

Supplementary Materials

High Serum PD-L1 Levels are Associated with Poor Survival in Urothelial Cancer Patients Treated with Chemotherapy and Immune Checkpoint Inhibitor Therapy

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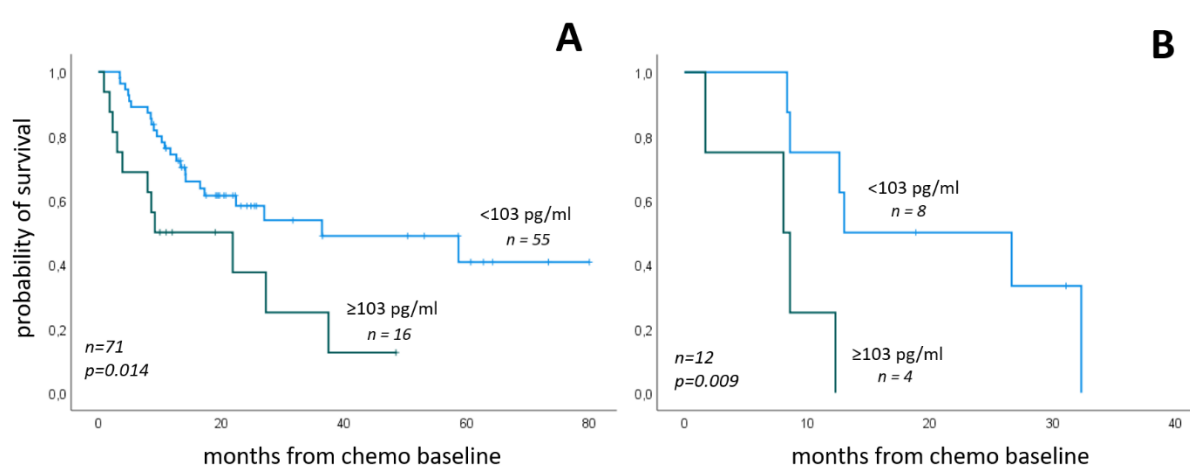


Figure S1. Overall survival stratified by pretreatment sPD-L1 levels in the subgroup of patients without distant metastasis (M0) (a) and with distant metastasis at the baseline of chemotherapy (M1) (b).

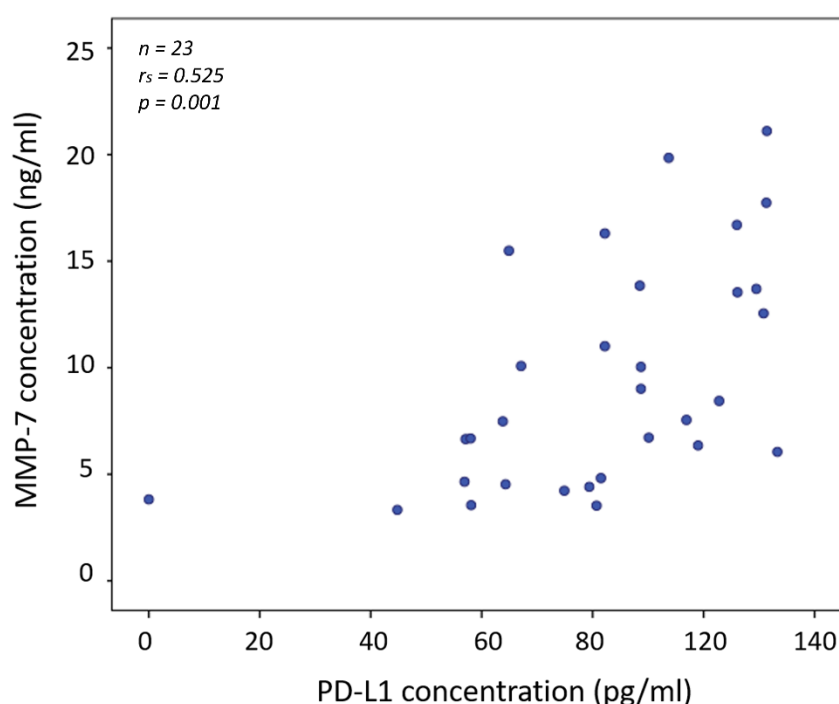


Figure S1. Correlation analysis between serum PD-L1 and MMP-7.

Table S1. Clinical characteristics in platinum-treated patients. ECOG PS- Eastern Cooperative Oncology Group performance status. LN - lymph node metastasis, R - positive surgical margin, RC - cystectomy, Gem/Cis - gemcitabine + cisplatin, Gem/Carbo -gemcitabine + carboplatin, ICI - immune checkpoint inhibitor.

variables	whole chemo cohort	neoadjuvant	adjuvant	palliative
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Total number of patients	83	22	33	28
Age at baseline median [range]	67 [41-81]	68 [48-74]	66 [41-80]	68 [48-81]
Gender				
male	64 (77)	16 (73)	25 (76)	23 (82)
female	19 (33)	6 (27)	8 (24)	5 (18)
ECOG PS at enrollment				
0	48 (58)	8 (36)	27 (82)	13 (46)
1	32 (37)	14 (64)	6 (18)	12 (43)
2	3 (3)	0 (0)	0 (0)	3 (11)
Cystectomy data				
Cystectomy performed	59 (71)	22 (100)	33 (100)	4 (14)
pT0	3 (5)	3 (14)	0 (0)	-
pT1	2 (3)	2 (9)	0 (0)	-
pT2	11 (19)	3 (14)	6 (18)	2 (7)
pT3	30 (51)	10 (45)	19 (58)	1 (4)
pT4	12 (20)	3 (14)	8 (24)	1 (4)
n.a.	1	1	0	0
R	10 (17)	0 (0)	10 (30)	0
LN metastasis at RC	30 (51)	5 (23)	25 (76)	0
Chemo baseline data				
LN at baseline	36 (43)	5 (23)	27 (82)	4 (14)
Distant metastasis at baseline	12 (15)	0 (0)	0 (0)	12 (43)
Soft tissue lesions (lung/liver)	9 (11)	0 (0)	0 (0)	9 (32)
Bone metastasis	3 (3)	0 (0)	0 (0)	3 (11)
Chemotherapy regimen				
Gem/Cis	61 (73)	16 (73)	29 (88)	12 (43)
Gem/Carbo	22 (27)	6 (27)	4 (12)	16 (57)
Atezolizumab	-	-	-	-
Pembrolizumab	-	-	-	-
Number of cycles median (range)	3 (1-9)	3 (1-6)	3 (1-9)	3 (1-6)
single (only one series)	9	1	2	6
Number of patients died (%)	45 (54)	7 (32)	20 (61)	18 (64)
Follow-up time in months median (range)	14 (1-80)	15 (5-48)	19 (2-80)	12 (1-73)
PD-L1 serum levels				
PD-L1 median (range) baseline [pg/ml]	83.0 (0.0 - 781)	93.6 (32.4 - 324.0)	80.7 (0.0 - 158.5)	83.6 (25.8 - 780.9)

PD-L1 median (range) 2-3 cycle [pg/ml] 78.5 (0.0 - 273.1) 88.3 (0.0 - 273.1) 76.2 (44.9 - 134.4) 77.9 (38.7 - 261.2)

Table S2. Correlation of pretreatment sPD-L1 levels (pg/ml) with clinicopathological parameters in platinum-treated patients. ECOG—Eastern Cooperative Oncology Group performance status, LN – lymph node metastasis, M – distant metastasis, ICI – immune checkpoint inhibitor. In the ICI cohort, due to the small number of cases no Cox regression analysis could be performed. Bold printed p-values were significant (<0.05).

variables	whole chemo cohort			neoadjuvant			adjuvant			palliative			ICI cohort		
	n	median (range)	P	n	median (range)	P	n	median (range)	P	n	median (range)	P	n	median (range)	P
Age															
≤ 65	35	82.2 (0.0-780.9)	0.43	8	93.6 (32.4-324.0)	0.946	16	76.8 (0.0-158.5)	0.815	11	74.9 (25.8-780.9)	0.323	3	86.6 (59.0-169.0)	-
> 65	48	84.0 (35.8-243.1)		14	89.7 (46.0-194.9)		17	80.7 (40.5-136.8)		17	85.5 (35.8-243.1)		9	93.3 (25.3-145.0)	
Sex															
Male	64	84.0 (0.0-780.9)	0.435	16	87.0 (32.4-324.0)	0.606	25	80.0 (0.0-136.8)	0.275	23	85.5 (25.8-780.9)	0.697	10	94.2 (59.0-169.0)	-
Female	19	82.2 (40.5-194.9)		6	100.3 (41.9-194.9)		8	91.5 (40.5-158.5)		5	82.2 (48.0-154.8)		2	26.1 (25.3-26.89)	
ECOG															
0	48	80.4 (0.0-158.5)	0.007	8	71.2 (32.4 - 111.4)	0.101	27	67.1 (0.0-158.5)	0.1	13	81.0 (25.8-111.3)	0.214	10	91.9 (26.9-169.0)	-
1-2	35	96.2 (35.8-780.9)		14	97.0 (41.9-324.0)		6	91.9 (79.4-136.8)		15	95.9 (35.8-780.9)		2	59.3 (25.3-93.3)	
Stage at cystectomy															
pT0-pT2	16	84.7 (32.4-194.9)	0.741	8	86.9 (32.4-194.9)	0.001	6	89.4 (52.3-109.5)	0.692	2	-	-	2	56.8 (26.9-86.6)	-
pT3-pT4	42	80.4 (0.0-324.0)		13	96.2 (41.9-324.0)		27	80.0 (0.0-158.5)		2	-	-	6	97.2 (59.0-169.0)	
LN / M status															
N0/M0	38	87.0 (38.5-324.0)	0.209	17	97.0 (41.9-324.0)	0.322	6	84.7 (67.1-102.2)	0.469	15	85.5 (38.5-189.5)	0.818	2	87.1 (80.9-93.3)	-
N+ or M+	45	80.7 (0.0-780.9)		5	91.0 (32.4-114.8)		27	79.4 (0.-158.5)		13	80.7 (25.8-780.9)		10	90.9 (25.3-169.0)	

Table 3. Cox univariate OS analysis in treatment subgroups of platinum-treated patients. ECOG - Eastern Cooperative Oncology Group, LN – lymph node metastasis, M – distant metastasis. Ref – referent. Bold p-values were <0.05. In the ICI cohort, due to the small case numbers no Cox analysis could be performed. Bold printed p-values were significant (<0.05).

variables	whole chemo cohort				neoadjuvant				adjuvant				palliative			
	n	HR	95% CI	P	n	HR	95% CI	P	n	HR	95% CI	P	n	HR	95% CI	P
Age																
≤ 65	35	ref.			8	ref.			16	ref.			11	ref.		
> 65	48	1.297	0.716 - 2.351	0.391	14	0.382	0.071 - 2.042	0.26	17	1.115	0.463 - 2.686	0.808	17	4.165	1.158 - 14.974	0.029
Gender																
Male	64	ref.			16	ref.			25	ref.			23	ref.		
Female	19	0.815	0.392 - 1.694	0.584	6	0.344	0.041 - 2.915	0.328	8	1.268	0.458 - 3.110	0.647	5	0.695	0.197 - 2.447	0.571
ECOG																
0	48	ref.			8	ref.			27	ref.			13	ref.		
1-2	35	2.615	1.381 - 4.950	0.003	14	2.703	0.490 - 14.913	0.254	6	3.032	1.043 - 8.814	0.042	15	3.33	1.137 - 9.752	0.028
Stage at cystectomy																
T0-T2	14	ref.			8	ref.			6	ref.				ref.		
T3-T4	40	1.135	0.483 - 2.664	0.772	13	2.964	0.345 - 25.484	0.322	27	0.926	0.308 - 1.778	0.89		-	-	-
LN / M status																
N0/M0	38	ref.			17	ref.			6	ref.			15	ref.		
N+ or M+	45	1.914	1.017-3.601	0.044	5	1.583	0.289 - 8.682	0.597	27	2.708	0.625 - 11.741	0.183	13	2.182	0.802 - 5.934	0.127
PD-L1 serum cc. / upper 25%																
< 103 pg/ml	63	ref.			16	ref.			27	ref.			20	ref.		
≥ 103 pg/ml	20	1.381	1.120 - 1.703	0.002	6	0.746	0.364 - 1.530	0.424	6	1.577	1.134 - 2.192	0.007	8	1.51	1.095 - 2.083	0.012
PD-L1 serum cc. / median																
< 83 pg/ml	42	ref.			10	ref.			18	ref.			14	ref.		
≥ 83 pg/ml	41	1.989	1.099 - 3.600	0.023	12	0.857	0.187 - 3.916	0.842	15	1.684	0.698 - 4.062	0.246	14	4.234	1.537 - 11.667	0.005