2]

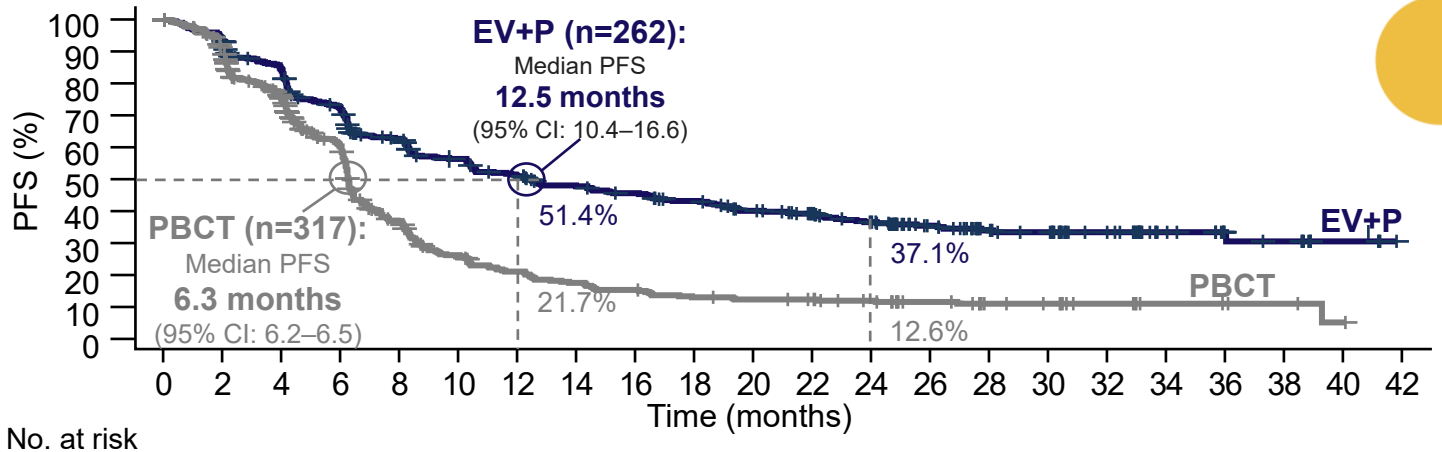
BICR, blinded independent central review; Carbo, carboplatin; Cis, cisplatin; CPS, combined positive score; ECOG, Eastern Cooperative Oncology Group; EV, enfortumab vedotin; Gem, gemcitabine; GFR, glomerular filtration rate; LA, locally advanced; m, metastatic; NYHA, New York Heart Association; ORR, objective response rate; OS, overall survival; P, pembrolizumab; PBCT, platinum-based chemotherapy; PD-1/L1, programmed cell death receptor/ligand 1; PFS, progression-free survival; PS, performance status; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumours; UC, urothelial carcinoma.

1. Powles T et al. *N Engl J Med* 2024;390:875–888; 2. Powles T et al. *N Engl J Med* 2024;390:875–888 (supplementary appendix).

EV-302: With an additional 1 year of follow-up, EV+P significantly improved PFS and OS vs. PBCT in the overall population

PFS benefit with EV+P was maintained with 1 additional year of follow-up

- PFS benefit was consistent across all pre-defined subgroups
- Median PFS with EV+P was 12.5 months
- **HR 0.48 (95% CI: 0.41–0.57), p<0.00001**
- **12 months**

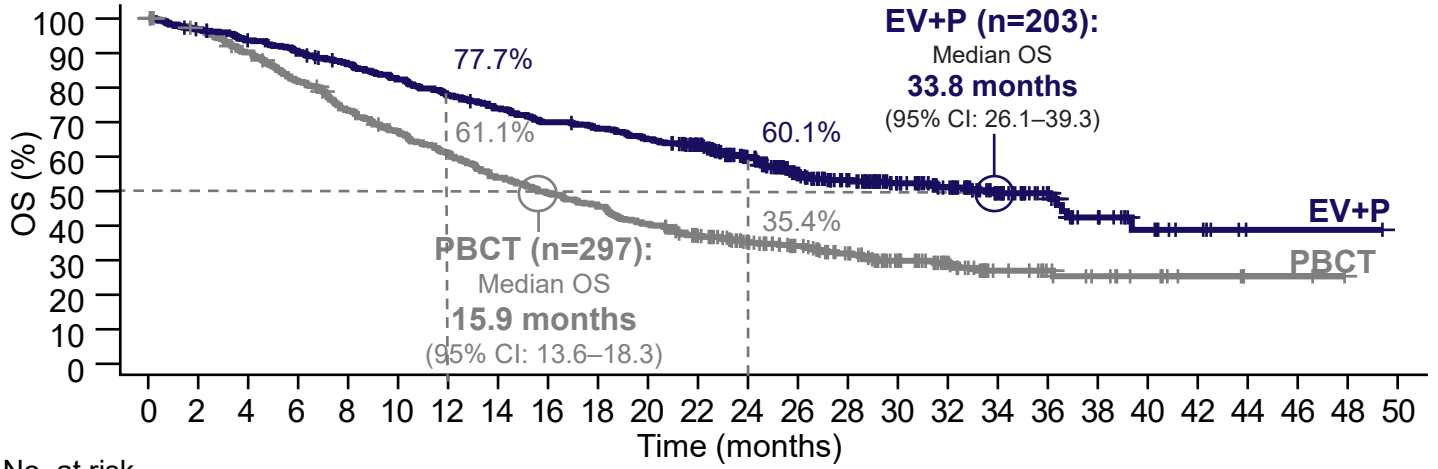


No. at risk

EV+P	442	409	361	304	254	223	200	182	172	159	143	128	109	82	62	57	42	22	14	10	4	
PBCT	444	379	296	213	125	86	68	57	50	42	39	37	31	23	16	14	9	5	4	3	1	

OS benefit with EV+P was also maintained with 1 additional year of follow-up

- OS benefit was consistent across all pre-defined subgroups
- Median OS with EV+P was 33.8 months
- **HR 0.51 (95% CI: 0.43–0.61), p<0.00001**



No. at risk

EV+P	442	426	409	394	375	356	336	319	302	293	280	252	206	161	133	102	79	52	32	19	11	6	1	1	1
PBCT	444	423	393	356	317	290	263	233	214	197	176	148	121	102	81	59	43	24	18	13	9	5	2	2	

Data cutoff: August 8, 2024.

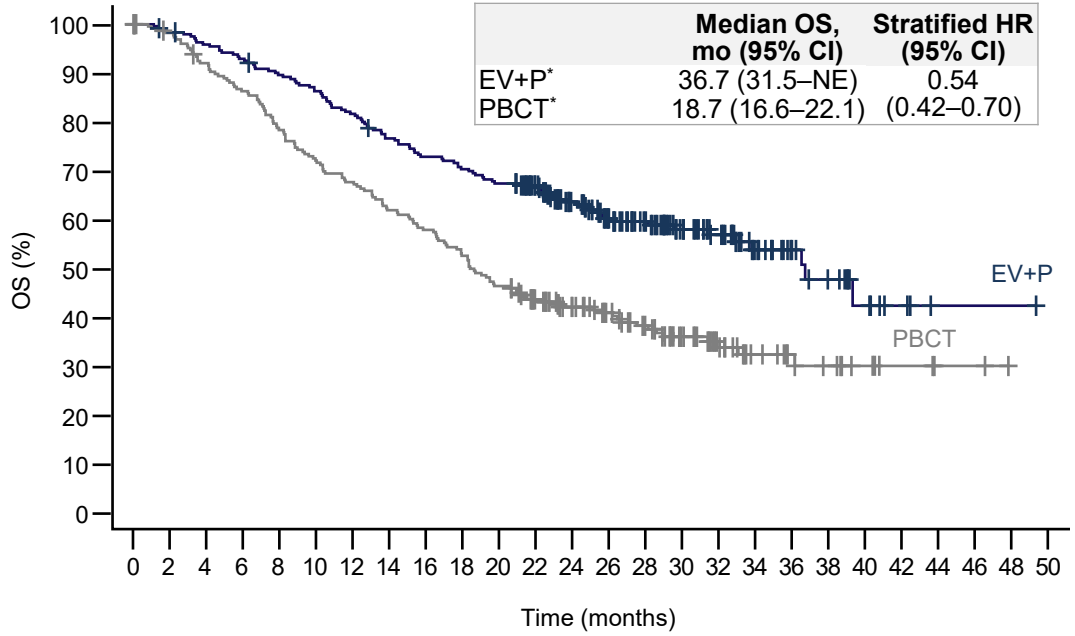
CI, confidence interval; EV, enfortumab vedotin; HR, hazard ratio; OS, overall survival; P, pembrolizumab; PBCT, platinum-based chemotherapy; PFS, progression-free survival.

Powles T presented at ASCO GU 2025. Abstract 664.

EV-302: OS by cisplatin eligibility

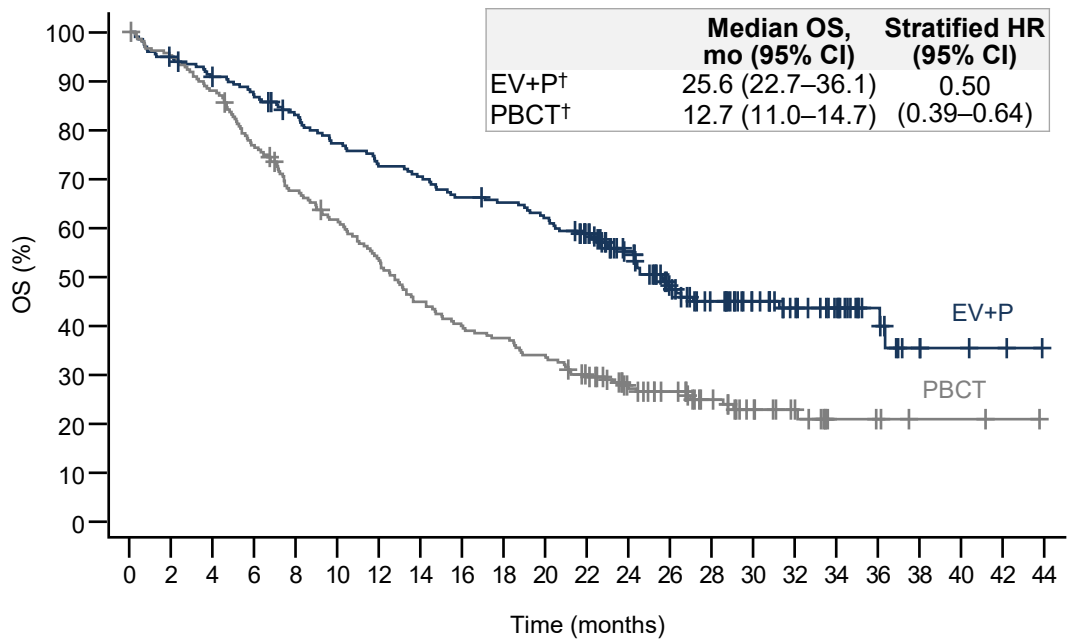
- **OS benefit was consistent with the overall population regardless of cisplatin eligibility**

Cisplatin eligible



No. at risk																								
EV+P	244	239	232	225	216	208	197	184	175	169	162	147	121	98	83	64	50	30	20	14	8	4	1	1	1
PBCT	234	224	209	196	178	164	154	141	132	120	106	90	77	65	54	41	30	19	14	11	7	4	2	2	

Cisplatin ineligible



No. at risk																								
EV+P	198	187	177	169	159	148	139	135	127	124	118	105	85	63	50	38	29	22	12	5	3	2		
PBCT	210	199	184	160	139	126	109	92	82	77	70	58	44	37	27	18	13	5	4	2	2	1		

Data cutoff: August 8, 2024.

*Events/N in the cisplatin-eligible population were 101/244 for EV+P and 143/234 for PBCT. †Events/N in the cisplatin-ineligible population were 102/198 for EV+P and 154/210 for PBCT.

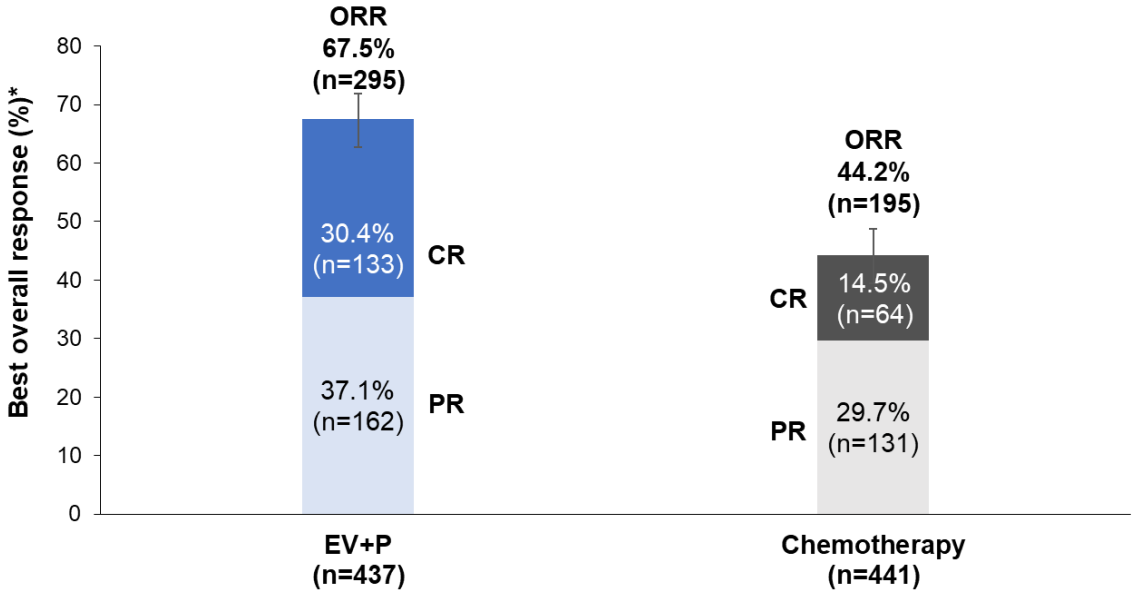
EV, enfortumab vedotin; HR, hazard ratio; mo, months; NE, not estimable; No., number; OS, overall survival; P, pembrolizumab; PBCT, platinum-based chemotherapy.

Powles T. Presented at ASCO GU 2025. Abstract 664.

EV-302: Confirmed ORR (CR+PR) for patients treated with EV+P was doubled vs. patients treated with PBCT

- **CR rate in the EV+P arm was twice that in the chemotherapy arm**
- Among patients with a confirmed CR, 66.2% in the EV+P arm and 59.4% in the chemotherapy arm had an initial PR, and later converted to CR
- Baseline characteristics among responders (CR+PR) in the EV+P arm were generally consistent with the ITT population

Confirmed ORR by BICR



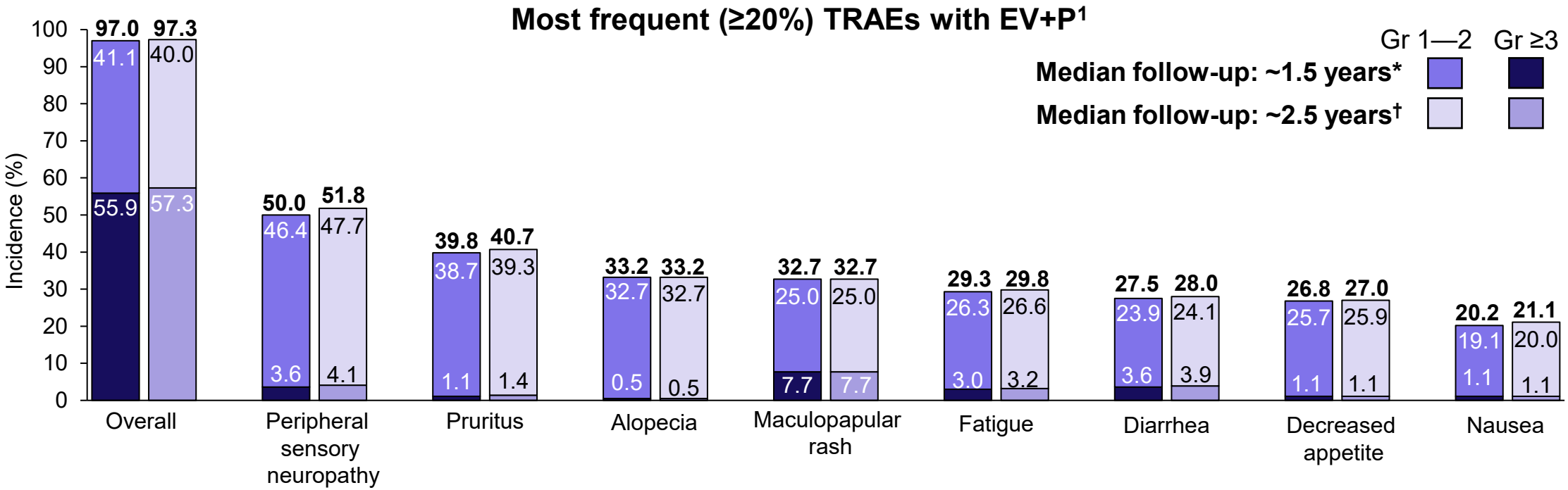
Baseline characteristics among responders (CR + PR)

	EV+P arm, ITT (n=442)	EV+P arm, responders (n=295)
Age, median (range), y	69 (37–87)	69 (37–87)
ECOG PS, n (%)		
0	223 (50.5)	160 (54.2)
1	204 (46.2)	129 (43.7)
2	15 (3.4)	6 (2.0)
Primary tumor location, n (%)		
Upper tract	135 (30.5)	90 (30.5)
Lower tract	305 (69.0)	204 (69.2)
Metastatic category, n (%)		
Visceral metastases	318 (71.9)	201 (68.1)
Liver	100 (22.6)	59 (20.0)
LN-only disease	103 (23.3)	79 (26.8)
Cisplatin eligibility status, n (%)		
Eligible	244 (55.2)	172 (58.3)
Ineligible	198 (44.8)	123 (41.7)

Data cutoff: 8 August 2024. Median follow-up time: 29.1 months (95% CI: 28.5–29.9).
*Best overall response according to RECIST v1.1. CR or PR was confirmed with repeat scans ≥28 days after initial response.
BICR, blinded independent central review; CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; ITT, intention-to-treat; LN lymph node; ORR, objective response rate; P, pembrolizumab; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours.
Gupta S et al. Presented at ASCO 2025. Abstract 4502.

With an additional 1 year of follow-up in EV-302, no new safety signals were identified with EV+P

- **With an additional 1 year of follow-up, the EV+P safety profile remained consistent**
- Frequency and grade of TRAEs remained consistent with the primary analysis
- EV treatment-related AESI and P treatment-emergent AESI rates were consistent with the primary analysis

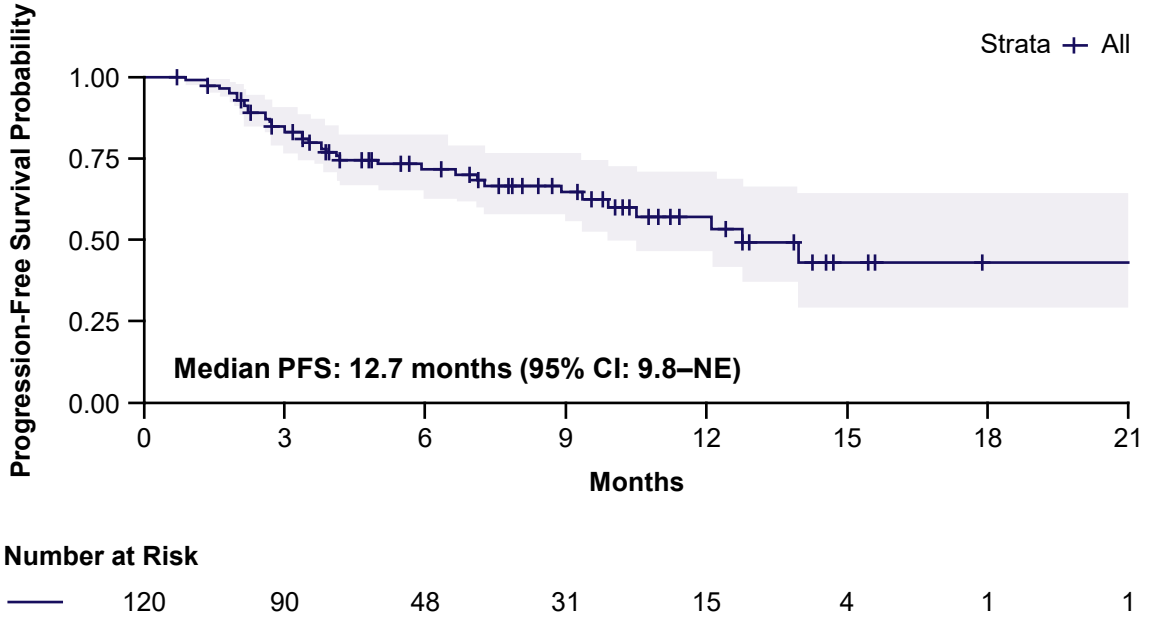


Data cutoff: *August 8; 2023; †August 8, 2024.
AESI, adverse event of special interest; EV, enfortumab vedotin; Gr, grade; P, pembrolizumab; TRAE, treatment-related adverse event.
Powles T. Presented at ASCO GU 2025. Abstract 664.

Real-world experience with EV+P at Mayo Clinic

- Retrospective study of 120 patients diagnosed with locally advanced or metastatic urothelial carcinoma between July 2022 and August 2024 who were treated with EV+P at the Mayo Clinic
- In this real-world setting, EV+P demonstrated efficacy comparable to the results obtained in EV-302

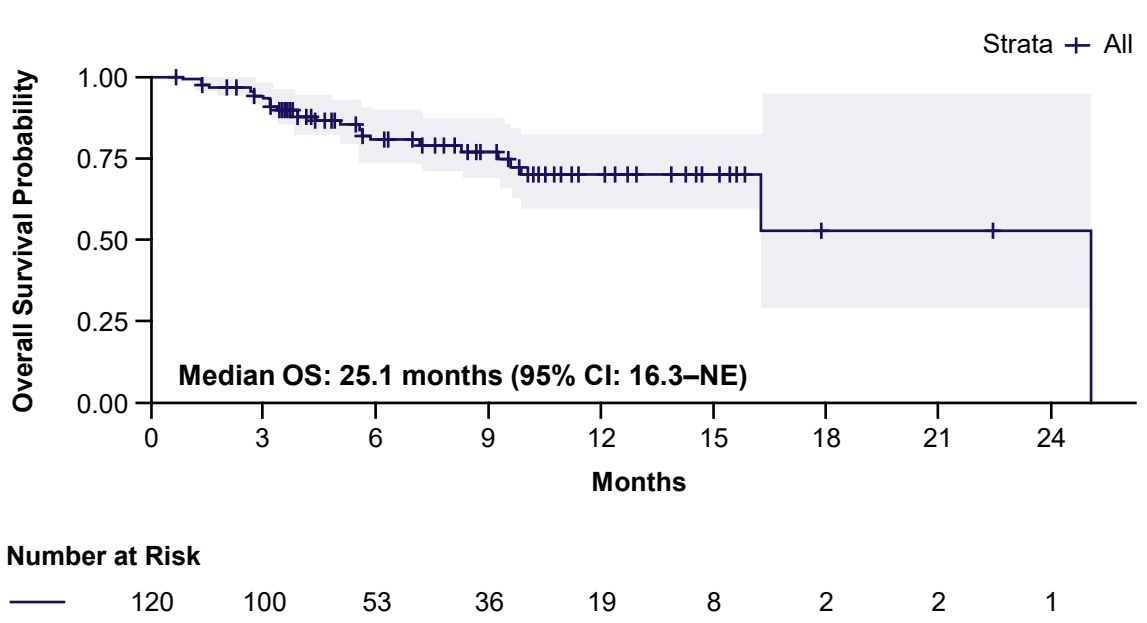
Kaplan-Meier Curve for Progression-Free Survival



Number at Risk

All	120	90	48	31	15	4	1	1

Kaplan-Meier Curve for Overall Survival



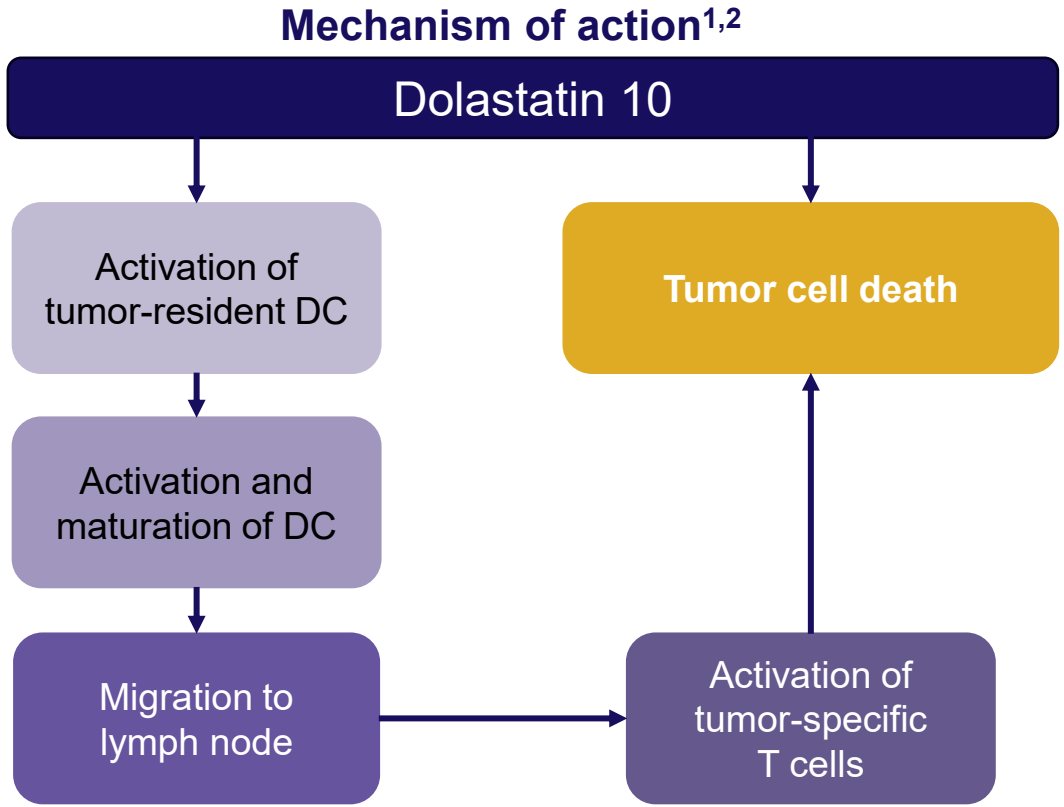
Number at Risk

All	120	100	53	36	19	8	2	2	1

CI, confidence interval; EV, enfortumab vedotin; NE, not estimated; OS, overall survival; P, pembrolizumab; PFS, progression-free survival.
Jain P, et al. Presented at ASCO-GU 2025, 13–15 February, San Francisco, CA. Abstract 745.

Why does MMAE combine so well with CPIs?

Microtubule-destabilizing drugs, such as dolastatin 10 or MMAE, are highly potent cytotoxics that inhibit polymerization of tubulin to form microtubules[1]



- MMAE is an analog of dolastatin 10[1]
- Human DCs exposed to MMAE upregulate costimulatory molecules and display enhanced T cell-stimulatory capacity[1]
- Preclinical studies have shown that EV induces:[3]
  - Early hallmarks of immunogenic cell death *in vitro*
  - Immunomodulatory changes in mouse xenografts
  - Gene expression patterns associated with immunogenic cell death

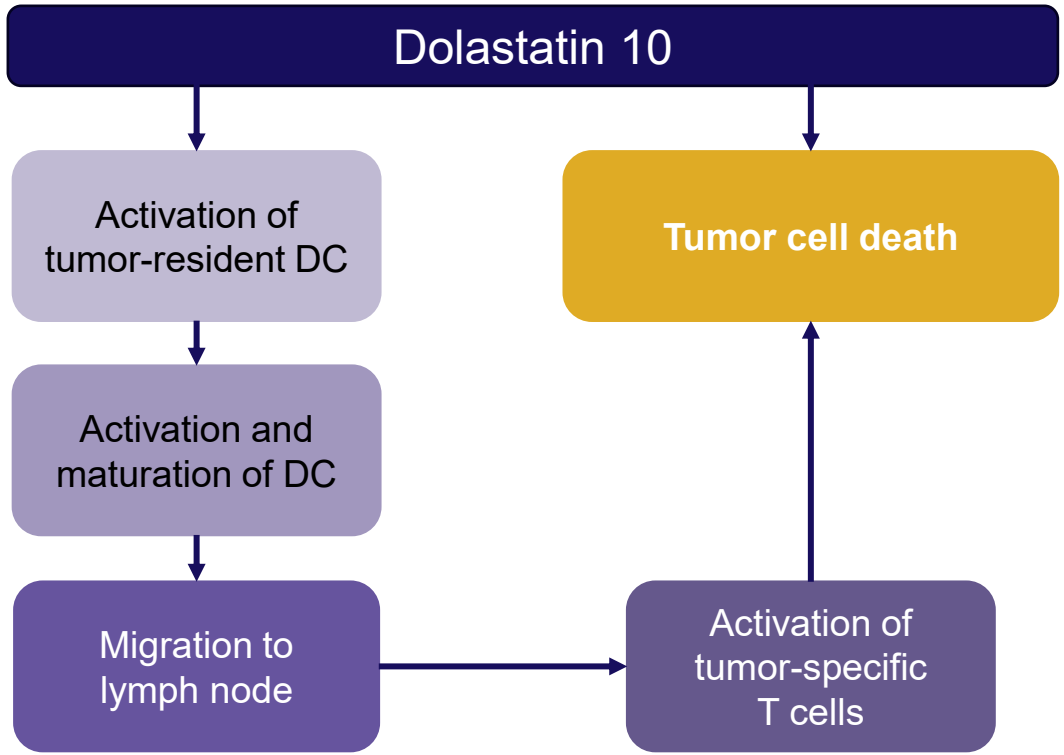
CPI, checkpoint inhibitor; DC, dendritic cell; EV, enfortumab vedotin; MMAE, monomethyl auristatin E.

1. Muller P et al. *OncoImmunology* 2014;3:954460; 2. Muller P et al. *Cancer Immunol Res* 2014;2:741–755; 3. Olson D et al. *J Immunother Cancer* 2022;10:A1187.

Why does MMAE combine so well with CPIs?

Microtubule-destabilizing drugs, such as dolastatin 10 or MMAE, are highly potent cytotoxics that inhibit polymerization of tubulin to form microtubules[1]

Mechanism of action[1,2]



A better understanding of the complementary mechanisms of EV+P will help us build on its therapeutic effect and target mechanisms of resistance[3]

CPI, checkpoint inhibitor; DC, dendritic cell; EV, enfortumab vedotin; MMAE, monomethyl auristatin E.

1. Muller P et al. *OncoImmunology* 2014;3:954460; 2. Muller P et al. *Cancer Immunol Res* 2014;2:741–755; 3. Olson D et al. *J Immunother Cancer* 2022;10:A1187.

Summary

Multiple 1L options now demonstrate survival benefit over chemotherapy alone, with EV+P emerging as a preferred regimen[1–4]

Treatment initiation should consider patient characteristics, comorbidities, treatment goals, and AE risk factors[5]

Recent data are reflected in clinical guideline updates[1,6]

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

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