Supplementary Materials: Circulating Levels of the Interferon-γ-Regulated Chemokines CXCL10/CXCL11, IL-6 and HGF Predict Outcome in Metastatic Renal Cell Carcinoma Patients Treated with Antiangiogenic Therapy

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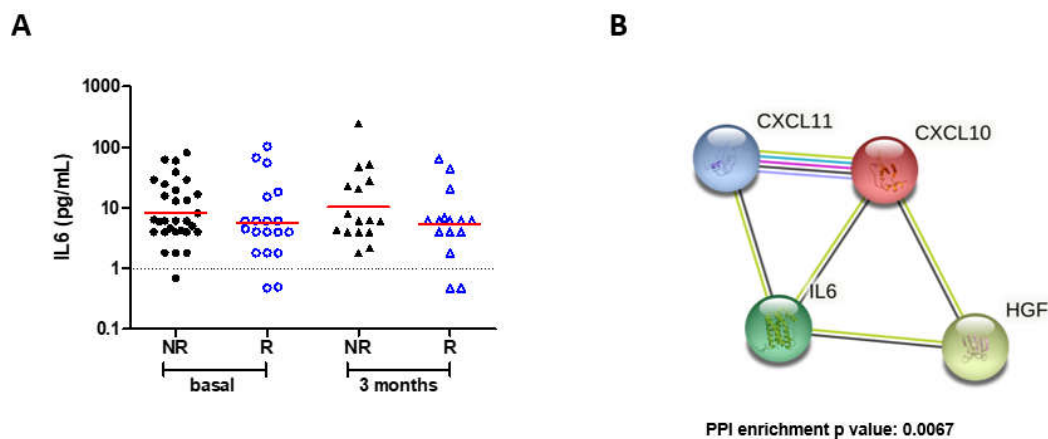

Figure S1. Blood levels of IL-6 in responder and non-responder patients (**A**). STRING network analysis reveals significant interactions between HGF, IL-6, CXCL10 and CXCL11 (PPI enrichment p value: 0.0067) (**B**).

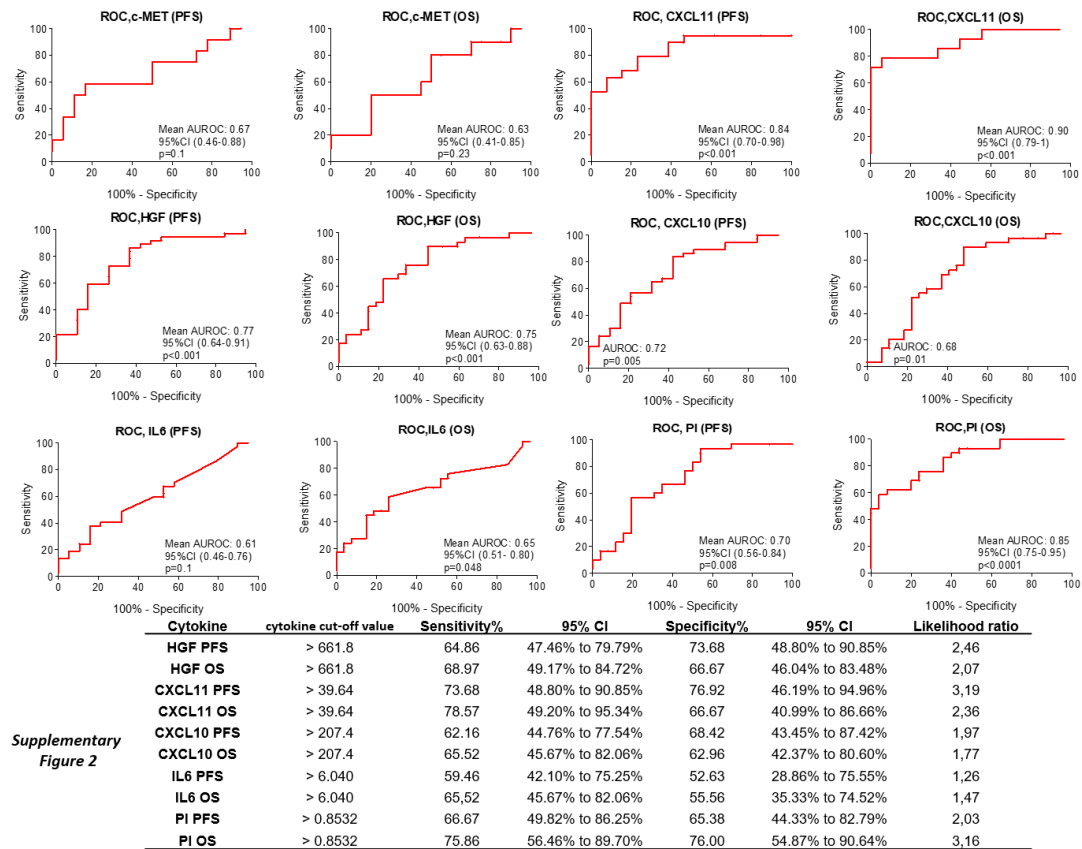| Cytokine	cytokine cut-off value	Sensitivity%	95% CI	Specificity%	95% CI	Likelihood ratio
HGF PFS	> 661.8	64.86	47.46% to 79.79%	73.68	48.80% to 90.85%	2,46
HGF OS	> 661.8	68.97	49.17% to 84.72%	66.67	46.04% to 83.48%	2,07
CXCL11 PFS	> 39.64	73.68	48.80% to 90.85%	76.92	46.19% to 94.96%	3,19
CXCL11 OS	> 39.64	78.57	49.20% to 95.34%	66.67	40.99% to 86.66%	2,36
CXCL10 PFS	> 207.4	62.16	44.76% to 77.54%	68.42	43.45% to 87.42%	1,97
CXCL10 OS	> 207.4	65.52	45.67% to 82.06%	62.96	42.37% to 80.60%	1,77
IL6 PFS	> 6.040	59.46	42.10% to 75.25%	52.63	28.86% to 75.55%	1,26
IL6 OS	> 6.040	65,52	45.67% to 82.06%	55.56	35.33% to 74.52%	1,47
PI PFS	> 0.8532	66.67	49.82% to 86.25%	65.38	44.33% to 82.79%	2,03
PI OS	> 0.8532	75.86	56.46% to 89.70%	76.00	54.87% to 90.64%	3,16

Supplementary Figure 2

Figure S2. Performance parameters for prediction of PFS and OS: ROC curves for the individual biomarkers and for the PI. Sensitivity and specificity data at the optimal cut-off value are shown in the Table below the graphics.

Table S1. Toxicities found in the study.

Toxicity						*p*
Presented Toxicity	No	2 (39%)	-	-	2 (3.3)	0.718
	Yes	49 (96.1)	4 (100)	5 (100)	58 (96.7)	

Toxicity (Grade)		Sunitinib n (%)	Pazopanib n (%)	Sunitinib / Pazopanib n (%)	Total	*p*
Asthenia	G1	10 (30.3)	-	1 (50.0)	11 (28.9)	0.281
	G2	17 (51.5)	2 (66.7)	-	19 (50.0)	
	G3	6 (18.2)	1 (33.3)	1 (50.0)	8 (21.1)	
	G4	-	-	-	-	
	✤	33 (64.7)	3 (75.0)	2 (40)	38 (63.3)	0.495
Neutropenia	G1	1 (16.7)	-	-	1 (16.7)	-
	G2	2 (33.3)	-	-	2 (33.3)	
	G3	3 (50.0)	-	-	3 (50.0)	
	G4	-	-	-	-	
	✤	6 (11.8)	-	-	6 (10)	0.356
Hand-foot syndrome	G1	4 (28.6)	-	-	4 (26.7)	0.242
	G2	7 (50.0)	-	-	7 (46.7)	
	G3	3 (21.4)	-	1 (100)	4 (26.7)	
	G4	-	-	-	-	
	✤	14 (27.5)	-	1 (20)	15 (25.0)	0.282
Hypertension	G1	9 (56.3)	1 (50.0)	-	10 (52.6)	0.121
	G2	6 (37.5)	-	-	6 (31.6)	

	G3	1 (6.3)	1 (50.0)	1 (100)	3 (15.8)	
	G4	-	-	-	-	
	✤	17 (33.3)	2 (50.0)	1 (20.0)	20 (33.3)	0.635
Hypothyroidism	G1	2 (50.0)	-	-	2 (50.0)	
	G2	2 50.0)	-	-	2 50.0)	
	G3	-	-	-	-	-
	G4	-	-	-	-	
	✤	5 (9.8)	-	-	5 (8.3)	0.427
Cardiotoxicity	G1	-	-	-	-	
	G2	-	-	-	-	
	G3	1 (100)	-	-	1 (100)	-
	G4	-	-	-	-	
	✤	1 (2.0)	-	-	1 (1.7)	0.849
Mucositis	G1	13 (48.1)	1 (100)	2 (40.0)	16 (48.5)	
	G2	10 (37.0)	-	2 (40.0)	12 (36.4)	
	G3	4 (14.8)	-	1 (20)	5 15.2)	0.805
	G4	-	-	-	-	
	✤	27 (52.9)	1 (25)	5 (100)	33 (55.0)	0.023
Diarrhea	G1	9 (52.9)	3 (100)	1 (50.0)	13 (59.1)	
	G2	6 (35.3)	-	1 (50.0)	7 (31.8)	
	G3	2 (11.8)	-	-	2 (9.1)	0.403
	G4	-	-	-	-	
	✤	18 (35.3)	3 (75.0)	2 (40.0)	23 (38.3)	*0.297*
Leukopenia	G1	4 (57.1)	-	-	4 (57.1)	
	G2	2 (28.6)	-	-	2 (28.6)	
	G3	1 (14.3)	-	-	1 (14.3)	-
	G4	-	-	-	-	
	✤	7 (13.7)	-	-	7 (11.7)	0.297
Anemia	G1	6 (42.9)	-	-	6 (42.9)	
	G2	6 (42.9)	-	-	6 (42.9)	
	G3	1 (7.1)	-	-	1 (7.1)	-
	G4	1 (7.1)	-	-	1 (7.1)	
	✤	14 (27.5)	-	-	14 (23.3)	0.073
Thrombocytopenia	G1	7 (50.0)	-	-	7 (41.2)	
	G2	3 (21.4)	-	1 (50.0)	4 (23.5)	
	G3	4 (28.6)	1 (100)	1 (50.0)	6 (35.3)	0.314
	G4	-	-	-	-	
	✤	15 (29.4)	1 (25)	2 (40.0)	18 (30.0)	0.864

Table S2. Chi^2 correlation results evaluating the Prognostic Index (PI) (low vs. high) and the clinicopathological variables.

Clinicopathological variables	PI Low n(%)	PI High n(%)	*p*
Gender			
Male	21 (77.8)	20 (71.4)	0.589
Female	6 (22.2%)	8 (28.6)	
Age at diagnosis (primary tumor)			
<65	12 (42.9)	15 (55.6)	0.346
≥65	16 (57.1)	12 (44.4)	
Age at metastasis			
<65	12 (42.9)	15 (55.6)	0.346
≥65	16 (57.1)	12 (44.4)	
Time between diagnosis and metastasis			

Metastasis at diagnosis	11 (39.3)	9 (33.3)	
≤1 years	6 (21.4)	9 (33.3)	0.655
≤5 years	8 (28.6)	5 (18.5)	
>5 years	3 (10.7)	4 (14.8)	
Metastatic disease at study enrollment			
Number of metastatic sites			
1	9 (32.1)	11 (42.3)	
2	17 (60.7)	9 (34.6)	0.086
3	0 (0.0)	4 (15.4)	
4	2 (7.1)	2 (7.7)	
Risk factor (MSKCC*)			
Good	7 (25.9)	2 (7.4)	
Intermediate	18 (66.7)	19 (67.9)	0.062
Bad	2 (7.4)	7(25.0)	
Therapy			
Sunitinib	24 (85.7)	25 (89.3)	
Pazopanib	1 (3.6%)	2 (7.1)	0.508
Sunitib + Pazopanib	3 (10.7)	1 (3.6)	

*MSKCC = Memorial Sloan Kettering Cancer Centre.

Table S3. Harrell's Concordance (C) coefficient for each individual biomarker and for the PI index.

Cytokine/ chemokine	PFS Harrell's C	95% CI	*p*	OS Harrell's C	95% CI	*p*
HGF	0.68	(0.60-0.75)	<0.0001	0.65	(0.55–0.74)	<0.0001
IL–6	0.60	(0.49–0.69)	<0.0001	0.61	(0.51–0.72)	<0.0001
CXCL10	0.58	(0.48–0.69)	<0.0001	0.58	(0.47–0.68)	<0.0001
CXCL11	0.68	(0.60–0.76)	<0.0001	0.67	(0.57–0.76)	<0.0001
PI	0.70	(0.63–0.78)	<0.0001	0.69	(0.61–0.77)	<0.0001
Comparison	**Coefficient**	**95% CI**	*p*	**Coefficient**	**95% CI**	*p*
PI vs. HGF	0.026	(−0.06–0.11)	0.54	0.043	(−0.04–0.13)	0.337
PI vs. IL–6	0.108	(0.004–0.21)	0.041	0.074	(−0.02–0.17)	0.128
PI vs. CXCL10	0.117	(0.02–0.21)	0.015	0.110	(0.006–0.21)	0.037
PI vs CXCL11	0.021	(−0.04–0.08)	0.52	0.023	(−0.04–0.95)	0.52