

Supplementary files

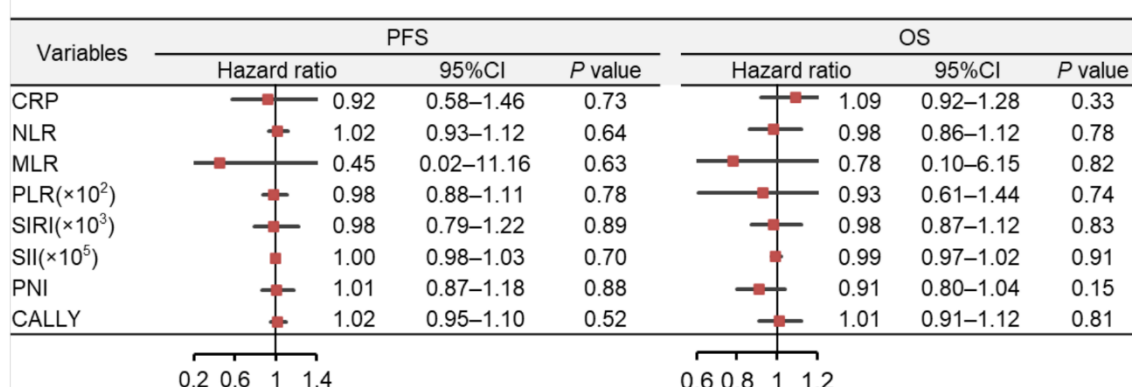


Figure S1. Association of progression-free survival (PFS) and overall survival (OS) with blood-based inflammation and nutrition markers in la/mUC patients treated with 1L EVP. 1L: first-line; CALLY: C-reactive protein–albumin–lymphocyte; CRP: C-reactive protein; EVP: enfortumab vedotin plus pembrolizumab; la/mUC: locally advanced or metastatic urothelial carcinoma; MLR: monocyte-to-lymphocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index.

Table S1. Details of patients diagnosed with la/mUC between October 2024 and December 2025 who did not receive 1L EVP therapy.

ID	Age	Sex	Clinical T category (the 8th edition)	Unresectable or metastatic lesions	Radical surgery	ECO G-PS	eGFR mL/min /1.73m²	Diabetes mellitus	Number of EVITA criteria	Selected 1L therapy	Best objective response to 1L therapy	Reason(s) not to select EVP
1	80	M	3	Lung	No	2	46	No	1	BSC	NE	Rapid progression during treatment of other comorbidity (common bile duct stones)

2	79	M	4	Primary tumor	No	0	40	No	1	DD-MVACarbo	PD	<p>i) Previous use of pembrolizumab for advanced lung cancer</p> <p>ii) Pembrolizumab caused interstitial lung disease at that time</p> <p>iii) Urothelial carcinoma diagnosed after pembrolizumab treatment (highly suspected primary</p>
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resistance to
pembrolizumab)

3	79	M	3	Local recurrence Lymph node	RNU	0	33	Yes (HbA1c, 7.6%)	1	GEM + PR Carbo	The attending physician had no experience with EVP use
4	85	F	1	Lymph node Lung	No	1	27	No	1	GEM + PD Carbo	Because of high age
5	77	M	2	Local recurrence Lymph node	RC	1	41	Yes (Glucose level,	1	GC PR	The attending physician had no experience with EVP use

										182mg/dL			
)			
6	86	M	3	Lymph node	No	0	52	No	0	GEM + NE Carbo	The patients refused EVP after sufficient shared decision-making		
7	76	M	4	Lymph node	No	0	59	Yes (HbA1c 9.0%)	1	DD- MVACarbo	NE Uncontrolled diabetes mellitus		
8	77	F	3	Local recurrence Lymph node	RNU	1	27	No	1	GEM + SD Carbo	i) Because of high age ii) Urothelial carcinoma diagnosed during		

adjuvant
nivolumab
treatment (highly
suspected
primary
resistance to PD-
1 inhibitors)

9	77	M	4	Lung	RNU	1	38	No	1	DD- MVACar bo	PR	The attending physician had no experience with EVP use
10	84	M	3	Primary tumor	No	1	50	Yes (HbA1c 6.4%)	1	GEM + Carbo	PR	Because of high age

1L: first-line; ACTH: adrenocorticotrophic hormone; BSC: best supportive care; DD-MVAC: dose-dense methotrexate, vinblastine, adriamycin, and cisplatin combination chemotherapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; eGFR: estimated glomerular

filtration rate; EVITA: Enfortumab Vedotin Ineligible Criteria; EVP: enfortumab vedotin plus pembrolizumab combination therapy; FT3: free triiodothyronine; FT4: free thyroxine; GC: gemcitabine plus cisplatin combination chemotherapy; IQR: interquartile range; la/mUC: locally advanced or metastatic urothelial carcinoma; NA: not available; RECIST: Response Evaluation Criteria in Solid Tumors; SLD: sum of longest diameter; TSH: thyroid-stimulating hormone; UTUC: upper urinary tract urothelial carcinoma.

Table S2. Baseline characteristics of patients with la/mUC: comparison among selected 1L treatment.

Variables		Total	EVP	GC	DD-MVAC	GCarbo	Other	BSC	<i>P</i> value
Total		642 (100%)	55 (8.6%)	281 (43.8%)	13 (2.0%)	178 (27.7%)	50 (7.8%)	65 (10.1%)	-
Age, years-old	Median (IQR)	75 (68–79)	74 (66–78)	73 (66–78)	76 (73–78)	75 (71–79)	75 (71–79)	80 (74–87)	< 0.01
Sex	Male	459 (71%)	40 (73%)	206 (73%)	13 (100%)	125 (70.2%)	40 (80%)	35 (53.8%)	< 0.01
	Female	183 (29%)	15 (27%)	75 (27%)	0	53 (29.8%)	10 (20%)	30 (46.2%)	
Smoking history	Never	213 (33%)	17 (31%)	83 (29%)	4 (31%)	68 (38%)	17 (34%)	24 (37%)	0.11
	Former	182 (28%)	20 (36%)	73 (26%)	6 (46%)	50 (28%)	18 (36%)	15 (23%)	

Diabetes mellitus	No	560 (87%)	48 (87%)	246 (88%)	10 (77%)	157 (88%)	46 (92%)	53 (82%)	0.51
	Yes	82 (13%)	7 (13%)	35 (12%)	3 (23%)	21 (12%)	4 (8.0%)	12 (18%)	
The use of steroids at baseline	No	633 (99%)	55 (100%)	275 (98%)	13 (100%)	177 (99%)	49 (98%)	64 (98%)	0.69
	Yes	9 (1.4%)	0	6 (2.1%)	0	1 (0.6%)	1 (2.0%)	1 (1.5%)	
Autoimmune disease	No	626 (98%)	54 (98%)	273 (97%)	13 (100%)	175 (98%)	48 (96%)	63 (97%)	0.90
	Yes	16 (2.5%)	1 (1.8%)	8 (2.8%)	0	3 (1.7%)	2 (4.0%)	2 (3.1%)	
Primary disease	Bladder	327 (51%)	29 (53%)	164 (58%)	5 (38%)	70 (39%)	25 (50%)	34 (52%)	0.05
	Renal pelvis	171 (27%)	15 (27%)	70 (25%)	5 (38%)	53 (30%)	13 (26%)	15 (23%)	
	Ureter	138 (21%)	11 (20%)	43 (15%)	3 (23%)	53 (30%)	12 (24%)	16 (25%)	
	Undefined	6 (0.9%)	0	4 (1.4%)	0	2 (1.1%)	0	0	
Concomitant bladder cancer and UTUC	No	633 (99%)	54 (98%)	281 (100%)	13 (100%)	174 (98%)	48 (96%)	63 (97%)	0.11

	Yes	9 (1.4%)	1 (1.8%)	0	0	4 (2.2%)	2 (4.0%)	2 (3.1%)	
Radical surgery	None	191 (30%)	30 (55%)	82 (29%)	9 (69%)	43 (24%)	9 (18%)	18 (28%)	<0.01
	Cystectomy	227 (35%)	16 (29%)	127 (45%)	2 (15%)	38 (21%)	18 (36%)	26 (40%)	
	Nephroureterectomy	197 (31%)	8 (15%)	69 (25%)	2 (15%)	85 (48%)	18 (36%)	15 (23%)	
	Both	27 (4.2%)	1 (1.8%)	3 (1.1%)	0	12 (6.7%)	5 (10%)	6 (9.2%)	
Unresectable or metastatic lesions	Local lesion	293 (46%)	31 (56%)	139 (49%)	8 (62%)	69 (39%)	20 (40%)	26 (40%)	0.07
	Lymph nodes	402 (63%)	40 (73%)	172 (61%)	10 (80%)	116 (65%)	32 (64%)	32 (49%)	0.10
	Lung	184 (29%)	17 (31%)	83 (30%)	1 (7.7%)	53 (30%)	10 (20%)	20 (31%)	0.40
	Liver	67 (10%)	13 (24%)	23 (8.2%)	1 (7.7%)	17 (9.6%)	4 (8.0%)	9 (14%)	0.13
	Bone	78 (12%)	9 (16%)	37 (13%)	0	18 (10%)	5 (10%)	9 (14%)	0.54
	Peritoneum	28 (4.4%)	2 (3.6%)	10 (36%)	1 (7.7%)	7 (3.9%)	2 (4.0%)	6 (9.2%)	0.46

	Retroperitoneum	12 (1.9%)	7 (13%)	3 (1.1%)	0	0	2 (4.0%)	0	< 0.01
	Adrenal gland	11 (1.7%)	1 (1.8%)	4 (1.4%)	0	4 (2.3%)	0	2 (3.1%)	0.81
SLD at baseline (mm), RECIST v1.1	Median (IQR)	38 (20–60)	49 (34–81)	40 (19–63)	47 (30–63)	33 (18–51)	28 (17–39)	37 (27–42)	0.01
EVITA criteria	HbA1c ≥ 8%	8 (1.3%)	1 (1.8%)	5 (1.8%)	1 (7.7%)	1 (0.6%)	0	0	0.12
	Grade ≥ 2 sensory or motor neuropathy	18 (2.8%)	0	5 (1.8%)	0	5 (2.8%)	0	8 (12%)	< 0.01

	Any corneal or retinal abnormality	11 (1.7%)	1 (1.8%)	2 (0.7%)	0	2 (1.1%)	0	5 (7.7%)	< 0.01
	eGFR < 45 mL/min/1.7 3 m ²	226 (35%)	22 (40%)	51 (18%)	6 (46%)	115 (65%)	31 (62%)	1 (1.5%)	< 0.01
	ECOG-PS ≥ 2	48 (7.5%)	6 (11%)	22 (7.8%)	0	9 (5.1%)	4 (8.0%)	12 (18%)	0.01
Number of EVITA criteria	0	368 (57%)	29 (53%)	209 (74%)	6 (46%)	59 (33%)	18 (36%)	47 (72%)	< 0.01
	1	241 (38%)	22 (40%)	62 (22%)	7 (54%)	110 (62%)	29 (58%)	11 (17%)	
	2	26 (4.0%)	4 (7.3%)	8 (2.9%)	0	5 (2.8%)	3 (6.0%)	6 (9.2%)	
	3	7 (1.1%)	0	2 (0.7%)	0	4 (2.3%)	0	1 (1.5%)	
Laboratory data, median (IQR)	Neutrophil, × 10 ³ /μL	4.1 (3.1– 5.6)	4.7 (3.5– 5.9)	4.2 (3.2– 5.7)	5.1 (4.4– 6.9)	3.9 (3.0– 5.1)	3.5 (2.5– 5.1)	5.3 (4.3– 5.6)	0.04

FT4, ng/dL	1.11	(0.99–	1.12	NA	NA	0.9	(0.9–	NA	NA	0.28
	1.28)		(0.99–			1.0)				
			1.29)							
TSH,	1.94	(1.34–	1.95	NA	NA	3.8	(2.8–	NA	NA	0.45
μIU/mL	3.06)		(1.32–			4.7)				
			3.05)							

1L, first-line; ACTH: adrenocorticotrophic hormone; BSC: best supportive care; DD-MVAC: dose-dense methotrexate, vinblastine, adriamycin, and cisplatin combination chemotherapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; eGFR: estimated glomerular filtration rate; EVITA: nfortumab Vedotin Ineligible criTeriA; EVP: enfortumab vedotin plus pembrolizumab combination therapy; FT3: free triiodothyronine; FT4: free thyroxine; GC: gemcitabine plus cisplatin combination chemotherapy; GCarbo: gemcitabine plus carboplatin combination chemotherapy; IQR: interquartile range; la/mUC: locally advanced or metastatic urothelial carcinoma; NA: not available; RECIST: Response Evaluation Criteria in Solid Tumors; SLD: sum of longest diameter; TSH: thyroid stimulating hormone; UTUC: upper urinary tract urothelial carcinoma.

Table S3. Baseline characteristics of patients with bladder cancer and UTUC.

Variables		Total	Bladder	UTUC	<i>P</i> value
Total		55	29	26	0.61
Age, years-old	Median (IQR)	74 (66–78)	73 (66–78)	75 (69–78)	
Sex	Male	40 (73%)	26 (90%)	14 (54%)	0.005
	Female	15 (27%)	3 (10%)	12 (46%)	
Smoking history	Never	17 (31%)	8 (28%)	9 (35%)	0.88
	Former	20 (36%)	10 (35%)	10 (39%)	
	Current	10 (18%)	6 (21%)	4 (15%)	
	Unknown	8 (15%)	5 (17%)	3 (12%)	
Charlson Comorbidity Score-Category	None (score 0)	33 (60%)	16 (55%)	17 (65%)	0.68
	Mild (score 1 or 2)	16 (29%)	9 (31%)	7 (27%)	

	Moderate (score 3 or 4)	4 (7.3%)	2 (6.9%)	2 (7.7%)	
	Severe (score 5 or more)	2 (3.6%)	2 (6.9%)	0 (0.0%)	
Diabetes mellitus	No	48 (87%)	23 (79%)	25 (96%)	0.11
	Yes	7 (13%)	6 (21%)	1 (3.8%)	
The use of steroids at baseline	No	55 (100%)	29 (100%)	26 (100%)	NA
	Yes	0	0	0	
Autoimmune disease	No	54 (98%)	28 (97%)	26 (100%)	1
	Yes	1 (1.8%)	1 (3.4%)	0	
Radical surgery	None	30 (55%)	13 (45%)	17 (65%)	<0.001
	Cystectomy	16 (29%)	16 (55%)	0 (0%)	
	Nephroureterectomy	8 (15%)	0	8 (31%)	
	Both	1 (1.8%)	0	1 (3.8%)	

Metastatic lesions	Local lesion	31 (56%)	14 (48%)	17 (65%)	0.28
	Lymph nodes	40 (73%)	22 (76%)	18 (69%)	0.76
	Lung	17 (31%)	10 (35%)	7 (27%)	0.57
	Liver	11 (20%)	6 (21%)	5 (19%)	1.00
	Bone	9 (16%)	5 (17%)	4 (15%)	1.00
	Peritoneum	2 (3.6%)	1 (3.4%)	1 (3.8%)	1.00
	Retroperitoneum	7 (13%)	1 (3.4%)	6 (23%)	0.04
	Adrenal gland	1 (1.8%)	1 (3.4%)	0	1.00
	SLD at baseline (mm), RECIST v1.1	Median (IQR)	49.8 (34.2–80.5)	47.2 (34.0–64.3)	53.5 (40.2–93.7)
EVITA score	0	29 (53%)	16 (55%)	13 (50%)	0.60
	1	22 (40%)	12 (41%)	10 (39%)	
	2	4 (7.3%)	1 (3.4%)	3 (12%)	

	3	0	0	0	
EVITA criteria	HbA1c $\geq 8\%$	1 (3.0%)	1 (5.9%)	0 (0%)	1.00
	Grade ≥ 2 neuropathy	0	0	0	NA
	Any corneal or retinal abnormality	1 (1.8%)	1 (3.4%)	0 (0%)	1.00
	eGFR < 45 mL/min/1.73 m ²	22 (41%)	9 (32%)	13 (50%)	0.27
	ECOG-PS ≥ 2	6 (11%)	3 (10%)	3 (12%)	1.00
The number of treatment cycles	Median (IQR)	3 (2–5)	4 (2–7)	4 (2–8)	0.86
Laboratory data, median (IQR)	Neutrophil, $\times 10^3/\mu\text{L}$	4.7 (3.5–5.9)	5.1 (3.8–5.9)	3.8 (3.3–5.8)	0.16
	Alb, g/dL	3.9 (3.7–4.1)	3.9 (3.7–4.1)	3.9 (3.7–4.0)	0.67
	eGFR, mL/min/1.73m ²	48.5 (39.3–57.9)	51.1 (41.2–63.8)	44.9 (37.5–51.8)	0.04
	ACTH, pg/mL	27.6 (18.8–37.0)	22.3 (15.8–34.9)	31.4 (21.0–38.8)	0.13
	Cortisol, $\mu\text{g/dL}$	12.4 (8.7–17.1)	12.3 (8.6–17.2)	12.4 (9.5–17.1)	0.81

FT3, ng/dL	2.43 (2.03–2.75)	2.66 (2.25–2.87)	2.34 (1.88–2.62)	0.04
FT4, ng/dL	1.12 (0.99–1.29)	1.03 (0.99–1.23)	1.17 (1.07–1.30)	0.17
TSH, μ IU/mL	1.95 (1.32–3.05)	1.83 (1.19–2.83)	2.36 (1.56–3.69)	0.21

1L, first-line; ACTH: adrenocorticotrophic hormone; BSC: best supportive care; DD-MVAC: dose-dense methotrexate, vinblastine, adriamycin, and cisplatin combination chemotherapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; eGFR: estimated glomerular filtration rate; EVITA: nfortumab Vedotin Ineligible criTeriA; EVP: enfortumab vedotin plus pembrolizumab combination therapy; FT3: free triiodothyronine; FT4: free thyroxine; GC: gemcitabine plus cisplatin combination chemotherapy; GCarbo: gemcitabine plus carboplatin combination chemotherapy; IQR: interquartile range; la/mUC: locally advanced or metastatic urothelial carcinoma; NA: not available; RECIST: Response Evaluation Criteria in Solid Tumors; SLD: sum of longest diameter; TSH: thyroid stimulating hormone; UTUC: upper urinary tract urothelial carcinoma.

Table S4. Details of EV-related adverse events in patients treated with first-line (1L) enfortumab vedotin plus pembrolizumab combination therapy (EVP).

Adverse events	CTCAE vs. 5.0 grading	Number of patients
<i>n</i>	-	40
Skin toxicity	0	15 (38%)
	1	13 (33%)
	2	9 (23%)
	3	3 (7.5%)
Anorexia	0	21 (53%)
	1	10 (25%)
	2	7 (18%)

	3	1 (2.5%)
	4	1 (2.5%)
Anemia	0	23 (58%)
	1	12 (30%)
	2	3 (7.5%)
	3	2 (5.0%)
Dysgeusia	0	27 (68%)
	1	9 (23%)
	2	4 (10%)
Gastrointestinal disorder	0	30 (75%)
	1	7 (18%)
	2	2 (5.0%)

	4	1 (2.5%)
Alopecia	0	31 (78%)
	1	6 (15%)
	2	3 (7.5%)
Hepatic dysfunction	0	32 (80%)
	1	6 (15%)
	2	2 (5.0%)
Renal dysfunction	0	32 (80%)
	1	5 (13%)
	2	2 (5.0%)
	5	1 (2.5%)
Peripheral sensory neuropathy	0	33 (83%)

	1	5 (13%)
	2	2 (5.0%)
Peripheral motor neuropathy	0	36 (90%)
	1	2 (5.0%)
	2	2 (5.0%)
Leukopenia	0	37 (93%)
	1	2 (5.0%)
	2	1 (2.5%)
Ocular disorder	0	37 (93%)
	1	3 (7.5)
Respiratory dysfunction	0	37 (93%)
	1	1 (2.5%)

	2	1 (2.5%)
	4	1 (2.5%)
Hyperglycemia	0	39 (98%)
	2	1 (2.5%)

Table S5. Details of pembrolizumab-related adverse events in patients treated with first-line (1L) enfortumab vedotin plus pembrolizumab combination therapy (EVP).

Adverse events	CTCAE ver 5.0 grading	Number of patients
<i>n</i>	-	40
Skin toxicity	0	30 (75%)
	1	6 (15%)
	2	3 (7.5%)
	3	1 (2.5%)
Interstitial lung disease	0	36 (90%)
	1	1 (2.5%)
	2	1 (2.5%)

	4	2 (5.0%)
Thyroid dysfunction	0	37 (93%)
	1	2 (5.0%)
	2	1 (2.5%)
Renal dysfunction	0	38 (95%)
	1	1 (2.5%)
	5	5 (13%)
Hepatic dysfunction	0	38 (95%)
	1	1 (2.5%)
	2	1 (2.5%)
