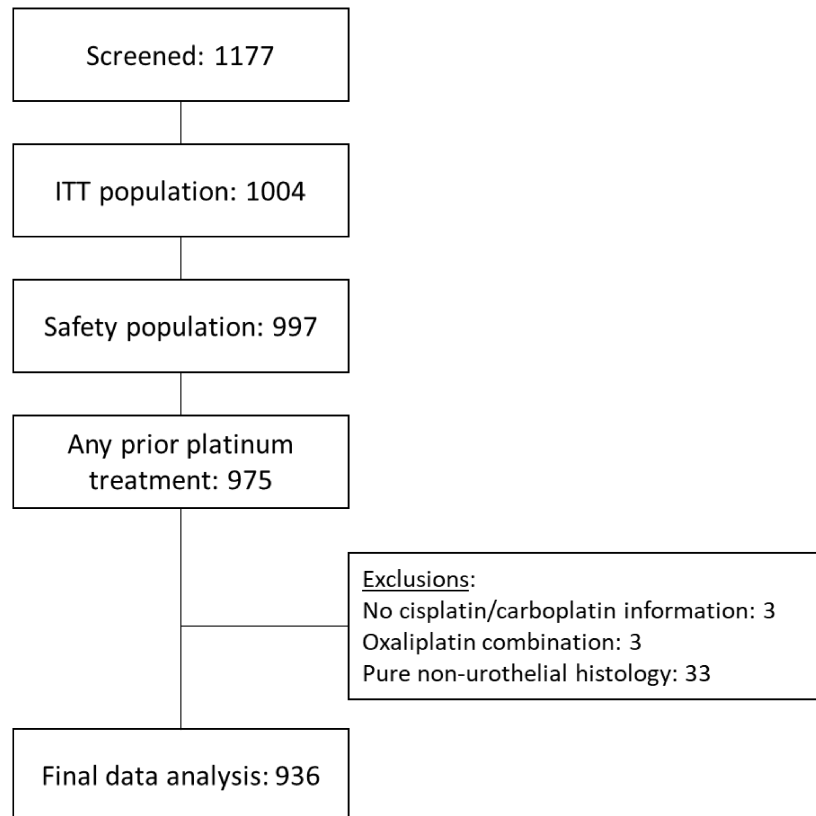
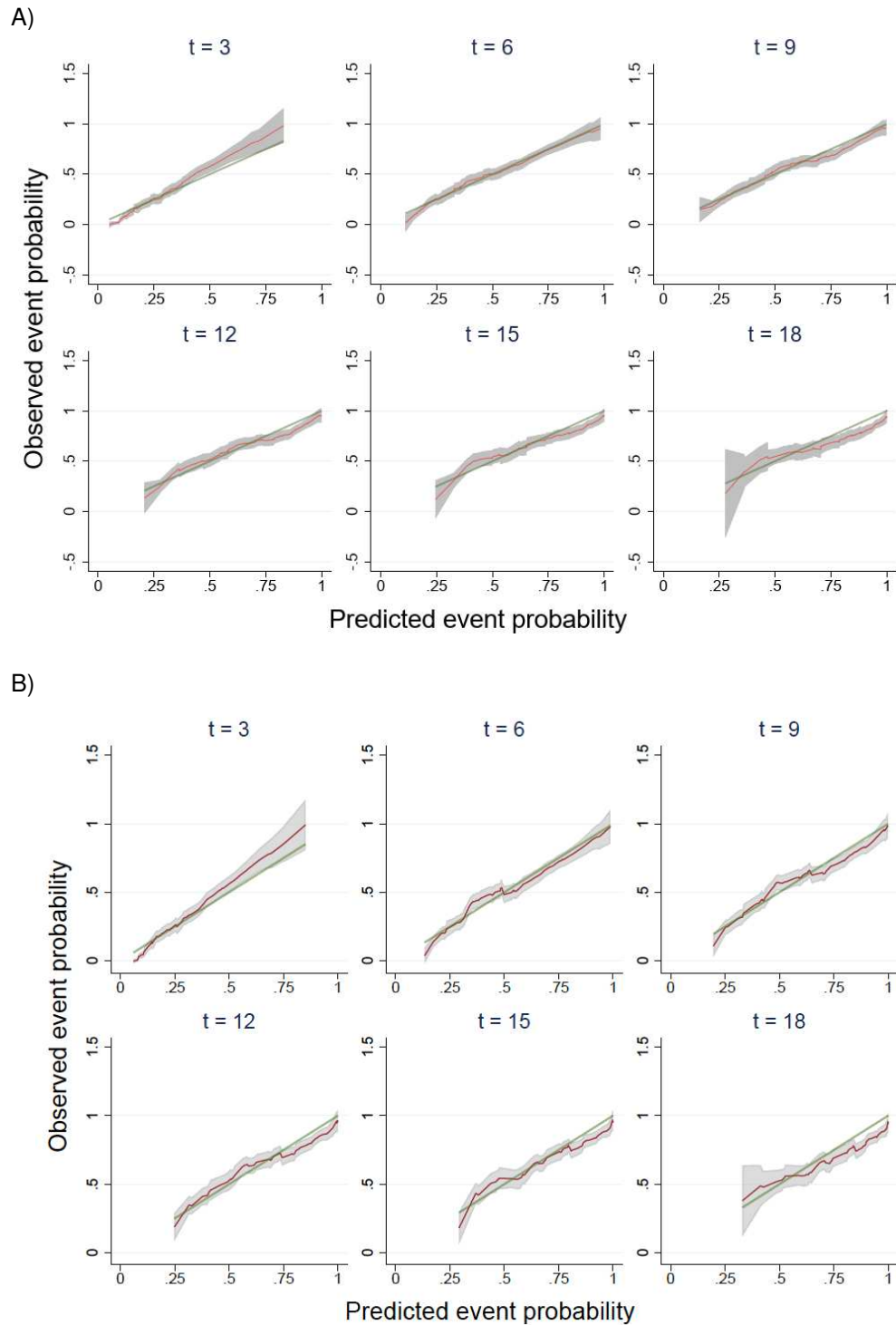


Supplementary Figure S1. Patient disposition

ITT, intention-to-treat.

Supplementary Figure S2. Calibration of the Cox model assessed at various time points A) with PD-L1 and B) without PD-L1.



Supplementary Table S1. Covariates included in the univariate analysis

Covariate	n	Variable type	Categories
Age	934	Continuous	
Age	934	Nominal	<68 years, ≥68 years
Biological sex	936	Nominal	Male, female
Histological type	936	Nominal	Pure urothelial, mixed
Location	936	Nominal	Bladder, other
Smoking history	936	Binary	
Perioperative chemotherapy	936	Binary	
TNM at diagnosis	924	Nominal	0, I, II, III, IV
Pelvic irradiation	936	Binary	
Creatinine clearance	916	Continuous	
Creatinine clearance	916	Binary	≤60, >60 & ≤30, >30 ml/min
Non-lymph node metastases	934	Binary	
Number of disease sites	934	Nominal	0, 1, 2, 3, >3
Lymph node metastases	934	Binary	
Lung metastases	934	Binary	
Bone metastases	934	Binary	
Liver metastases	934	Binary	
CNS metastases	934	Binary	
ECOG PS	936	Nominal	0, ≥1
Number of previous lines for advanced disease	936	Nominal	0, >1
Previous chemotherapy	936	Nominal	Cisplatin, carboplatin
Time from diagnosis of UC to study treatment	935	Continuous	
Time from diagnosis of UC to study treatment	935	Nominal	≤1 year, >1 year
Time from last chemotherapy	936	Continuous	
Time from last chemotherapy	936	Nominal	≤6 months, >6 months
Haemoglobin	914	Nominal	<10, ≥10 g/L
AST	919	Nominal	High, low/normal
Alkaline phosphatase	920	Nominal	High, low/normal
PD-L1 expression	873	Nominal	IC0/1, IC2/3
NLR	928	Continuous	
NLR	928	Binary	≤3, >3 & ≤4, >4 & ≤5, >5
SII	914	Continuous	
SII	914	Nominal	≤median, >median

AST, aspartate transaminase; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ICs, immune cells; NLR, neutrophil-to-lymphocyte ratio; PD-L1, programmed cell death ligand-1; SII, systemic inflammatory index; TNM, tumor-node-metastases; UC, urothelial carcinoma.

Supplementary Table S2. Key baseline characteristics

Characteristic	Cohort (N=936)
Median age*, years (IQR)	68 (61–74)
Sex, n (%)	
Female	204 (21.8)
Male	732 (78.2)
ECOG PS, n (%)	
0	400 (42.7)
1	437 (46.7)
2	99 (10.6)
PD-L1 expression score**, n (%)	
IC0	230 (24.6)
IC1	393 (42)
IC2/3	250 (26.7)
Missing	63 (6.7)
Number of prior lines for advanced/metastatic disease, n (%)	
0	355 (37.9)
1	512 (54.7)
2	49 (5.2)
3	20 (2.1)
Perioperative chemotherapy, n (%)	
No	488 (52.1)
Yes	448 (47.9)
Neoadjuvant	
0 prior lines***	148 (15.8)
≥1 prior lines***	36 (3.8)
Adjuvant	
0 prior lines***	218 (23.2)
≥1 prior lines***	60 (6.4)
Both	
0 prior lines***	355 (37.9)
≥1 prior lines***	93 (9.9)
Histological type, n (%)	
Urothelial	924 (98.7)
Non-urothelial/mixed	12 (1.3)
Haemoglobin, n (%)	
<10 g/dL	767 (81.9)
≥10 g/dL	147 (15.7)
Missing	22 (2.4)
Liver metastases, n (%)	
No	677 (72.3)
Yes	257 (27.5)
Missing	2 (0.2)
Bellmunt risk factors****, n (%)	
0	283 (30.2)
1	370 (39.5)
2	224 (23.9)
3	35 (3.7)
Missing	24 (2.6)
Prior platinum compound, n (%)	
Cisplatin	560 (59.8)
Carboplatin	376 (40.2)

Primary tumour location, n (%)	
Bladder	710 (75.9)
Renal pelvis	114 (12.2)
Ureter	97 (10.3)
Urethra	8 (0.9)
Multiple primaries	7 (0.7)
Time since last therapy, n (%)	
≤3 months	341 (36.4)
>3 months	595 (63.6)
≤6 months	570 (60.9)
>6 months	366 (39.1)
≤9 months	738 (78.9)
>9 months	198 (21.1)

Percentages may not add to 100% due to rounding.

ECOG PS, Eastern Cooperative Oncology Group performance status; ICs, immune cells; IQR, interquartile range; PD-L1, programmed cell death ligand-1.

*Missing: n=2.

**IC0 = expression on <1% of tumour-infiltrating ICs; IC1 = expression on 1% to <5% of tumour-infiltrating ICs; IC2/3 = expression on ≥5% of tumour-infiltrating ICs.

***lines for advanced/metastatic disease prior to study treatment.

****Bellmunt risk factors: ECOG performance status ≥1, haemoglobin <10 g/dL and presence of liver metastasis.[4]

Supplementary Table S3. Univariate cox regression analysis of selected baseline characteristics on OS

Covariate	n	Median OS (months) (95% CI)		HR (95% CI)		p
Age (continuous)	934			0.99	0.99–1.003	.22
Age						.85
<68 years	453	9.3	7.8–10.4	1		
≥68 years	481	8.2	7.3–10.6	1.02	0.85–1.21	
Biological sex						.53
Female	204	8.4	6.5–10.2	1		
Male	732	8.9	7.5–10.4	0.94	0.76–1.15	
Histological type						.049
Pure urothelial	924	8.8	7.8–9.9	1		
Mixed	12	3.4	1.1–NR	1.94	1.00–3.75	
Location						.95
Bladder	711	8.9	7.8–10.1	1		
Other	225	8.3	6.2–10.7	1.01	0.82–1.23	
Smoking history						.65
No	300	9	7–12.4	1		
Yes	636	8.6	7.5–9.9	1.04	0.87–1.26	
Perioperative chemotherapy						.013
No	488	7.8	6.5–9	1		
Yes	448	10.4	8.4–12.5	0.81	0.67–0.95	
TNM at diagnosis						.59
0, I	159	9.7	7.3–13.8	1		
II, III, IV	765	8.6	7.5–9.9	1.07	0.85–1.34	
TNM at diagnosis						.044
0, I, II	333	10.3	8.3–13.9	1		
III, IV	591	8	7–9.1	1.21	1.005–1.46	
TNM at diagnosis						.38
0, I, II, III	471	9.3	7.8–10.6	1		
IV	453	8.3	7–10.2	1.08	0.91–1.29	
Pelvic irradiation						.16
No	827	8.9	7.8–10.1	1		
Yes	109	5.7	4–11.1	1.21	0.93–1.57	

Creatinine clearance (continuous)	916			0.999	0.996–1.002	0.556
Creatinine clearance (continuous, log)	916			0.87	0.7–1.09	0.223
Creatinine clearance						0.532
≥60 ml/min	471	9.4	7.9–10.6	1		
<60 ml/min	445	7.8	6.5–9.3	1.06	0.89–1.26	
Creatinine clearance						.021
>30 ml/min	875	8.8	7.8–10.1	1		
≤30 ml/min	41	5.7	3.9–9.4	1.55	1.07–2.26	
Number of disease sites						<.001
≤1	279	14.7	12.3–NR	1		
>1	657	7	6–7.8	1.89	1.54–2.32	
Number of disease sites						<.001
≤2	616	11.6	10–13.7	1		
>2	320	5.3	4.2–6.5	1.85	1.55–2.21	
Number of disease sites						<.001
≤3	821	9.9	8.6–11	1		
>3	115	3.5	2.8–4.6	2.19	1.73–2.78	
Non-lymph node metastases						<.001
Yes	695	7	6.1–8	1		
No	241	15.7	11.9–NR	0.54	0.44–0.67	
Lymph node metastases						.096
No	355	7.9	6.5–9.3	1		
Yes	579	9.4	7.8–11	0.86	0.72–1.03	
Lung metastases						.29
No	541	9.7	7.8–11	1		
Yes	393	7.9	6.5–9.4	1.1	0.92–1.31	
Bone metastases						<.001
No	697	10.3	8.7–11.9	1		
Yes	237	5.8	4.4–7	1.68	1.39–2.02	
Liver metastases						<.001
No	677	11.1	9.7–12.8	1		
Yes	257	4.2	3.4–5.1	2.2	1.83–2.64	
CNS metastases						.006
No	920	8.9	7.8–10.1	1		
Yes	14	3.5	1.5–7	2.3	1.27–4.19	

ECOG PS						<.001
0	400	18	12.4–NR	1		
≥1	536	5.4	4.5–6.7	2.31	1.92–2.78	
Number of previous lines for advanced disease						.19
0	355	9.9	7.8–12.4	1		
≥1	581	8.3	7.2–9.4	1.13	0.94–1.35	
Previous chemotherapy						.072
Cisplatin-based	560	9.4	8.1–11.4	1		
Carboplatin-based	376	7.5	6.4–9.5	1.17	0.99–1.39	
Time from diagnosis of UC to study treatment (continuous, days)	935			0.99	0.99–1.001	.16
Time from diagnosis of UC to study treatment (continuous, log)	935			0.83	0.75–0.92	<.001
Time from diagnosis of UC to study treatment						<.001
>1 year	659	9.9	8.6–11.4	1		
≤1 year	276	6.1	4.9–7.5	1.41	1.18–1.69	
Time from last chemotherapy (continuous, days)	936			1.001	1.001–1.002	<.001
Time from last chemotherapy (continuous, log)	936			0.79	0.72–0.86	<.001
Time from last chemotherapy						<.001
>6 months	366	11.9	10.5–NR	1		
≤6 months	570	7	5.9–9	1.57	1.31–1.89	
Haemoglobin						<.001
≥10 g/L	767	10.2	8.9–11.6	1		
<10 g/L	147	3.6	2.7–4.6	2.29	1.85–2.84	
AST						<.001
High	45	2.6	1.4–5.3	1		
Low/Normal	874	9	8–10.3	0.43	0.3–0.6	
Alkaline phosphatase						<.001
Low/Normal	699	10.6	9.2–11.9	1		
High	221	3.9	3.1–5	2.11	1.75–2.55	
PD-L1 expression						.003
IC2/3	250	11.7	8.9–18.8	1		
IC0/1	623	7.8	6.5–9	1.37	1.11–1.68	
NLR (continuous)	928			1.1	1.09–1.11	<.001
NLR (continuous, log)	928			2.51	2.19–2.89	<.001
NLR >3						<.001

No	326	18	112.4–NR	1		
Yes	602	6.1	5.2–7.4	2.11	1.73–2.57	
NLR >4						<.001
No	508	12.8	10.9–18.6	1		
Yes	420	4.6	4–5.6	2.21	1.85–2.63	
NLR >5						<.001
No	625	12.3	10.6–14.7	1		
Yes	303	3.7	3.2–4.4	2.57	2.16–3.07	
SII (continuous)	914			1.0002	1.0001–1.0002	<.001
SII (continuous, log)	914			2.03	1.83–2.26	<.001
SII						<.001
≤median	457	13.9	11.7–NR	1		
>median	457	4.6	4–5.4	2.43	2.03–2.9	

AST, aspartate transaminase; CI, confidence interval; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ICs, immune cells; NLR, neutrophil-to-lymphocyte ratio; NR, not reached; OS, overall survival; PD-L1, programmed cell death ligand-1; SII, systemic inflammatory index; TNM, tumor-node-metastases; UC, urothelial carcinoma.

Supplementary Table S4. Multivariate cox regression analysis and final model including variables identified in the univariate analysis after multiple imputation (n=936)

Covariate	With PD-L1			Without PD-L1		
	HR	95% CI	p-value	HR	95% CI	p-value
ECOG PS			<.001			<.001
0	1			1		
≥1	1.82	1.5–2.2		1.78	1.47–2.16	
Haemoglobin			<.001			<.001
≥10 g/L	1			1		
<10 g/L	1.52	1.21–1.92		1.5	1.2–1.88	
Liver metastases			<.001			<.001
No	1			1		
Yes	1.84	1.53–2.21		1.89	1.57–2.27	
Time from last chemotherapy			.001			.001
>6 months	1			1		
≤6 months	1.39	1.15–1.68		1.36	1.13–1.64	
NLR >5			<.001			<.001
No	1			1		
Yes	1.9	1.58–2.3		1.84	1.53–2.22	
Bone metastases						.002
No				1		
Yes				1.35	1.11–1.63	
Alkaline phosphatase			<.001			<.001
Low/Normal	1			1		
High	1.72	1.42–2.1		1.68	1.37–2.04	
PD-L1 expression			.003			
IC2/3	1					
IC0/1	1.37	1.11–1.68				

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ICs, immune cells; NLR, neutrophil-to-lymphocyte ratio; PD-L1, programmed cell death ligand-1.