

Supplementary Materials

Baseline and Early Changes in Eosinophil Count and Neutrophil-to-Eosinophil Ratio Predict Outcomes in Metastatic Renal Cell Carcinoma Treated with Nivolumab

Ondřej Fiala^{1,2#*}, Katarína Rejleková³, Tomas Buchler⁴, Hana Študentová⁵, Alexandr Poprach^{6,7}, Michal Vočka⁸, Petr Hošek², Jindřich Kopecký⁹, Martin Matějů⁸, Anežka Zemánková⁵, Martina Spisarová⁵, Michaela Tkadlecová^{1,2}, Peter Priester⁹, Jan Kouřil¹⁰, Radka Lohynská¹¹, Lucie Grmelová^{6,7}, Alexander Savka¹², Katarína Štefániková¹³, Jana Obertová³, Dominika Šíková¹⁴, Petr Stránský¹⁴, Bohuslav Melichar⁵, Patrik Palacka^{3,15}

¹Department of Oncology and Radiotherapeutics, Faculty of Medicine and University Hospital in Pilsen, Charles University, Czech Republic, alej Svobody 80, 304 60 Pilsen, Czech Republic

²Biomedical Center, Faculty of Medicine in Pilsen, Charles University, alej Svobody 76, 304 60 Pilsen, Czech Republic

³2nd Department of Oncology, Faculty of Medicine, Comenius University, and National Cancer Institute, Bratislava, Slovakia

⁴Department of Oncology, Second Faculty of Medicine, Charles University and Motol University Hospital, V Úvalu 84, 150 06 Prague, Czech Republic

⁵Department of Oncology, Palacký University Medical School and Teaching Hospital, I.P. Pavlova 6, 775 20 Olomouc, Czech Republic

⁶Department of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute, Zlutý kopec 7, 656 53 Brno, Czech Republic

⁷Department of Comprehensive Cancer Care, Faculty of Medicine, Masaryk University, Kamenice 5, 625 00 Brno, Czech Republic

⁸Department of Oncology, First Faculty of Medicine, Charles University and General University Hospital, U Nemocnice 499/2, 128 08 Prague, Czech Republic

⁹Department of Oncology, University Hospital in Hradec Králové, Sokolská 581, Hradec Králové 50005, Czech Republic

¹⁰Institute of Biostatistics and Analyses, Ltd., Poštovská 68/3, 602 00 Brno, Czech Republic

¹¹Department of Oncology, First Faculty of Medicine, Charles University and Thomayer University Hospital, Vídenská 800, 140 59 Prague, Czech Republic

¹²Department of Oncology, F. D. Roosevelt University General Hospital, Banská Bystrica, Slovakia

¹³Department of Oncology, East Cancer Slovak Institute, Kosice, Slovakia

¹⁴Department of Urology, Faculty of Medicine and University Hospital in Pilsen, Charles University, Czech Republic, Edvarda Beneše 1128/13, 301 00 Pilsen, Czech Republic

¹⁵Cancer Research Institute, Biomedical Research Center of the Slovak Academy of Sciences, Bratislava, Slovakia.

***Corresponding author:** Ondřej Fiala, M.D., Ph.D., Department of Oncology and Radiotherapeutics, Faculty of Medicine and University Hospital in Pilsen, Charles University, Czech Republic, alej Svobody 80, 304 60 Pilsen, Czech Republic. Tel.: +42 0728655488, e-mail: fialao@fnplzen.cz

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Table 1S. Progression-free survival (PFS) and overall survival (OS) data in the specified subgroups

	PFS						OS				
	median (months, 95% CI)	6 month	12 month	24 month	p-value		median (months, 95% CI)	12 month	24 month	36 month	p-value
Whole sample	8.3 (6.9–10.1)	57.8% (53.2–62.3)	40.1% (35.5–44.7)	23.0% (18.9–27.1)			23.8 (20.7–28.6)	70.4% (66.1–74.7)	49.9% (45.0–54.9)	35.0% (29.8–40.3)	
AEC at baseline											
≥70 cells/μL	9.7 (7.7–11.0)	62.6% (57.6–67.7)	42.6% (37.4–47.7)	24.4% (19.7–29.1)	0.004		26.4 (22.3–32.5)	74.6% (70.0–79.2)	54.0% (48.5–59.5)	37.5% (31.6–43.5)	0.001
<70 cells/μL	4.8 (3.9–5.8)	38.6% (28.3–48.8)	29.1% (19.5–38.8)	16.7% (8.2–25.3)			14.4 (8.2–20.8)	52.8% (42.2–63.5)	33.3% (22.3–44.3)	23.8% (11.6–36.0)	
AEC one month after nivolumab initiation											
≥70 cells/μL	9.9 (7.9–11.3)	62.0% (57.0–67.0)	43.7% (38.5–48.9)	24.5% (19.8–29.2)	0.002		28.6 (24.6–33.0)	76.7% (72.2–81.2)	56.3% (50.7–61.8)	39.0% (32.8–45.1)	<0.001
<70 cells/μL	5.1 (3.4–7.3)	41.8% (29.6–54.0)	22.7% (12.2–33.2)	13.6% (4.5–22.6)			10.1 (5.5–15.5)	43.7% (31.4–56.0)	23.1% (12.2–34.0)	NA	
ΔAEC											
≥30%	9.6 (7.4–11.1)	60.1% (55.0–65.1)	43.0% (37.8–48.2)	24.7% (20.0–29.4)	0.044		28.1 (21.8–32.6)	74.6% (70.1–79.2)	53.4% (47.8–58.9)	38.2% (32.1–44.2)	<0.001
<30%	7.5 (4.8–8.8)	53.4% (40.5–66.3)	25.5% (14.0–37.0)	14.1% (4.5–23.7)			13.1 (6.7–23.7)	53.2% (40.1–66.3)	36.8% (23.6–49.9)	17.7% (6.3–29.1)	
NER at baseline											
<65	10.1 (8.1–11.3)	64.4% (59.3–69.4)	43.3% (38.0–48.6)	24.9% (20.1–29.7)	<0.001		26.6 (23.0–33.0)	75.7% (71.1–80.3)	54.6% (49.0–60.3)	38.3% (32.2–44.4)	<0.001
≥65	4.8 (3.5–5.4)	35.1% (25.6–44.5)	28.0% (19.0–36.9)	15.9% (8.2–23.7)			12.8 (7.9–20.5)	51.4% (41.5–61.4)	33.8% (23.7–43.9)	22.2% (11.9–32.5)	
NER one month after nivolumab initiation											
<65	10.2 (8.5–11.8)	64.0% (58.9–69.1)	44.3% (39.0–49.7)	25.3% (20.4–30.2)	<0.001		29.7 (25.5–33.8)	78.7% (74.3–83.2)	57.6% (51.9–63.3)	40.2% (34.0–46.5)	<0.001
≥65	4.4 (3.4–5.8)	38.0% (27.3–48.6)	24.3% (14.8–33.8)	13.2% (5.4–21.1)			8.1 (5.3–13.1)	41.6% (30.6–52.5)	24.0% (14.0–34.1)	NA	
ΔNER											
<125%	9.7 (8.0–11.3)	61.6% (56.6–66.5)	43.5% (38.4–48.6)	24.9% (20.3–29.6)	<0.001		26.3 (22.5–31.9)	74.0% (69.5–78.5)	53.9% (48.5–59.3)	36.8% (30.9–42.7)	0.001
≥125%	4.3 (3.4–6.3)	36.6% (21.8–51.3)	13.9% (3.2–24.6)	NA			11.7 (5.2–15.5)	49.5% (34.0–64.9)	26.6% (12.1–41.1)	NA	
PFS - progression-free survival; OS - overall survival; CI - confidence interval; AEC - absolute eosinophil count; NER - neutrophil-to-eosinophil ratio											

Table 2S. Detailed results of the multivariable Cox models performed for each eosinophil-based parameter separately

Parameter	Category	PFS				OS		
		Hazard Ratio	95% CI	p-value		Hazard Ratio	95% CI	p-value
Age								
	Age<70 years	1		0.210		1		0.318
	Age≥70 years	0.849	0.657-1.097			0.859	0.637-1.158	
Sex								
	Female	1		0.176		1		0.488
	Male	0.828	0.629-1.089			1.124	0.808-1.563	
Synchronous metastatic disease								
	No	1		0.624		1		0.401
	Yes	1.073	0.810-1.422			1.157	0.823-1.628	
Grade								
	Grade 1-2	1		0.738		1		0.303
	Grade 3-4	1.044	0.810-1.347			0.854	0.632-1.153	
Line								
	Second	1		0.556		1		0.223
	Third and further	1.083	0.830-1.414			1.210	0.891-1.643	
IMDC group								
	Good/intermediate	1		<0.001		1		<0.001
	Poor	2.055	1.422-2.971			2.832	1.884-4.258	
Bone metastases								
	No	1		0.073		1		0.434
	Yes	1.338	0.973-1.840			1.156	0.804-1.661	
Prior nephrectomy								
	No	1		0.183		1		0.019
	Yes	0.778	0.537-1.126			0.615	0.409-0.924	
Histology								
	Clear cell	1		0.968		1		0.236
	Other	0.990	0.590-1.659			1.402	0.802-2.451	

Parameter	Category	PFS				OS		
		Hazard Ratio	95% CI	p-value		Hazard Ratio	95% CI	p-value
ECOG PS								
	0	1		<0.001		1		<0.001
	1	1.970	1.498-2.590			2.236	1.629-3.070	
AEC at baseline								
	<70 cells/ μ L	1		0.009		1		0.002
	$\geq$ 70 cells/ μ L	0.663	0.487-0.901			0.583	0.413-0.823	
Age								
	Age<70 years	1		0.488		1		0.692
	Age $\geq$ 70 years	0.912	0.702-1.184			0.941	0.694-1.274	
Gender								
	Female	1		0.145		1		0.702
	Male	0.814	0.617-1.073			1.068	0.764-1.493	
Synchronous metastatic disease								
	No	1		0.435		1		0.313
	Yes	1.122	0.841-1.497			1.199	0.843-1.706	
Grade								
	Grade 1-2	1		0.491		1		0.522
	Grade 3-4	1.097	0.844-1.425			0.903	0.660-1.235	
Line								
	Second	1		0.600		1		0.206
	Third and further	1.074	0.822-1.403			1.220	0.896-1.662	
IMDC group								
	Good/intermediate	1		0.002		1		<0.001
	Poor	1.870	1.269-2.754			2.470	1.607-3.795	
Bone metastases								
	No	1		0.025		1		0.338
	Yes	1.444	1.046-1.992			1.1980	0.828-1.734	

Parameter	Category	PFS				OS		
		Hazard Ratio	95% CI	p-value		Hazard Ratio	95% CI	p-value
Prior nephrectomy								
	No	1		0.190		1		0.023
	Yes	0.771	0.522-1.138			0.609	0.397-0.935	
Histology								
	Clear cell	1		0.640		1		0.613
	Other	0.875	0.500-1.531			1.169	0.639-2.140	
ECOG PS								
	0	1		<0.001		1		<0.001
	1	1.781	1.343-2.362			2.347	1.678-3.283	
AEC one month after nivolumab initiation								
	<70 cells/ μ L	1		<0.001		1		<0.001
	$\geq$ 70 cells/ μ L	0.544	0.382-0.776			0.331	0.227-0.485	
Age								
	Age<70 years	1		0.593		1		0.893
	Age $\geq$ 70 years	0.931	0.716-1.211			0.979	0.722-1.328	
Sex								
	Female	1		0.138		1		0.688
	Male	0.809	0.611-1.071			1.072	0.763-1.506	
Synchronous metastatic disease								
	No	1		0.455		1		0.222
	Yes	1.117	0.836-1.492			1.248	0.875-1.781	
Grade								
	Grade 1-2	1		0.485		1		0.791
	Grade 3-4	1.099	0.843-1.434			0.958	0.696-1.319	
Line								
	Second	1		0.514		1		0.249
	Third and further	1.093	0.837-1.429			1.198	0.881-1.628	

Parameter	Category	PFS				OS		
		Hazard Ratio	95% CI	p-value		Hazard Ratio	95% CI	p-value
IMDC group								
	Good/intermediate	1		<0.001		1		<0.001
	Poor	2.065	1.401-3.043			3.076	2.003-4.725	
Bone metastases								
	No	1		0.022		1		0.293
	Yes	1.452	1.055-1.997			1.213	0.847-1.738	
Prior nephrectomy								
	No	1		0.183		1		0.035
	Yes	0.766	0.518-1.133			0.630	0.411-0.967	
Histology								
	Clear cell	1		0.660		1		0.603
	Other	0.882	0.503-1.546			1.174	0.641-2.151	
ECOG PS								
	0	1		<0.001		1		<0.001
	1	1.677	1.267-2.219			2.044	1.475-2.831	
ΔAEC								
	≥-30%	1		0.136		1		<0.001
	<-30%	1.309	0.918-1.866			2.132	1.447-3.145	
Age								
	Age<70 years	1		0.139		1		0.222
	Age≥70 years	0.823	0.636-1.065			0.830	0.615-1.120	
Sex								
	Female	1		0.156		1		0.535
	Male	0.820	0.623-1.079			1.110	0.799-1.541	
Synchronous metastatic disease								
	No	1		0.616		1		0.392
	Yes	1.075	0.811-1.426			1.162	0.824-1.638	

Parameter	Category	PFS				OS		
		Hazard Ratio	95% CI	p-value		Hazard Ratio	95% CI	p-value
Grade								
	Grade 1-2	1		0.732		1		0.278
	Grade 3-4	1.046	0.811-1.349			0.846	0.626-1.144	
Line								
	Second	1		0.706		1		0.288
	Third and further	1.052	0.808-1.371			1.180	0.870-1.600	
IMDC group								
	Good/intermediate	1		<0.001		1		<0.001
	Poor	1.923	1.323-2.794			2.602	1.715-3.948	
Bone metastases								
	No	1		0.058		1		0.305
	Yes	1.361	0.990-1.871			1.206	0.843-1.725	
Prior nephrectomy								
	No	1		0.135		1		0.012
	Yes	0.755	0.522-1.092			0.595	0.397-0.893	
Histology								
	Clear cell	1		0.893		1		0.286
	Other	0.965	0.575-1.621			1.354	0.776-2.364	
ECOG PS								
	0	1		<0.001		1		<0.001
	1	1.930	1.470-2.534			2.172	1.585-2.977	
NER at baseline								
	≥65	1		0.058		1		0.014
	<65	0.750	0.558-1.009			0.664	0.478-0.922	
Age								
	Age<70 years	1		0.518		1		0.679
	Age≥70 years	0.917	0.705-1.193			0.938	0.692-1.271	
Sex								
	Female	1		0.212		1		0.538
	Male	0.837	0.633-1.107			1.112	0.793-1.558	

Parameter	Category	PFS				OS		
		Hazard Ratio	95% CI	p-value		Hazard Ratio	95% CI	p-value
Synchronous metastatic disease								
	No	1		0.579		1		0.339
	Yes	1.,086	0.811-1.454			1.191	0.832-1.705	
Grade								
	Grade 1-2	1		0.669		1		0.295
	Grade 3-4	1.059	0.814-1.378			0.844	0.615-1.159	
Line								
	Second	1		0.611		1		0.235
	Third and further	1.072	0.820-1.402			1.207	0.885-1.646	
IMDC group								
	Good/intermediate	1		0.002		1		<0.001
	Poor	1.860	1.264-2.739			2.505	1.638-3.829	
Bone metastases								
	No	1		0.021		1		0.257
	Yes	1.464	1.060-2.021			1.237	0.857-1.785	
Prior nephrectomy								
	No	1		0.156		1		0.016
	Yes	0.754	0.511-1.113			0.591	0.386-0.906	
Histology								
	Clear cell	1		0.291		1		0.691
	Other	0.736	0.418-1.299			0.885	0.485-1.615	
ECOG PS								
	0	1		<0.001		1		<0.001
	1	1.718	1.297-2.275			2.243	1.610-3.124	
NER one month after nivolumab initiation								
	≥65	1		<0.001		1		<0.001
	<65	0.552	0.402-0.757			0.326	0.230-0.463	

Parameter	Category	PFS				OS		
		Hazard Ratio	95% CI	p-value		Hazard Ratio	95% CI	p-value
Age								
	Age<70 years	1		0.514		1		0.623
	Age≥70 years	0.916	0.703-1.193			0.926	0.682-1.257	
Sex								
	Female	1		0.183		1		0.408
	Male	0.826	0.624-1.094			1.155	0.821-1.625	
Synchronous metastatic disease								
	No	1		0.539		1		0.265
	Yes	1.095	0.820-1.464			1.223	0.859-1.741	
Grade								
	Grade 1-2	1		0.561		1		0.345
	Grade 3-4	1.081	0.831-1.408			0.859	0.627-1.177	
Line								
	Second	1		0.582		1		0.269
	Third and further	1.078	0.825-1.409			1.188	0.875-1.614	
IMDC group								
	Good/intermediate	1		0.001		1		<0.001
	Poor	1.950	1.325-2.870			3.010	1.975-4.588	
Bone metastases								
	No	1		0.012		1		0.124
	Yes	1.511	1.094-2.087			1.330	0.925-1.911	
Prior nephrectomy								
	No	1		0.250		1		0.065
	Yes	0.794	0.537-1.176			0.667	0.434-1.025	
Histology								
	Clear cell	1		0.702		1		0.671
	Other	0.898	0.516-1.562			1.137	0.629-2.055	

Parameter	Category	PFS				OS		
		Hazard Ratio	95% CI	p-value		Hazard Ratio	95% CI	p-value
ECOG PS								
	0	1		<0.001		1		<0.001
	1	1.748	1.316-2.321			2.258	1.613-3.161	
ΔNER								
	<125%	1		<0.001		1		<0.001
	≥125%	1.950	1.319-2.882			2.680	1.735-4.140	
PFS – progression-free survival; OS – overall survival; HR – hazard ratio; CI – confidential interval; AEC - absolute eosinophil count; NER - neutrophil-to-eosinophil ratio								

Table 3S. Baseline characteristics across subgroups defined by absolute eosinophil count (AEC) and neutrophil-to-eosinophil ratio (NER) at baseline, one month after nivolumab initiation, and their dynamic changes.

Characteristic (n=458)	AEC at baseline			AEC at one month			ΔAEC			NER at baseline			NER at one month			ΔNER		
	n (%)		p	n (%)		p	n (%)		p	n (%)		p	n (%)		p	n (%)		p
	<70 cells/μL	≥70 cells/μL		<70 cells/μL	≥70 cells/μL		<-30%	≥-30%		<65	≥65		<65	≥65		<125%	≥125%	
Sex																		
Male	58 (63.7%)	279 (76.6%)	0.0158	46 (70.8%)	270 (74.2%)	0.5451	43 (72.9%)	273 (74.4%)	0.8727	273 (77.1%)	64 (63.4%)	0.0069	261 (75.7%)	53 (64.6%)	0.0510	286 (75.1%)	28 (65.1%)	0.1976
Female	33 (36.3%)	85 (23.4%)		19 (29.2%)	94 (25.8%)		16 (27.1%)	94 (25.6%)		81 (22.9%)	37 (36.6%)		84 (24.3%)	29 (35.4%)		95 (24.9%)	15 (34.9%)	
Age at nivol. initiation																		
Median (range, years)	66.6 (41.1–87.5)	67.5 (30.4–87.9)	0.8557	67.6 (41.4–84.1)	67.4 (30.4–87.9)	0.7918	66.6 (36.8–86.5)	67.6 (30.4–87.9)	0.8224	67.4 (30.4–87.9)	66.8 (36.5–87.5)	0.7837	67.5 (30.4–87.9)	67.5 (36.5–84.1)	0.8251	67.6 (30.4–87.9)	66.5 (44.5–83.6)	0.3960
ECOG PS																		
0	29 (33.3%)	104 (30.8%)	0.0019	16 (26.7%)	109 (32.1%)	<0.0001	18 (31.6%)	106 (31.2%)	0.0095	106 (32.2%)	27 (28.1%)	0.0005	109 (33.9%)	16 (21.1%)	<0.0001	111 (31.3%)	13 (32.5%)	=0.0004
1	45 (51.7%)	218 (64.5%)		30 (50.0%)	220 (64.7%)		30 (52.6%)	218 (64.1%)		209 (63.5%)	54 (56.3%)		203 (63.0%)	45 (59.2%)		228 (64.2%)	18 (45.0%)	
2	13 (14.9%)	16 (4.7%)		14 (23.3%)	11 (3.2%)		9 (15.8%)	16 (4.7%)		14 (4.3%)	15 (15.6%)		10 (3.1%)	15 (19.7%)		16 (4.5%)	9 (22.5%)	
Unknown	4	26		5	24		2	27		25	5		23	6		26	3	
Histology																		
Clear cell carcinoma	85 (94.4%)	338 (92.9%)	0.8154	62 (95.4%)	338 (93.1%)	0.7843	57 (96.6%)	340 (92.9%)	0.4013	331 (93.5%)	92 (92.0%)	0.6532	324 (94.2%)	74 (90.2%)	0.2145	355 (93.4%)	40 (93.0%)	1.0000
Other	5 (5.6%)	26 (7.1%)		3 (4.6%)	25 (6.9%)		2 (3.4%)	26 (7.1%)		23 (6.5%)	8 (8.0%)		20 (5.8%)	8 (9.8%)		25 (6.6%)	3 (7.0%)	
Unknown	1	0		0	1		0	1		0	1		1	0		1	0	
Primary tumor grade																		
G1-2	31 (39.2%)	139 (46.2%)	0.3097	24 (47.1%)	139 (45.0%)	0.8795	24 (50.0%)	136 (44.0%)	0.4408	137 (46.8%)	33 (37.9%)	0.1767	136 (46.7%)	26 (38.8%)	0.2768	144 (45.3%)	15 (40.5%)	0.6055
G3-4	48 (60.8%)	162 (53.8%)		27 (52.9%)	170 (55.0%)		24 (50.0%)	173 (56.0%)		156 (53.2%)	54 (62.1%)		155 (53.3%)	41 (61.2%)		174 (54.7%)	22 (59.5%)	
Unknown	12	63		14	55		11	58		61	14		54	15		63	6	
IMDC risk group																		
Favorable-risk group	18 (21.2%)	104 (30.9%)	0.0061	10 (16.7%)	104 (31.0%)	<0.0001	10 (17.9%)	102 (30.3%)	0.0856	105 (32.2%)	17 (17.8%)	<0.0001	100 (31.7%)	14 (17.7%)	<0.0001	107 (30.6%)	5 (12.2%)	0.0048
Intermediate-risk group	47 (55.3%)	196 (58.2%)		31 (51.7%)	199 (59.2%)		35 (62.5%)	194 (57.6%)		191 (58.6%)	52 (54.2%)		187 (59.4%)	41 (51.9)		202 (57.7%)	25 (61.0%)	
Poor	20 (23.5%)	37 (11.0%)		19 (31.7%)	33 (9.8%)		11 (19.6%)	41 (12.2%)		30 (9.2%)	27 (28.1%)		28 (8.9%)	24 (30.4%)		41 (11.7%)	11 (26.8%)	
Unknown	6	27		5	28		3	30		28	5		30	3		31	2	
Synchronous metastases																		
Yes	38 (44.7%)	134 (39.2%)	0.3877	31 (50.8%)	125 (36.8%)	0.0457	29 (50.9%)	127 (37.2%)	0.0573	131 (39.6%)	41 (42.7%)	0.6367	114 (35.6%)	41 (51.9%)	0.0098	133 (37.5%)	22 (53.7%)	0.0619
No	47 (55.3%)	208 (60.8%)		30 (49.2%)	215 (63.2%)		28 (49.1%)	214 (62.8%)		200 (60.4%)	55 (57.3%)		206 (64.4%)	38 (48.1%)		222 (62.5%)	19 (46.3%)	
Unknown	6	22		4	24		2	26		23	5		25	3		26	2	
Line of systemic therapy																		
Second	67 (73.6%)	217 (59.6%)	0.0153	41 (63.1%)	227 (62.4%)	1.0000	33 (55.9%)	232 (63.2%)	0.3123	213 (60.2%)	71 (70.3%)	0.0803	211 (61.2%)	55 (67.1%)	0.3753	235 (61.7%)	28 (65.1%)	0.7415
Third or higher	24 (26.4%)	147 (40.4%)		24 (36.9%)	137 (37.6%)		26 (44.1%)	135 (36.8%)		141 (39.8%)	30 (29.7%)		134 (38.8%)	27 (32.9%)		146 (38.3%)	15 (34.9%)	
Previous nephrectomy																		
Yes	67 (73.6%)	306 (84.1%)	0.0318	48 (73.8%)	308 (84.6%)	0.0471	43 (72.9%)	310 (84.5%)	0.0392	297 (83.9%)	76 (75.2%)	0.0560	294 (85.2%)	60 (73.2%)	0.0137	322 (84.5%)	29 (67.4%)	0.0093
No	24 (26.4%)	58 (15.9%)		17 (26.2%)	56 (15.4%)		16 (27.1%)	57 (15.5%)		57 (16.1%)	25 (24.8%)		51 (14.8%)	22 (26.8%)		59 (15.5%)	14 (32.6%)	
Bone metastases																		
Yes	24 (26.4%)	63 (17.3%)	0.0537	18 (27.7%)	64 (17.6%)	0.0612	15 (25.4%)	67 (18.3%)	0.2132	61 (17.2%)	26 (25.7%)	0.0625	60 (17.4%)	22 (26.8%)	0.0610	70 (18.4%)	12 (27.9%)	0.1531
No	67 (73.6%)	301 (82.7%)		47 (72.3%)	300 (82.4%)		44 (74.6%)	300 (81.7%)		293 (82.8%)	75 (74.3%)		285 (82.6%)	60 (73.2%)		311 (81.6%)	31 (72.1%)	
ECOG PS - Eastern Cooperative Oncology Group performance status; IMDC - International Metastatic RCC Database Consortium; AEC - absolute eosinophil count; NER - neutrophil-to-eosinophil ratio; * percentage within group (column), not including unknown cases.																		