

Supplemental Material

Table S1. Association between PD-L1 status, immunophenotype, and WHO/ISUP grade.

(A) PD-L1 status, immunophenotype, and WHO/ISUP grade.

Characteristic			PD-L1 Negative		PD-L1 Positive	
			(N = 334)		(N = 234)	
Immunophenotype	Desert	(N = 242)	220	90.9%	22	9.1%
	Excluded	(N = 288)	108	37.5%	180	62.5%
	Inflamed	(N = 38)	6	15.8%	32	84.2%
WHO/ISUP grade	Grade 1/2	(N = 215)	168	78.1%	47	21.9%
	Grade 3	(N = 215)	118	54.9%	97	45.1%
	Grade 4	(N = 138)	48	34.8%	90	65.2%

(B) Immunophenotype and WHO/ISUP grade.

Characteristic			WHO/ISUP Grade					
			Grade 1/2		Grade 3		Grade 4	
			(N = 215)		(N = 215)		(N = 138)	
Immunophenotype	Desert	(N = 242)	127	52.5%	80	33.1%	35	14.5%
	Excluded	(N = 288)	85	29.5%	124	43.1%	79	27.4%
	Inflamed	(N = 38)	3	7.9%	11	28.9%	24	63.2%

ISUP, International Society of Urologic Pathologists; PD-L1, programmed death ligand 1; WHO, World Health Organization.

Table S2. Comparison of baseline characteristics at the time of initial diagnosis by time to metastasis (≤ 12 months vs. > 12 months).

Characteristic, n (%)	≤ 12 mo (N = 388)	> 12 mo (N = 180)	Total (N = 568)	<i>p</i> -Value ^a	Standardized Difference
Sex					
Male	298 (76.8)	136 (75.6)	434 (76.4)	0.744	0.0
Female	90 (23.2)	44 (24.4)	134 (23.6)		0.0
Age					
Mean (standard deviation)	63.2 (11.0)	62.7 (9.8)	63.0 (10.6)	0.376	0.1
Median [range]	64.0 [23, 87]	64.0 [32, 84]	64.0 [23, 87]		
Age category					
< 65 y	203 (52.3)	101 (56.1)	304 (53.5)	0.122	-0.1
≥ 65 and < 75 y	121 (31.2)	61 (33.9)	182 (32.0)		-0.1
≥ 75 y	64 (16.5)	18 (10.0)	82 (14.4)		0.2
Histology					
Clear cell	360 (92.8)	167 (92.8)	527 (92.8)	0.998	0.0
Non-clear cell	28 (7.2)	13 (7.2)	41 (7.2)		0.0
Sarcomatoid component					
Absent	331 (85.3)	173 (96.1)	504 (88.7)	0.0002	-0.4
Present	57 (14.7)	7 (3.9)	64 (11.3)		0.4
Growth pattern					
Expansive	120 (30.9)	87 (48.3)	207 (36.4)	< 0.0001	-0.4
Infiltrative	114 (29.4)	28 (15.6)	142 (25.0)		0.3
Indeterminable	154 (39.7)	65 (36.1)	219 (38.6)		0.1
Fuhrman grade					
Grade 1/2	99 (25.5)	86 (47.8)	185 (32.6)	< 0.0001	-0.5
Grade 3	200 (51.5)	80 (44.4)	280 (49.3)		0.1
Grade 4	89 (22.9)	14 (7.8)	103 (18.1)		0.4
WHO/ISUP grade					
Grade 1/2	112 (28.9)	103 (57.2)	215 (37.9)	< 0.0001	-0.6
Grade 3	160 (41.2)	55 (30.6)	215 (37.9)		0.2
Grade 4	116 (29.9)	22 (12.2)	138 (24.3)		0.4

Characteristic, n (%)	≤ 12 mo (N = 388)	> 12 mo (N = 180)	Total (N = 568)	<i>p</i> -Value ^a	Standardized Difference
Necrosis					
Absent	187 (48.2)	132 (73.3)	319 (56.2)	< 0.0001	-0.5
Present	199 (51.3)	48 (26.7)	247 (43.5)		0.5
Indeterminable	2 (0.5)	0 (0.0)	2 (0.4)		0.1
Lymphovascular invasion					
Absent	249 (64.2)	140 (77.8)	389 (68.5)	0.0006	-0.3
Present	117 (30.2)	27 (15.0)	144 (25.4)		0.4
Indeterminable	22 (5.7)	13 (7.2)	35 (6.2)		-0.1
TIME					
PD-L1 expression					
IC0	200 (51.5)	134 (74.4)	334 (58.8)	< 0.0001	-0.5
IC1	110 (28.4)	34 (18.9)	144 (25.4)		0.2
IC2	47 (12.1)	7 (3.9)	54 (9.5)		0.3
IC3	31 (8.0)	5 (2.8)	36 (6.3)		0.2
PD-L1 expression					
Negative ^b	200 (51.5)	134 (74.4)	334 (58.8)	< 0.0001	-0.5
Positive ^c	188 (48.5)	46 (25.6)	234 (41.2)		0.5
Immunophenotype					
Desert	142 (36.6)	100 (55.6)	242 (42.6)	< 0.0001	-0.4
Excluded	215 (55.4)	73 (40.6)	288 (50.7)		0.3
Inflamed	31 (8.0)	7 (3.9)	38 (6.7)		0.2

^a *p*-values were calculated using the chi-square test for categorical variables and Kruskal-Wallis test for continuous variables.

^b Defined as IC0. ^c Defined as IC1/2/3.

ISUP, International Society of Urologic Pathologists; PD-L1, programmed death ligand 1; TIME, tumor immune microenvironment; WHO, World Health Organization.

Table S3. Metastatic sites of synchronous and metachronous metastatic renal cell carcinoma.

(A) Synchronous vs. metachronous.

Metastatic Site, n (%)	Synchronous^a (N = 307)	Metachronous^b (N = 261)	Total (N = 568)	<i>p</i>- Value^c	Standardized Difference
Lung	212 (69.1)	145 (55.6)	357 (62.9)	0.0027	0.3
Bone	98 (31.9)	68 (26.1)	166 (29.2)	0.179	0.1
Lymph node	81 (26.4)	46 (17.6)	127 (22.4)	0.026	0.2
Liver	32 (10.4)	28 (10.7)	60 (10.6)	0.550	0.0
Adrenal glands	24 (7.8)	13 (5.0)	37 (6.5)	0.222	0.1
Pleura	16 (5.2)	11 (4.2)	27 (4.8)	0.478	0.0
Brain	13 (4.2)	8 (3.1)	21 (3.7)	0.426	0.1
Pancreas	8 (2.6)	17 (6.5)	25 (4.4)	0.042	-0.2
Kidney	8 (2.6)	9 (3.4)	17 (3.0)	0.465	0.0
Other soft tissue	7 (2.3)	11 (4.2)	18 (3.2)	0.232	-0.1
Mediastinum	4 (1.3)	2 (0.8)	6 (1.1)	0.458	0.1
Peritoneum	3 (1.0)	8 (3.1)	11 (1.9)	0.109	-0.1
Bronchus	1 (0.3)	0 (0.0)	1 (0.2)	0.363	0.1
Breast	1 (0.3)	0 (0.0)	1 (0.2)	0.363	0.1
Duodenum	1 (0.3)	1 (0.4)	2 (0.4)	0.551	0.0
Bone marrow	2 (0.7)	1 (0.4)	3 (0.5)	0.504	0.0
Skin	3 (1.0)	0 (0.0)	3 (0.5)	0.155	0.1
Other	5 (1.6)	7 (2.7)	12 (2.1)	0.378	-0.1

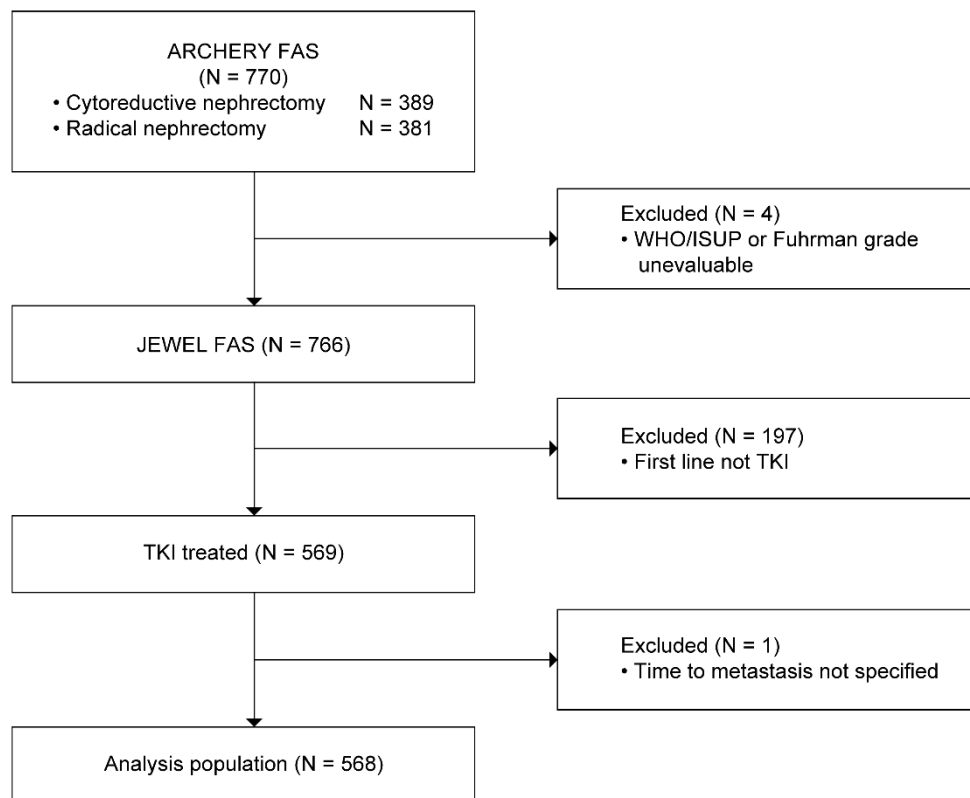
^a Defined as metastasis \leq 3 months of initial diagnosis of renal cell carcinoma.^b Defined as metastasis diagnosed $>$ 3 months after initial diagnosis of renal cell carcinoma.^c *p*-values were calculated using the chi-square test.

(B) By time to metastasis.

Metastatic Site, n (%)	≤ 3 mo (N = 307)	> 3–12 mo (N = 81)	> 12–24 mo (N = 52)	> 24 mo –5 y (N = 86)	> 5 y (N = 42)	<i>p</i> -Value ^a
Lung	212 (69.1)	51 (63.0)	30 (57.7)	36 (41.9)	28 (66.7)	0.0008
Bone	98 (31.9)	18 (22.2)	17 (32.7)	23 (26.7)	10 (23.8)	0.286
Lymph node	81 (26.4)	10 (12.3)	6 (11.5)	22 (25.6)	8 (19.0)	0.025
Liver	32 (10.4)	13 (16.0)	4 (7.7)	8 (9.3)	3 (7.1)	0.318
Adrenal glands	24 (7.8)	3 (3.7)	5 (9.6)	4 (4.7)	1 (2.4)	0.267
Pleura	16 (5.2)	4 (4.9)	1 (1.9)	4 (4.7)	2 (4.8)	0.571
Brain	13 (4.2)	1 (1.2)	3 (5.8)	1 (1.2)	3 (7.1)	0.215
Pancreas	8 (2.6)	5 (6.2)	2 (3.8)	4 (4.7)	6 (14.3)	0.019
Kidney	8 (2.6)	0 (0.0)	2 (3.8)	5 (5.8)	2 (4.8)	0.187
Other soft tissue	7 (2.3)	5 (6.2)	3 (5.8)	3 (3.5)	0 (0.0)	0.183
Mediastinum	4 (1.3)	1 (1.2)	0 (0.0)	0 (0.0)	1 (2.4)	0.436
Peritoneum	3 (1.0)	3 (3.7)	1 (1.9)	3 (3.5)	1 (2.4)	0.294
Bronchus	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.596
Breast	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.596
Duodenum	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0.185
Bone marrow	2 (0.7)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0.504
Skin	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.417
Other	5 (1.6)	1 (1.2)	1 (1.9)	3 (3.5)	2 (4.8)	0.385

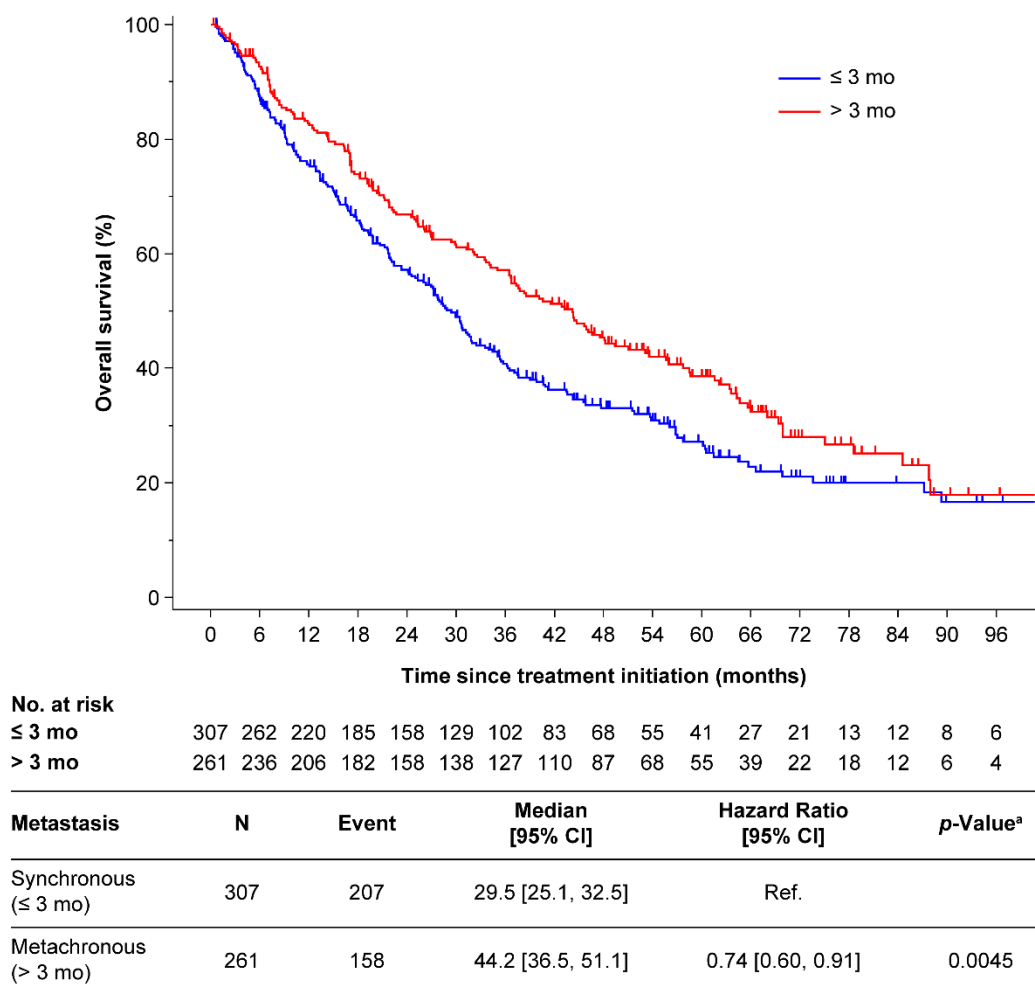
^a *p*-values were calculated using the chi-square test.

Figure S1. Study population.



FAS, full analysis set; ISUP, International Society of Urologic Pathologists; TKI, tyrosine kinase inhibitor; WHO, World Health Organization.

Figure S2. Overall survival after first-line tyrosine kinase inhibitor treatment by time from diagnosis to metastasis (synchronous/metachronous).



^a p-value was calculated using Wald test for a parameter of the univariate Cox proportional hazards model.

CI, confidence interval; ref., reference.