Supplementary Materials

Abbreviations:

Symbols: Green Cell= positive association, Red Cell= negative association, Normal Cell= no significant difference, † = total sample size of patients with measured biomarker ‡ = total sample size of study (n of direct comparison not available).

Treatments: A=avelumab, At=atezolumab, Ax=axitinib, B=bevacizumab, E=Everolimus, ICI= immune checkpoint inhibitor, INFa= interferon alpha,Ip=ipilimumab, N=nivolumab, P=Pazopanib, Pm=Pembrolizumab, S=sunitinib.

Histology: RCC = renal cell carcinoma, ccRCC = clear cell RCC, NccRCC = Non-small-cell RCC.

Outcome: CI = 95% Confidence interval, CSS = Cancer Specific Survival, DFS=Disease Free Survival, HR=Hazard Ratio, n = sample size of biomarker available for comparison, NSD=No Significant Difference, ORR = Overall Response Rate, OS = Overall Survival, PFS=Progression Free Survival, RR=Relative Risk.

Serum Markers: ALP= alkaline phosphatase, ANC= absolute neutrophil count, Ca= calcium, COP-NLR= combined platelet count and neutrophil to lymphocyte ratio, CRP= C-reactive protein, BAP= ubiquitin carboxyl-terminal hydrolase, CRP= c-reactive protein, ESR= erythrocyte sedimentation rate, Hg= hemoglobin, LDH= lactate dehydrogenase, NLR= neutrophil to lymphocyte ratio, PLR= platelet to lymphocyte ratio, s-TATI= serum tumor-associated trypsin inhibitor, TIMP= Tissue inhibitor matrix metalloproteinase. VEGF= serum Vascular Endothelial Growth Factor, WBC= white blood cell.

Genetic Markers: LOF= loss of function, GOF= gain of function, CAIX= carbonic anhydrase IX, CDKN= cyclin dependent kinase inhibitor, *CIMP*= CpG island methylator phenotype, CTLA= cytotoxic T-lymphocyte-associated protein, EEF1D= elongation factor 1-delta, EZR= ezrin, FH= fumarate hydratase, *hERV*= human endogenous retrovirus, HPCAL= hippocalcin-like protein, HSP= heat shock protein, *MET*= mesenchymal to epithelial transition, *mTOR*= mechanistic target of rapamycin, NDUFS1= NADH:ubiquinone oxidoreductase core subunit S1, *NQO1*= NADPH quinone dehydrogenase 1, *PBRM-1*= polybromo-1, PDL1= programmed death-ligand=1, PTEN= Phosphatase and tensin homolog, SLC= solute carrier, *TERT*= telomerase reverse transcriptase, TMB= tumor mutational burden, TSC= tuberous sclerosis.

Table S1: Serum Prognostic Biomarkers

Biomarker	Cohort Therapy or Histology	PFS/DFS	OS (CSS)	n
ALP (high vs low)[49,14]	Untreated		HR 1.52, $p=0.014$	416
			RR 1.46, $p<0.0001$	2217
Ca (high vs low) [9,10,49,11,14]	INFa		RR 1.93, $p<0.0001$	463
	Untreated		Shorter, $p<0.001$	308
			HR 2.01, $p<0.001$	416
			RR 3.05, $p<0.0001$	601
			RR 0.94, $p=0.16$	2564
Ca (low vs high)[50]	N +Ip		HR 0.63, CI 0.46-0.86	550
COP-NLR (high vs low)[16]	P or S		HR 1.78, $p=0.008$	276‡
CRP (high vs low)[17]	S	HR 2.48, $p<0.05$	HR 3.17, $p<0.05$	200
Hg (high vs low)[50]	S		HR 0.56, CI 0.43-0.74	546
Hg (low vs high)[13,9,10,49,11,14]	Cytokine		RR 1.4, $p<0.001$	782
	INFa		RR 1.53, $p<0.0001$	463
	Untreated		HR 1.66, $p=0.005$	416
			Shorter, $p<0.001$	308
			RR 2.33, $p<0.0001$	612
			RR 1.56, $p<0.0001$	3547
LDH (high vs low) [9,11,14]	INFa		RR 3.23, $p<0.0001$	463
			RR 1.67, $p=0.001$	544
			RR 1.2, $p<0.0001$	2360
LDH (low vs high)[50]	N +Ip		HR 0.50, CI 0.30-0.82	550
	S		HR 0.25, CI 0.15-0.41	546
Neutrophil count (high vs low) [49,11]	Untreated	HR 2.04, $p<0.001$	HR 2.61, $p<0.001$	416
			RR 4.58, $p<0.0001$	583
Neutrophils (low vs high)[13]	Cytokine		RR 1.403, $p=0.004$	782
NLR (high vs low) [51,16,51]	ICI	HR 2.20, CI 1.61–3.01	HR 3.92, CI 2.00–7.69	6461‡
	P or S		HR 1.70, $p<0.001$	276‡
		HR 2.09, $p<0.001$	HR 1.90, $p<0.001$ (CSS HR 2.31, $p<0.001$)	5768
NLR (low vs high)[50]	N +Ip		HR 0.61, CI 0.42-0.81	550
	S		HR 0.55, CI 0.42-0.72	546

Platelets (high vs low)[11]			RR 2.56, p<0.0001	607
PLR (high vs low) [52,16]	P or S		HR 1.57, p=0.002	276‡
	ccRCC		HR 1.35, p<0.001 (CSS HR 1.32, p<0.001)	1505
Ras p21 (high vs low)[15]		HR 1.0, CI 1.0-1.0	HR 1.0, CI 1.0-1.0	125
s-TATI (high vs low)[18]			HR 1.01, p=0.03 (CSS HR 1.01, p=0.004)	132
sVEGFR-2 (high vs low)[15]		NSD	NSD	713
TIMP-1 mRNA (high vs low)[15,21]		HR 1.0, CI 1.0-1.0	HR 1.0, CI 1.0-1.0	123
			Associated, p=0.030	61
VEGF (continuous)[19]	Placebo	Shorter, p=0.0231	Shorter, p=0.0416	452
VEGF (high vs low)[15,19]	Sorafenib		p=0.0145	451
		HR 1.0, CI 1.0-1.0	HR 0.998, CI 1.0-1.0	712
WBC (high vs low)[14]			RR 1.37, p<0.0001	2261

Table S2: Gene Mutation, Gene Expression, and Histologic Prognostic Biomarkers

	Biomarker	Cohort Therapy or Histology	PFS/DFS	OS (CSS)	n
Gene Expression	DUX4 GES (high vs low)[27]	A +Ax	HR 1.55, CI 0.93-2.59		720†
		S	HR 1.12, CI 0.59-2.15		720†
	ERV (high vs low)[34]	N	7 vs 2.6 months, p=0.01		99
	ERV3-2 (high vs low)[35]	ICI	HR 0.15, CI 0.05-0.44		24
	NQO1 expression (high vs low)[23]	Papillary RCC		Shorter, p=0.001	161
	TIS (high vs low)[26,62]	N +Ip or S	NSD		213†
Gene Mutations	*BAP1* (vs WT)[27,22]	A +Ax or S	NSD		739†
		Anti-VEGF		28.7 vs not reached, p=0.02	105
	CDKN2A (vs WT)[23]	Papillary RCC		Shorter, p<0.0001	161
	CIMP / FH (vs WT)[23]	Papillary RCC		Shorter, p<0.0001	161
	ERV (2282, 3382) (continuous)[24]	N	Associated, p<0.05	Associated, p<0.05	181
	ERV GOF (vs WT)[24]	N	NSD	NSD	181
	mTOR (vs WT)[27]	A +Ax or S	NSD		739†
	PBRM-1 LOF (vs WT)[27,31,24,30,31,26,27,26]	A +Ax	HR 1.14, CI 0.81-1.61		720†
		E	HR 0.83, p=0.32	HR 0.81, p=0.27	193
		N	Associated, p=0.0056	Associated, p<0.001	261
			HR 0.067, p=0.03	HR 0.65, p=0.03	189
			Longer, p=0.029	Longer, p=0.0074	35
		N +Ip	NSD	NSD	481†
		S	HR 0.88, CI 0.65-1.2		720†
			NSD	NSD	481†

	PBRM-1 LOF + pancreatic mets (vs WT)[53]	Anti-Angiogenic	HR 0.34, p=0.007		12
		N	HR 2.15, p=0.034		9
				HR 0.25, p<0.001	31
	TERT (vs WT)[22]	Anti-VEGF		29.6 vs 52.6 months, p=0.03	105
	TMB (high vs low)[27,28,29,44,26,27,25]	A +Ax	HR 1.09, CI 0.79-1.50		739†
		A +Ax or S	NSD		886‡
		At +/- B or S	NSD		201
		ccRCC	Shorter, p<0.05	Shorter, p<0.05	1118
		N or E	NSD	NSD	592‡
		S	HR 0.79, CI 0.60-1.05		739†
			NSD	NSD	481†
				NSD	50
	VHL (vs WT)[27]	A +Ax or S	NSD		739†
Histology	CAIX ≤85% (vs>85%)[36]			(CSS HR 3.10, p<0.001)	321
	CAIX (high vs low)[36]		HR 1.0, CI 1.0-1.0	HR 1.0, CI 1.0-1.0	128
	CAIX >85% (vs≤85%)[20]		NSD	NSD	813
	CAIX score ≥200 (vs≤100)[20]		HR 0.69, p=0.01	HR 0.60, p=0.01 (CSS HR 0.69, p=0.01)	813
	CD8+ density in Tumor Center (higher vs lower)[27]	A +Ax	NSD		804†
		S	HR 0.62, CI 0.47-0.82		804†
	CD8+ density in Tumor Invasive Margin (higher vs lower)[27]	A +Ax	NSD		804†
		S	HR 0.69, CI 0.46-1.03		804†
	Type 1 macrophage infiltration (high vs low)[37]	Anti-Angiogenic TKIs	HR 1.22, CI 0.95–1.56	HR 1.54, CI 1.17–2.03	409
	Type 2 macrophage infiltration (high vs low)[37]	Anti-Angiogenic TKIs	HR 1.40, CI 1.09–1.78	HR 1.38, CI 1.06–1.81	409

Table S3: Gene Mutation, Gene Expression, and Serum Predictive Biomarkers

	Biomarker	Cohort Therapy or Histology	TTF	ORR	n
Gene Mutation	*BAP1* (vs WT) [22]	Anti-VEGF	6.4 vs 11.0 months, p=0.01		105
	MET GOF (vs WT) [38]	Papillary RCC, on foretinib		50% vs 9%, no p	67
	mTOR (vs WT) [41]	*mTOR* inhib		OR 0.08, CI 0.008-0.79	87
	mTOR, TSC1, TSC2 (vs WT)[39]	*mTOR* inhib		Associated, p=0.06	79
	PBRM-1 LOF (vs WT) [22,30,32,32,31]	Anti-PD-1 +/- Anti-CTLA-4		Increased, p=0.0071	63
		Anti-VEGF	12 vs 6.9 months, p=0.01		105
		At		Decreased, p=0.04	105
		At + B		Decreased, p=0.04	96
		At +/- B		Decreased, p=0.04	128
		E		NSD	193
		N		Increased, no p	442†
				Increased, p=0.012	35
	TMB (high vs low) [44,45,24,25]	ccRCC		NSD	1118
		ICI		NSD	34
		N or E		NSD	592‡
				NSD	50
Gene Expression	*ERV* (high vs low) [34]	N		35.6% vs 12.5%, p=0.036	99
	*ERV*3-2 (high vs low) [35]	ICI		OR 45.0, CI 3.5–584.3	24
	FOXP3, CCR4, KLRK1, ITK, and TIGIT (high vs low) [43]	ICI		31% vs 2%, p=0.001	86
	T-effector expression (high vs low) [43,54]	ICI		23% vs 12%, p=0.256	86
		S	11.9 vs 28.0 months		232
	PTEN (low vs high) [41]	*mTOR* inhib		OR 0.16, CI 0.04-0.62	53
Serum Marker	CRP >5mg/L (vs≤)[17]	S		61% vs 32%	200
	Hg (low vs high) [13]	Cytokine	RR 1.51, p=0.024		782
	Neutrophils ≤7500/ml (vs>)[13]	Cytokine	RR 2.13, p=0.003		782

Table S4: Select Gene Expression Signatures as Predictive and Prognostic Biomarkers

Biomarker	Cohort Therapy or Histology	PFS/DFS	ORR	n
IMmotion 150 Angio (high vs low)[27,28,28,26,28,27,26,46]	A +Ax	HR 1.00, CI 0.73-1.38		350
	At	HR 0.74, CI 0.42-1.28	24% vs 40%, p=0.20	86
	At +B	HR 0.90, CI 0.54-1.51	21% vs 26%, p=0.80	88
	N +Ip	HR 1.23, CI 0.79–1.92	Decreased, no p	213†
	S	HR 0.31, CI 0.18-0.55	46% vs 9%, p<0.001	75
		HR 0.64, CI 0.48-0.85		370
		HR 0.58, CI 0.37-0.92	Increased, p NR	213†
		HR 0.59, CI 0.47-0.75		823‡
IMmotion 150 Angio (high)[28]	At (vs S)	HR 1.46, CI 0.81-2.60		87
	At +B (vs S)	HR 1.36, CI 0.78-2.36		89
IMmotion 150 Angio (low)[28]	At (vs S)	HR 0.75, CI 0.46-1.25		88
	At +B (vs S)	HR 0.59, CI 0.35-0.98		88
IMmotion 150 Myeloid (high vs low)[27,28,28,27,28]	A +Ax	HR 1.15, CI 0.83-1.59		350
	At	HR 2.98, CI 1.68–5.29		263†
	At +B	HR 1.71, CI 1.01–2.88		263†
	S	HR 1.18, CI 0.89-1.57		370
		NSD		263†
IMmotion 150 Myeloid (high)[28]	At (vs S)	HR 2.03, CI 1.21–3.40		263†
	At +B (vs S)	NSD		263†
IMmotion 150 Teff (high vs low)[27,28,28,28,27]	A +Ax	HR 0.79, CI 0.58-1.08		350
	At	HR 0.83, CI 0.48-1.45	31% vs 15%, p=0.15	86
	At +B	HR 0.50, CI 0.30-0.86	49% vs 16%, p=0.002	88
	S	HR 1.31, CI 0.77-2.23	25% vs 28%, p=0.96	89
		HR 1.12, CI 0.85-1.48		370
IMmotion 150 Teff (high)[28,46]	At (vs S)	HR 0.85, CI 0.50-1.43		89
	At +B (vs S)	HR 0.55, CI 0.32-0.95		86
		HR 0.76, CI 0.59-0.99		823‡
IMmotion 150 Teff or Myeloid (high vs low)[26]	N +Ip or S	NSD		213†
IMmotion 150 Teff/Myeloid (high/high)[28]	At +B (vs At)	HR 0.25, CI 0.10-0.60		41
IMmotion 150 Teff/Myeloid high/high (vs high/low)[27,28,27]	A +Ax	HR 1.22, CI 0.89-1.68		332
	At	HR 3.82, CI 1.70–8.60		46
	S	HR 1.20, CI 0.90-1.59		360

JAVELIN Renal 101 Angio (high vs low)[27]	A +Ax	HR 0.98, CI 0.71-1.34		350
	S	HR 0.56, CI 0.42-0.74		370
JAVELIN Renal 101 Immuno (high vs low)[27]	A	Longer, p=0.007		53
	A +Ax	HR 0.36, CI 0.16-0.81		55
		HR 0.60, CI 0.44-0.83		350
	S	HR 0.89, CI 0.67-1.17		370
Beuselinck Angio (high vs low)[37,47]	Anti-Angiogenic TKIs		Improved, p=0.03	409
	S		Improved p=0.017	53
	S		Improved, p<0.05	104

Table S5: PDL1 status as a Predictive and Prognostic Biomarker

Biomarker	Cohort Therapy or Histology	PFS/DFS	OS (CSS)	ORR	n
PDL1 (neg vs pos)[50]	S		HR 0.70, CI 0.52-0.93		546
PDL1 (pos vs neg)[8,26,27,44,45,54–56,63]	A +Ax	HR 0.89, CI 0.65-1.22			804†
	ccRCC	Shorter, p =0.0027	Shorter, p =0.002		537
	ICI			Weak/possible predictive, no p	5
	ICI			NSD	34
	ICI, S, or E	HR 0.75, CI 0.63-0.89	HR 0.72, CI 0.63-0.81		4635
	N +Ip or S	NSD	NSD		980†
	N or E		NSD		756
	P		median 15.1 vs. 35.6, p=0.03		221
	S		median 15.3 vs 27.8 months, p=0.03		232
	S	HR 1.57, CI 1.16-2.14			804†
			RR 2.37, p <0.001 (CSS RR 3.92, p<0.001)		306
PDL1 (neg)[8,56,58,59,64,65]	ICI (vs S or E)	HR 0.95, CI 0.82-1.09	HR 0.73, CI 0.62-0.87		2597
	N (vs E)		HR 0.77, CI 0.60-0.97		575
	N +Ip (vs S)	HR 1.0, CI 0.8-1.25	HR 0.73, CI 0.56-0.96		633
	On At + B (vs S)	HR 0.93, CI 0.75-1.15	HR 0.59, CI 0.34-1.03		553
	Pm +Ax (vs S)	HR 0.87, CI 0.62–1.23	HR 0.59, CI 0.34–1.03	NSD	325
PDL1 (pos)[8,28,29,56–60]	A +Ax (vs S)	HR 0.61, CI 0.47-0.79	HR 0.82, CI 0.53-1.27		560
	A +Ax (vs S)	HR 0.62, CI 0.49-0.78	HR 0.83, CI 0.60-1.15		560
	A +Ax (vs S)	HR 0.63, CI 0.49-0.81			886‡
	At (vs S)	HR 1.03, CI 0.63-1.67		28% vs 27%, no p	114
	At +B (vs S)	HR 0.64, CI 0.38-1.08		46% vs 27%, no p	110

	At +B (vs S)	HR 0.74, CI 0.57-0.96	HR 0.84, CI 0.62-1.15		362
	ICI (vs S or E)	HR 0.65, CI 0.56-0.76	HR 0.68; CI 0.54–0.87		2038
	N (vs E)		HR 0.79, CI 0.53 to 1.17		181
	N +Ip (vs S)	HR 0.46, CI 0.31-0.68	HR 0.45, CI 0.29-0.70		214
	On At + B (vs S)	HR 0.74, CI 0.57-0.96	HR 0.84, CI 0.62-1.15, p>0.05		362
	Pm +Ax (vs S)	HR 0.62 , CI 0.47-0.80	HR 0.54, CI 0.35-0.84	NSD	497
	Sarcomatoid histology, At +B (vs S)	HR 0.45, CI 0.26-0.77	HR 0.61, CI 0.35-1.08		86
PDL1 ≥5%, lymphocytes (vs<)[55,61]			(CSS RR 4.53, p<0.001)		196
PDL1 expression ≥1% (vs<)[48]		HR 3.70, CI 2.07–6.62	HR 1.98, CI 1.22–3.22		1644
PDL1 H-Score >55 and intratumor CD8-positive T-cell counts >300 (vs ≤55 and ≤300)[54]	P		9.6 vs 36.8 months		221
	S		11.9 vs 28.0 months		232