7th ANNUAL UC COURSE

Emerging personalized therapies for the management of urothelial carcinomas

7th MAY 2026
MADRID

The treatment landscape in metastatic UC

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DISCLOSURES

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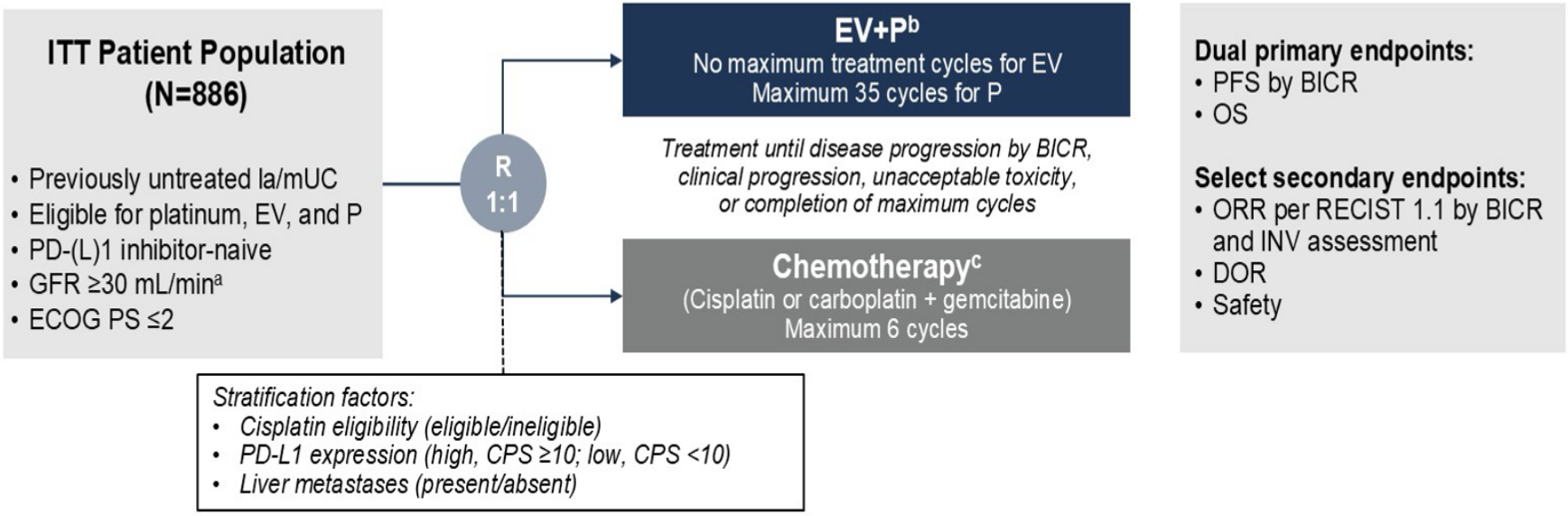
EV+P


ARE THERE ANY OPTIONS NOW BESIDES EV+P?
HOW CAN WE OPTIMIZE - BEAT EV+P?

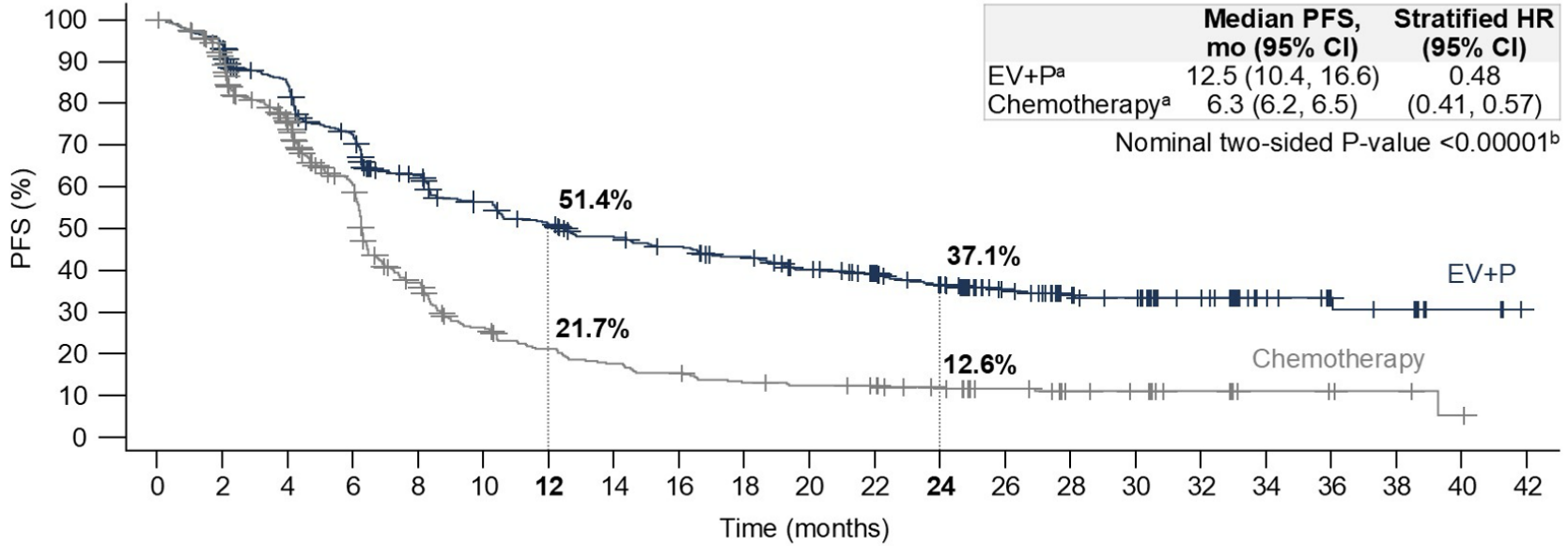
EV-302/KEYNOTE-A39 Design and Disposition



Powles T et al. N Engl J Med 2024

PFS by BICR in the Overall Population

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



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
Chemotherapy	444	379	296	213	125	86	68	57	50	42	39	37	31	23	16	14	9	5	4	3	1

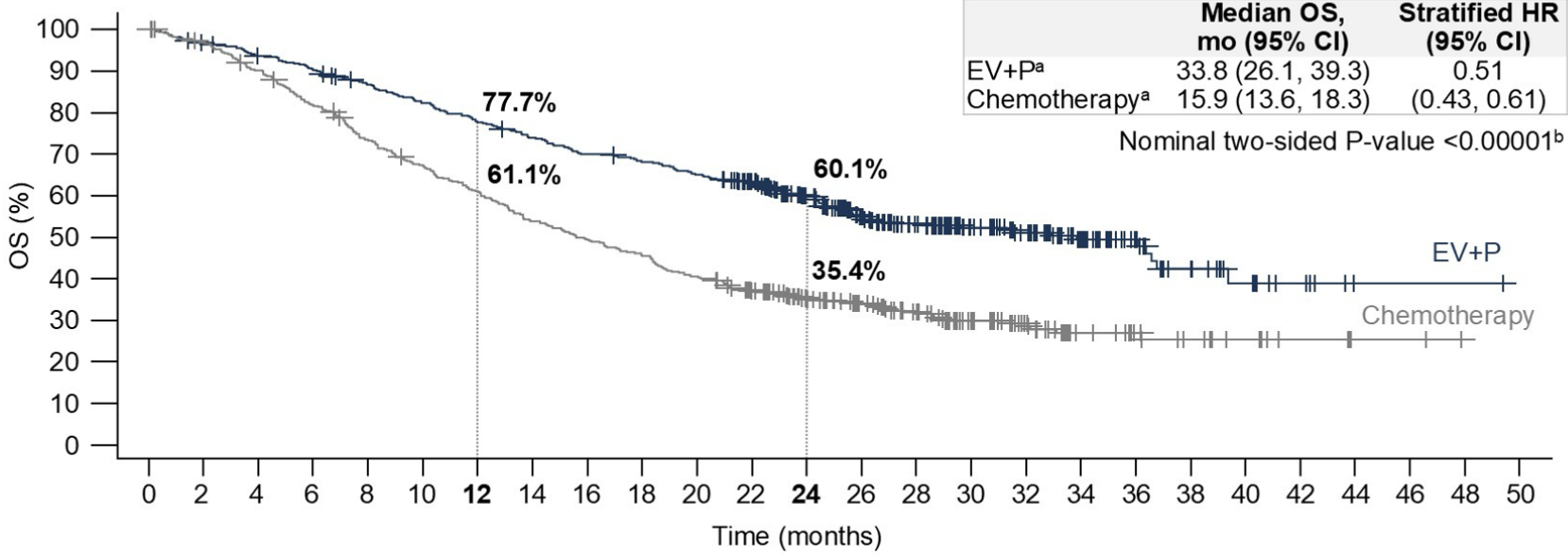
Powles T et al. Ann Oncol 2025

OS in the Overall Population

Risk of death was reduced by almost 50%

	Median OS, mo (95% CI)	Stratified HR (95% CI)
EV+P[a]	33.8 (26.1, 39.3)	0.51
Chemotherapy[a]	15.9 (13.6, 18.3)	(0.43, 0.61)

Nominal two-sided P-value <0.00001[b]



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
Chemotherapy	444	423	393	356	317	290	263	233	214	197	176	148	121	102	81	59	43	24	18	13	9	5	2	2	

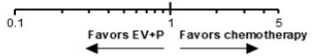
Powles T et al. Ann Oncol 2025

OS in Prespecified Subgroups

OS benefit was consistent across prespecified subgroups

	Median OS, months (event/N) EV+P	Chemotherapy	HR (95% CI)
Overall	33.8 (203/442)	15.9 (297/444)	0.513 (0.428, 0.614)
Age			
<65 years	39.3 (59/144)	18.7 (87/135)	0.434 (0.307, 0.614)
≥65 years	27.1 (144/298)	14.6 (210/309)	0.544 (0.439, 0.674)
Race			
White	26.1 (158/308)	15.1 (207/290)	0.521 (0.422, 0.644)
Other	36.3 (45/134)	19.1 (90/154)	0.436 (0.302, 0.629)
Region			
North America	25.7 (57/103)	21.0 (54/85)	0.672 (0.451, 1.000)
Europe	25.6 (90/172)	14.6 (140/197)	0.522 (0.397, 0.687)
Rest of world	NR (56/167)	15.5 (103/162)	0.386 (0.277, 0.539)
Sex			
Female	25.4 (46/98)	14.6 (70/108)	0.549 (0.371, 0.811)
Male	33.8 (157/344)	16.4 (227/336)	0.501 (0.407, 0.617)
ECOG PS			
0	36.5 (77/223)	18.7 (136/215)	0.394 (0.296, 0.524)
1-2	22.8 (126/219)	13.3 (160/227)	0.621 (0.490, 0.787)
Primary disease site of origin			
Upper tract	36.5 (60/135)	18.3 (63/104)	0.538 (0.371, 0.781)
Lower tract	32.9 (142/305)	15.6 (233/339)	0.504 (0.408, 0.623)

	Median OS, months (event/N) EV+P	Chemotherapy	HR (95% CI)
Overall	33.8 (203/442)	15.9 (297/444)	0.513 (0.428, 0.614)
Liver metastases			
Present	19.1 (68/100)	10.1 (82/99)	0.556 (0.399, 0.776)
Absent	39.3 (135/342)	18.3 (215/345)	0.496 (0.400, 0.615)
PD-L1 expression			
Low (CPS <10)	31.2 (91/184)	15.1 (136/185)	0.472 (0.361, 0.618)
High (CPS ≥10)	36.5 (111/254)	17.1 (158/254)	0.550 (0.431, 0.703)
Cisplatin eligibility			
Eligible	36.7 (101/244)	18.7 (143/234)	0.541 (0.419, 0.699)
Ineligible	25.6 (102/198)	12.7 (154/210)	0.498 (0.386, 0.642)
Metastatic disease site			
Visceral metastases	25.7 (163/318)	13.5 (235/318)	0.505 (0.412, 0.619)
Lymph node only	NR (34/103)	24.4 (54/104)	0.512 (0.332, 0.789)
Renal function			
Normal	39.3 (33/84)	18.6 (61/95)	0.496 (0.318, 0.773)
Mild	36.5 (69/165)	18.4 (101/162)	0.502 (0.365, 0.689)
Moderate/severe	25.6 (101/193)	13.3 (135/187)	0.528 (0.405, 0.689)



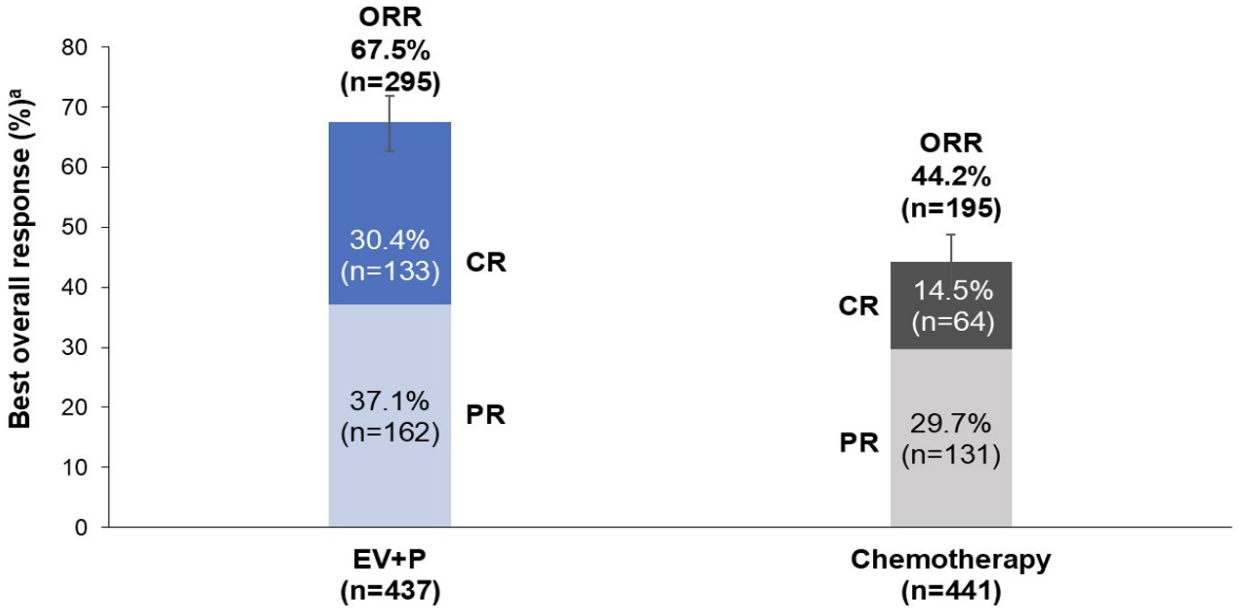
Data cutoff: August 8, 2024.

CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; P, pembrolizumab; PD-L1, programmed death ligand 1; OS, overall survival.

Powles T et al. Ann Oncol 2025

Confirmed objective response rate (CR+PR) by BICR[1,2]

CR rate in the EV+P arm was twice that in the chemotherapy arm

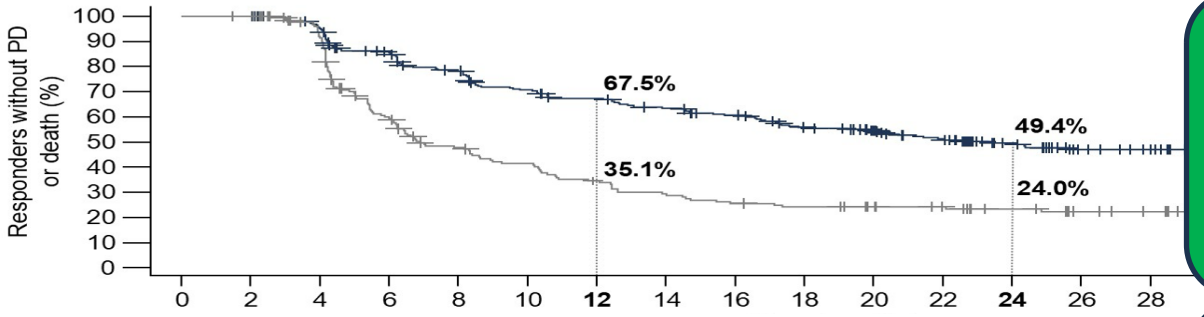


- Among patients with a confirmed CR, 66.2% in the EV+P arm and 59.4% in the chemotherapy arm had an initial PR, and later converted to CR

Gupta S et al. ASCO 2025

Duration of Response (CR or PR) by BICR

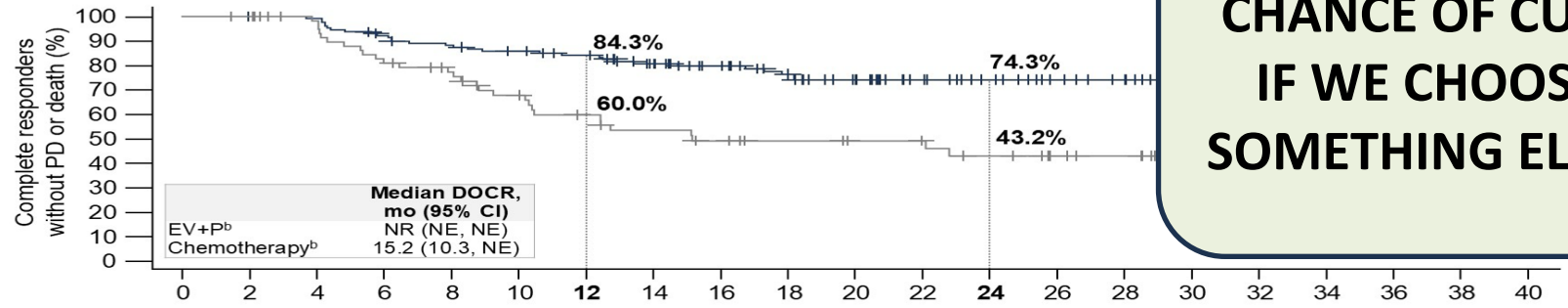
Among responders, the probability of maintained response at 24 months was ~50% with EV+P



ARE WE "CURING" THESE PATIENTS?

Duration of Confirmed Completed Response

Probability of maintained CR at 24 months was 74% with EV+P

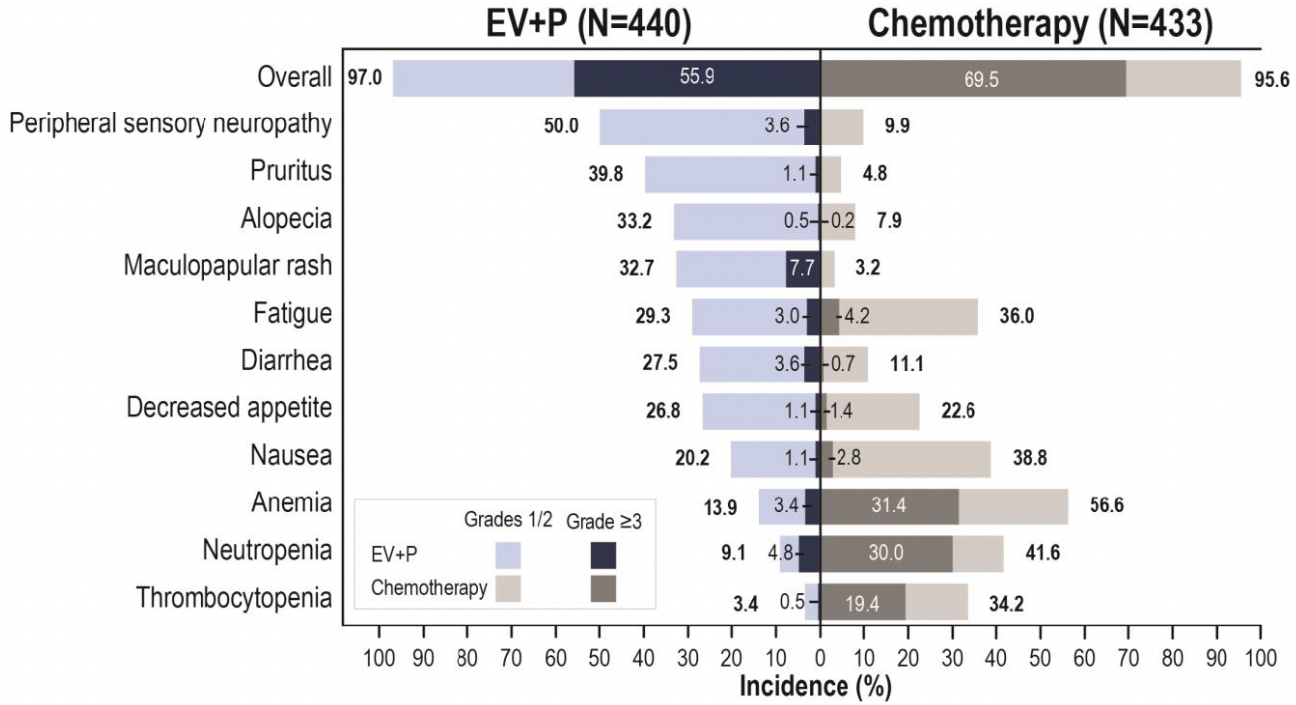


ARE WE MISSING A CHANCE OF CURE IF WE CHOOSE SOMETHING ELSE?

Powles T et al. Ann Oncol 2025

Treatment-Related Adverse Events

Grade ≥3 events were 56% in EV+P and 70% in chemotherapy

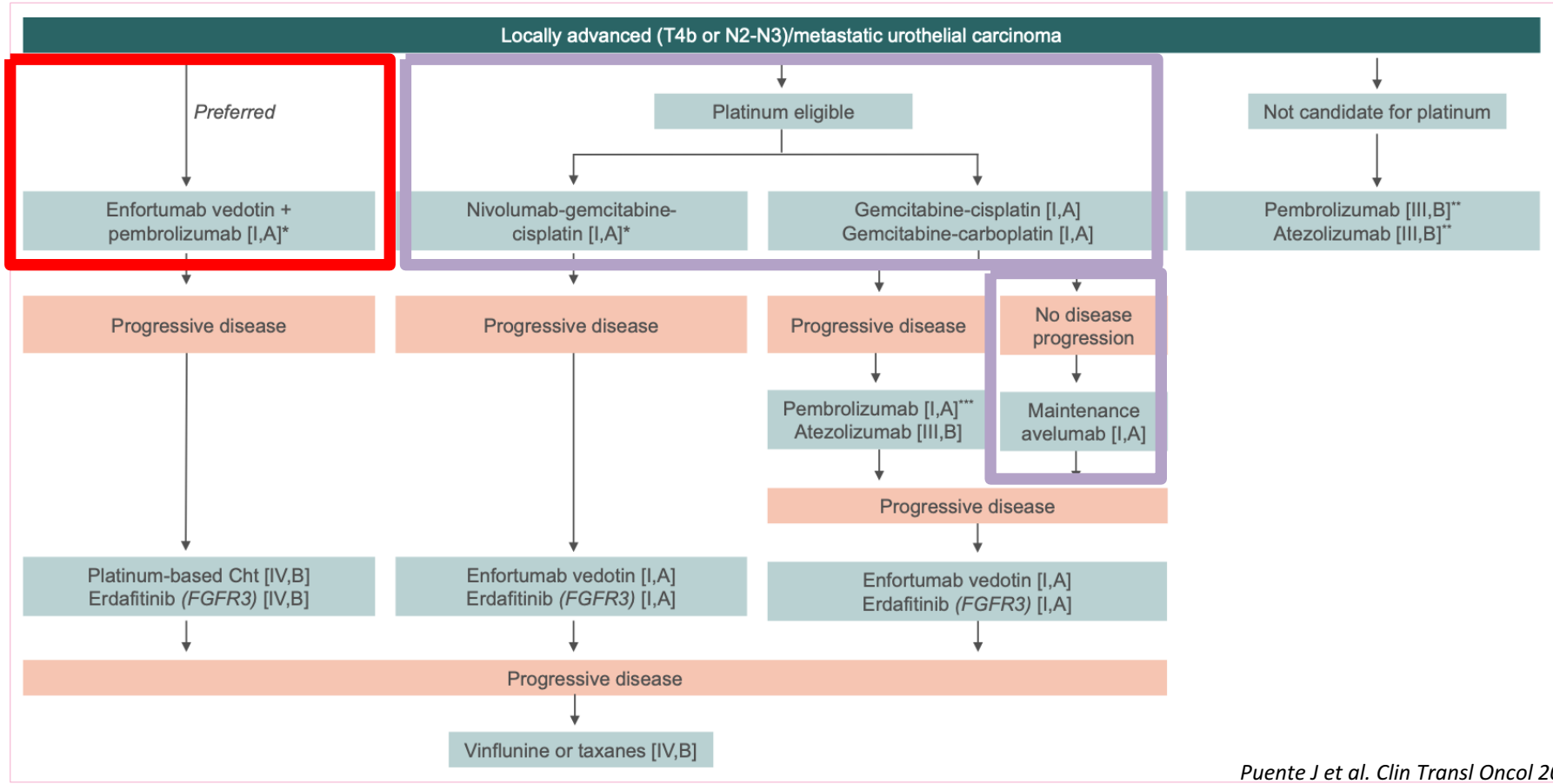


Serious TRAEs:
- 122 (27.7%) EV+P
- 85 (19.6%) chemotherapy

TRAEs leading to death (per investigator):
EV+P: 4 (0.9%)
- Asthenia
- Diarrhea
- Immune-mediated lung disease
- Multiple organ dysfunction syndrome

Chemotherapy: 4 (0.9%)
- Febrile neutropenia
- Myocardial infarction
- Neutropenic sepsis
- Sepsis

Powles T et al. N Engl J Med 2024



Puente J et al. Clin Transl Oncol 2025

All endpoints measured post randomization (after chemotherapy)

- CR, PR, or SD with standard 1st-line chemotherapy (4-6 cycles)
  - Cisplatin + gemcitabine or
  - Carboplatin + gemcitabine
- Unresectable locally advanced or metastatic UC

Treatment-free interval 4-10 weeks

N=700

R 1:1

Avelumab 10 mg/kg IV Q2W + BSC* n=350

BSC alone* n=350

Until PD, unacceptable toxicity, or withdrawal

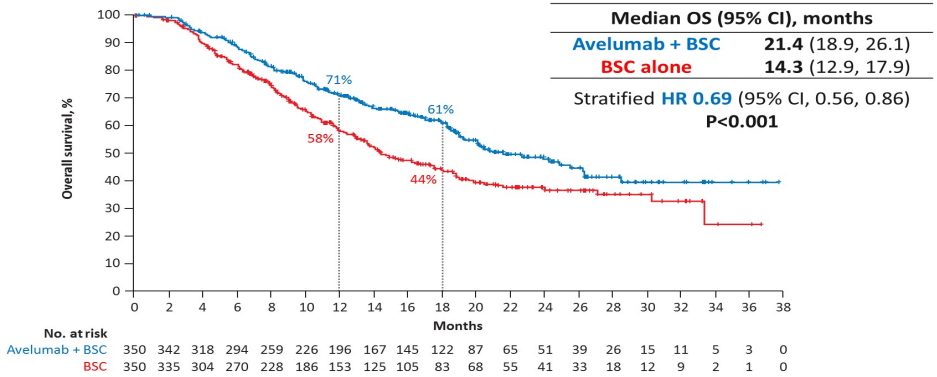
Primary endpoint
- OS

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

Secondary endpoints
- PFS and objective response per RECIST 1.1
- Safety and tolerability
- PROs

Stratification
- Best response to 1st-line chemo (CR or PR vs SD)
- Metastatic site (visceral vs non-visceral)

OS in the overall population



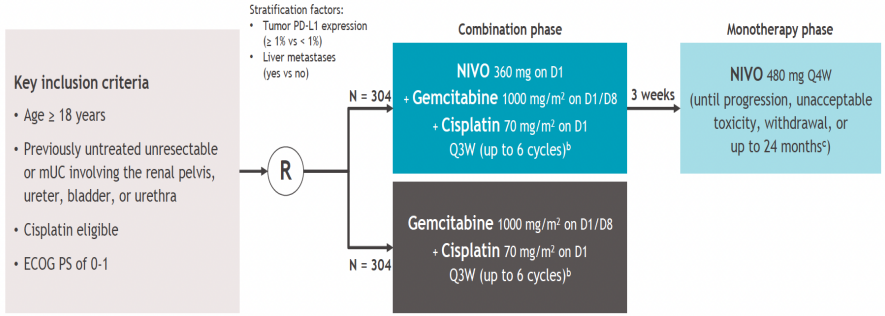
Median OS (95% CI), months	
Avelumab + BSC	**21.4** (18.9, 26.1)
BSC alone	**14.3** (12.9, 17.9)

Stratified **HR 0.69** (95% CI, 0.56, 0.86)
P<0.001

OS improvement regardless:
- PD-L1 expression
- Cis- o Carbo- as 1st line chemo
- Quality of response (CR,PR,SD)
- Favourable safety profile

Several controversies:
- Selected population (responders)
- No improvement in 1st line efficacy, just ”early 2nd line”

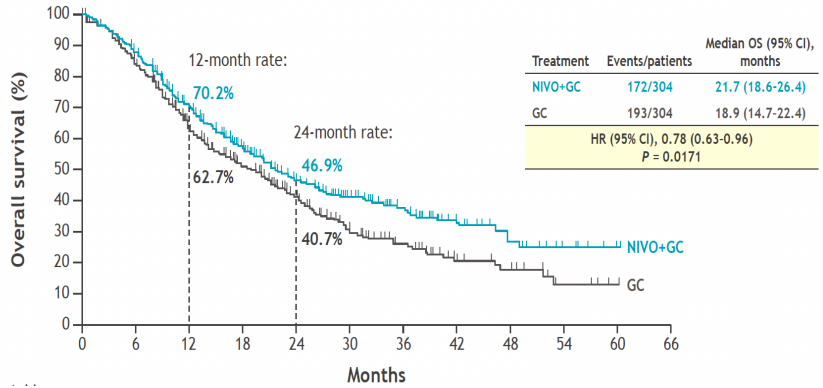
Powles et al. N Engl J Med 2020



Median (range) study follow-up, 33.6 (7.4-62.4) months

Primary endpoints: OS, PFS per BICR
Key secondary endpoints: OS and PFS by PD-L1 ≥ 1%,[d] HRQoL
Key exploratory endpoints: ORR per BICR, safety

OS (primary endpoint)



Treatment	Events/patients	Median OS (95% CI), months
NIVO+GC	172/304	21.7 (18.6-26.4)
GC	193/304	18.9 (14.7-22.4)
HR (95% CI), 0.78 (0.63-0.96) *P* = 0.0171		

Improved efficacy
- OS, PFS, ORR
- No significant added toxicity

Several controversies:
- The efficacy improvement is modest, compared with EV-302
- Benefit after 6-8 months of therapy (why concomitant?)
- Who is unfit for EV+P, but fit for this schedule?

Van der Heijden et al. N Engl J Med 2023


OLD-SCHOOL
GAINS

ELDERLY COMORBIDITIES

LOW VOLUME INDOLENT DISEASE

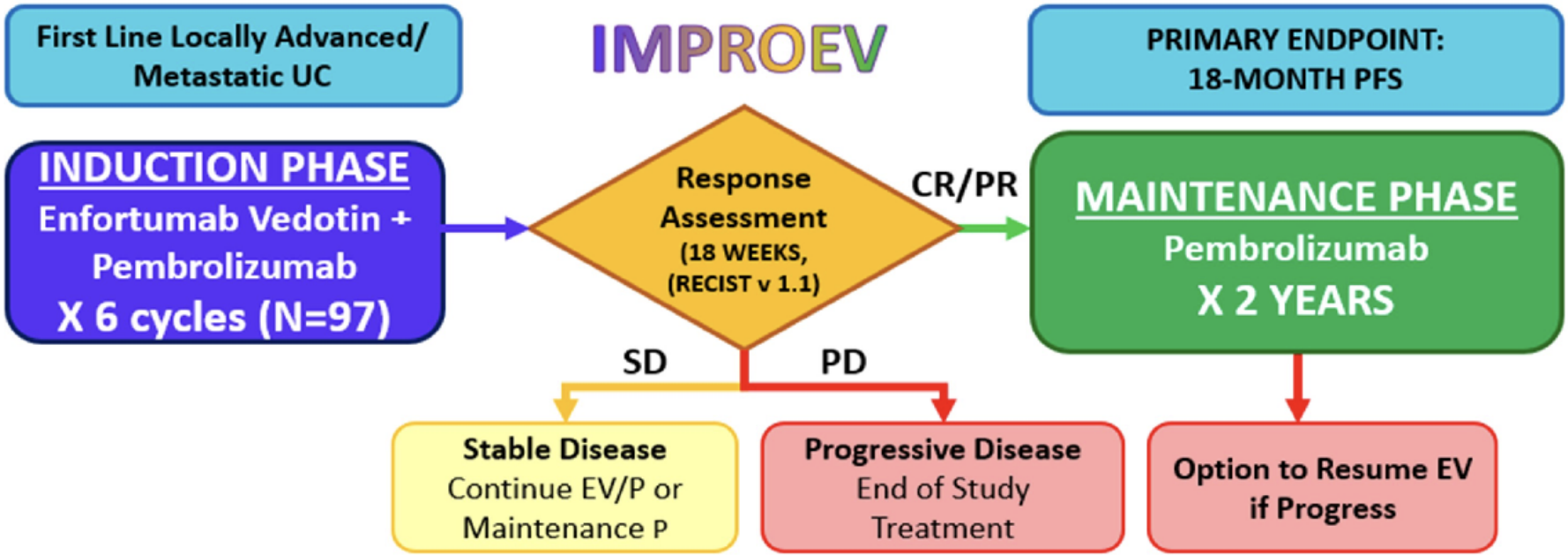
TOXICITY PROFILE

PATIENT PREFERENCE

VARIANT HISTOLOGIES

TREATMENT SEQUENCE


EV+P



Ghatalia et al. ASCO GU 2026

Key Inclusion criteria

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

R 1:1

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

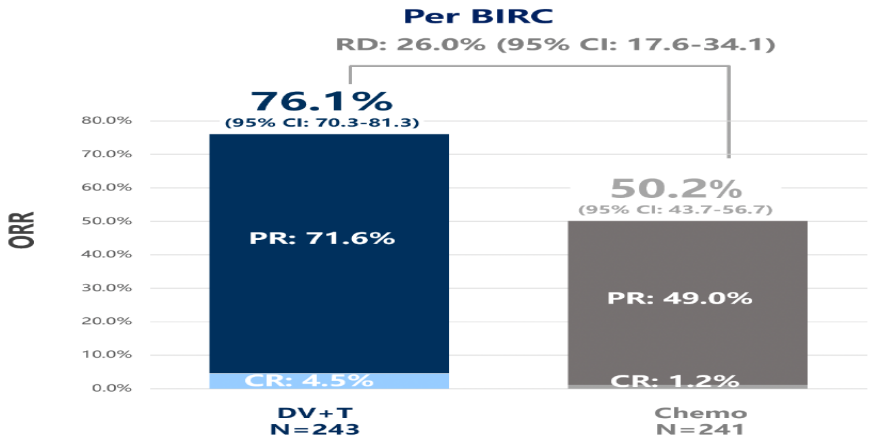
N=241 **Gemcitabine + Cisplatin/Carboplatin** — a maximum of 6 cycles

Dual primary endpoints:

- PFS assessed by BIRC
- OS

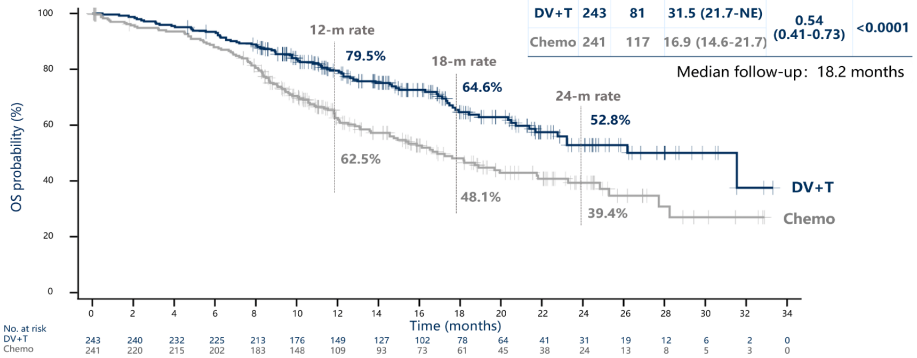
Secondary endpoints:

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



Overall Survival

Clinically meaningful reduction in the risk of death by 46% with DV+T



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

Median follow-up: 18.2 months

Phase III: SGNDV-001 / KN-D74

Eligibility:
- LA/mUC
- Previously untreated
- Eligible for platinum
- Central laboratory HER2 status ≥ IHC 1+

(n=700)

RND 1:1

DV + Pembrolizumab
DV treatment until progression; Pembrolizumab × 18 cycles

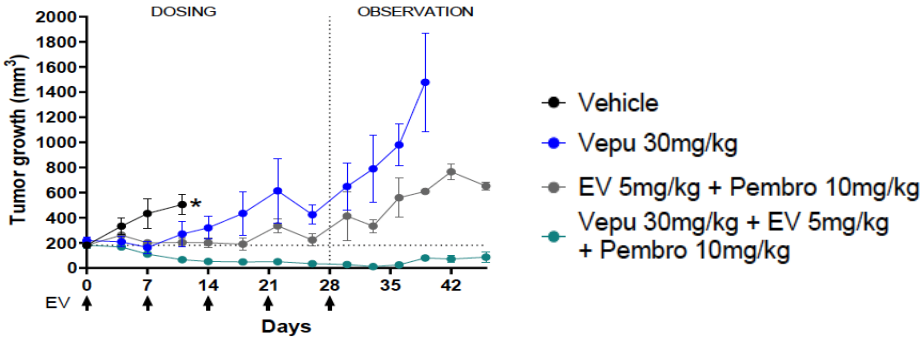
Stratification Factors:
- Cisplatin eligibility
- Presence of visceral metastasis
- HER2 status
- Intent of avelumab maintenance use

Cisplatin/Carboplatin + Gemcitabine
× 4-6 cycles

Dual-Primary Endpoints
- PFS by BICR
- OS

Sheng et al. N Engl J Med 2025

FORAGER-2: A Randomized Phase 3 Study Evaluating the Efficacy and Safety of Vepugratinib Combined with Enfortumab Vedotin and Pembrolizumab in Untreated Locally Advanced or Metastatic Urothelial Carcinoma with an FGFR3 Genetic Alteration



ELIGIBILITY CRITERIA

- Untreated LA/mUC
- Susceptible FGFR3 genetic alteration identified by blood or tissue
- Measurable disease per RECIST v1.1
- ECOG PS 0-2[a]

[a] Patients with ECOG performance status of 2 must also have hemoglobin ≥10 g/dL and eGFRCr ≥50 mL/min.

Safety Lead-In (N~40) Vepugratinib + EV+P

R 1:1 N=450

- EV + P + Vepugratinib
- EV + P + Placebo

Primary Endpoint: PFS by BICR

Treatment until radiographic progression or unacceptable toxicity

STRATIFICATION:

- ECOG PS
- Geographical Region
- Liver/bone mets

Drakaki et al. ESMO 2025; Reimers et al. ASCO GU 2026

KEYMAKER-U04 Substudy 04B Study Design (NCT05845814)

Key Eligibility Criteria
- Age ≥18 years
- Histologically confirmed la/mUC
- Measurable disease per RECIST v1.1
- ECOG PS 0 or 1
- No prior systemic therapy for la/mUC

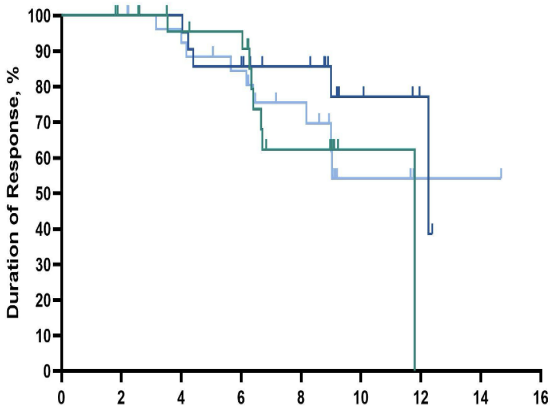
Stratification factor:
Liver metastasis (yes vs no)

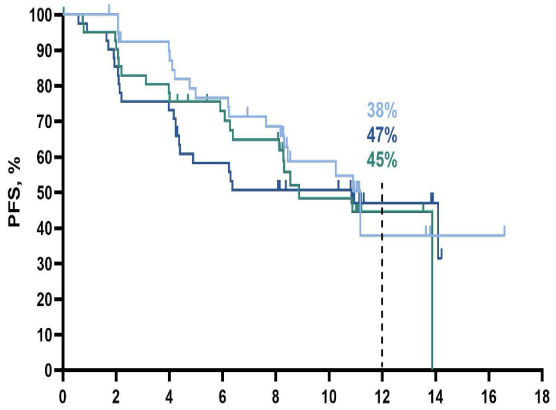
R 1:1:1

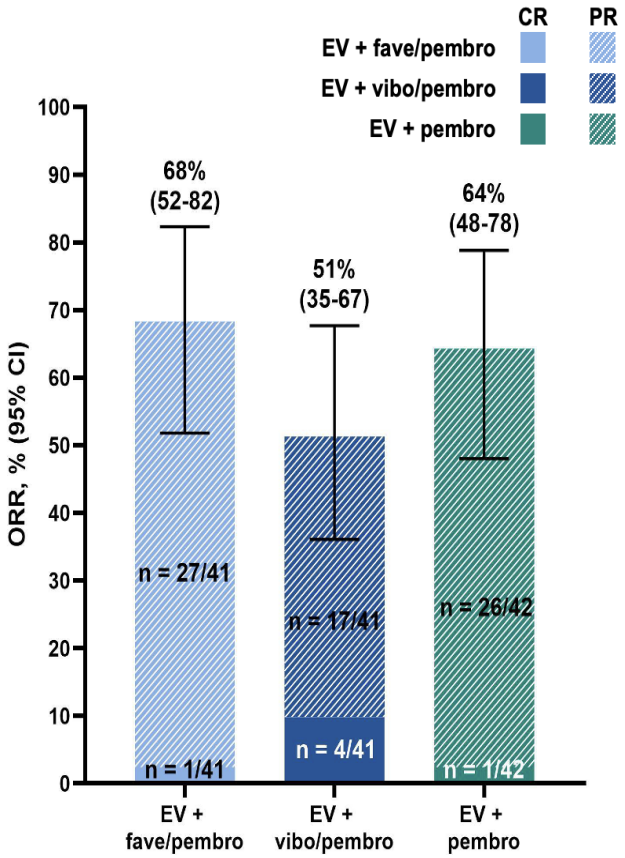
Arm A
EV[a] + coformulated favezelimab 800 mg/ pembrolizumab 200 mg IV Q3W
n = 41

Arm B
EV[a] + coformulated vibostolimab 200 mg/ pembrolizumab 200 mg IV Q3W
n = 41

Arm C
EV[a] + pembrolizumab 200 mg IV Q3W
n = 42

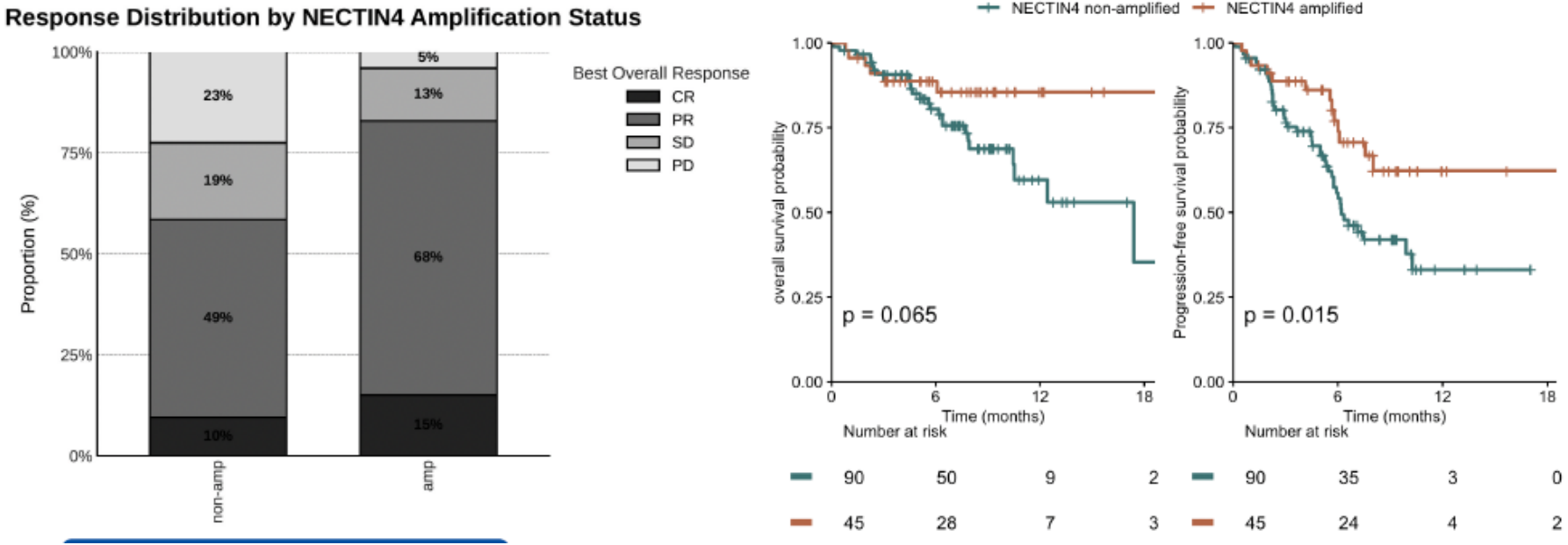






Van der Heijden et al. ASCO GU 2026

NECTIN4 Amplification as a Predictive Biomarker of Response to Enfortumab Vedotin Plus Pembrolizumab in First-Line Metastatic Urothelial Carcinoma: A Multicenter Cohort Study

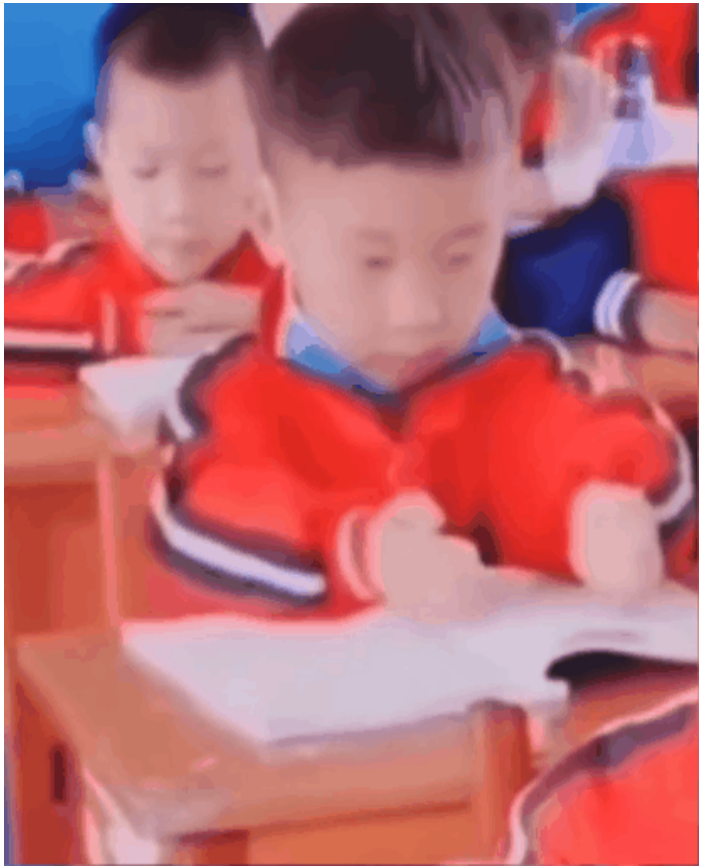


Klumper et al. ESMO 2025


EV+P

THERE IS A LOT TO LEARN !!

- How to optimize the efficacy and safety of EV+P in clinical practice
- How to choose between different treatment options in 1st line
- How to incorporate biomarkers in the 1st line setting



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THANK YOU FOR YOUR ATTENTION

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