Fig. S1. Study designs. (a) Cohort 1: clear cell renal cell carcinoma (ccRCC) cases undergoing radical surgery, and (b) Cohort 2: metastatic ccRCC cases.

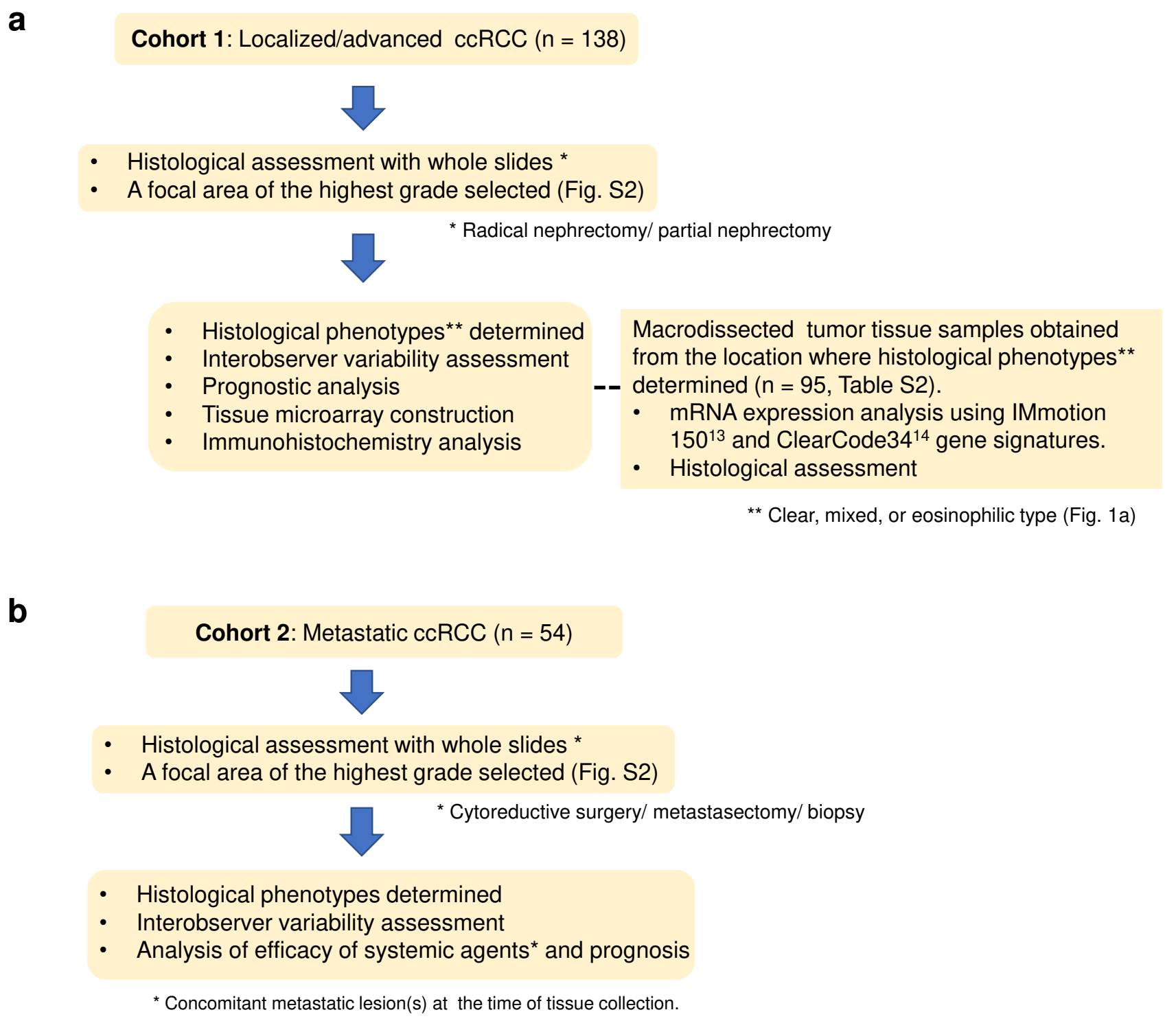


Fig. S2. An example case how to determine the histological phenotype. 1) Confirm several representative areas to find the highest WHO/ISUP (WHO, World Health Organization; ISUP, International Society of Urological Pathology) grade lesion. 2) Determine its histological phenotypes such as clear (pale), mixed, or eosinophilic type. If the highest grades of two or more locations are equivalent, priority is given to types with a large amount of eosinophilic components.

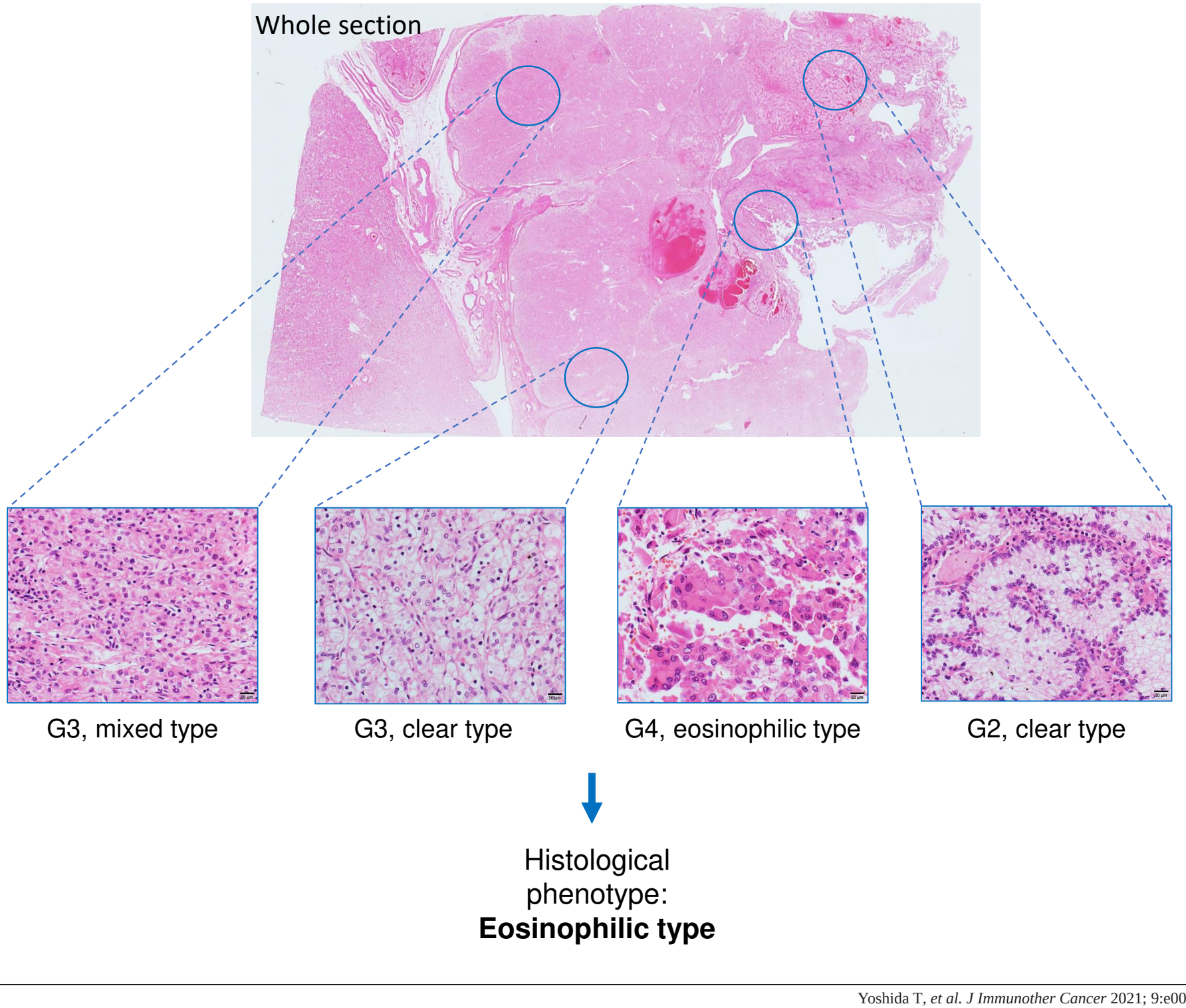


Table S1. Summary of immunohistochemical stains.

Primary Antibodies	Product number	Company information	Dilution	Detection
Anti-CA9 (TH22) (Mouse monoclonal)	NCL-L-CAIX	Leica Biosystems, Newcastle Upon Tyne, UK	1:100	The OptiView DAB IHC Detection Kit (Ventana Medical System, Tucson, USA)
Anti-CD31 (JC70A) (Mouse monoclonal)	PA0414	Leica Biosystems, Newcastle Upon Tyne, UK	Prediluted	The Bond Polymer Refine Detection (Leica Biosystems, Melbourne, Australia)
Anti-FOXM1 (G-5) (Mouse monoclonal)	sc-376471	Santa Cruz Biotechnology, Dallas, Texas, USA	1:250	The Bond Polymer Refine Detection
Anti-Ki-67 (EPR3610) (Rabbit monoclonal)	Ab92742	Abcam, Cambridge, UK	1:1000	The Bond Polymer Refine Detection
Anti-PBRM1 (Rabbit polyclonal)	HPA015629	Atlas Antibodies AB,Bromma, Sweden	1:200	The OptiView DAB IHC Detection Kit
Anti-BAP1 (C-4) (Mouse monoclonal)	sc-28383	Santa Cruz Biotechnology, Dallas, Texas, USA	1:200	The OptiView DAB IHC Detection Kit
Anti-PD-L1(28-8) (Rabbit monoclonal)	Ab205921	Abcam, Cambridge, UK	1:400	The OptiView DAB IHC Detection Kit
Anti-CD8 (4B11) (Mouse monoclonal)	PA0183	Leica Biosystems, Newcastle Upon Tyne, UK	Prediluted	The Bond Polymer Refine Detection

Fig. S3. Association between histological phenotypes and pathological factors in 95 tumor samples for gene expression analysis. Percentage of cases of each phenotype based on pathological factors; Chi-square test was used for statistical analysis.

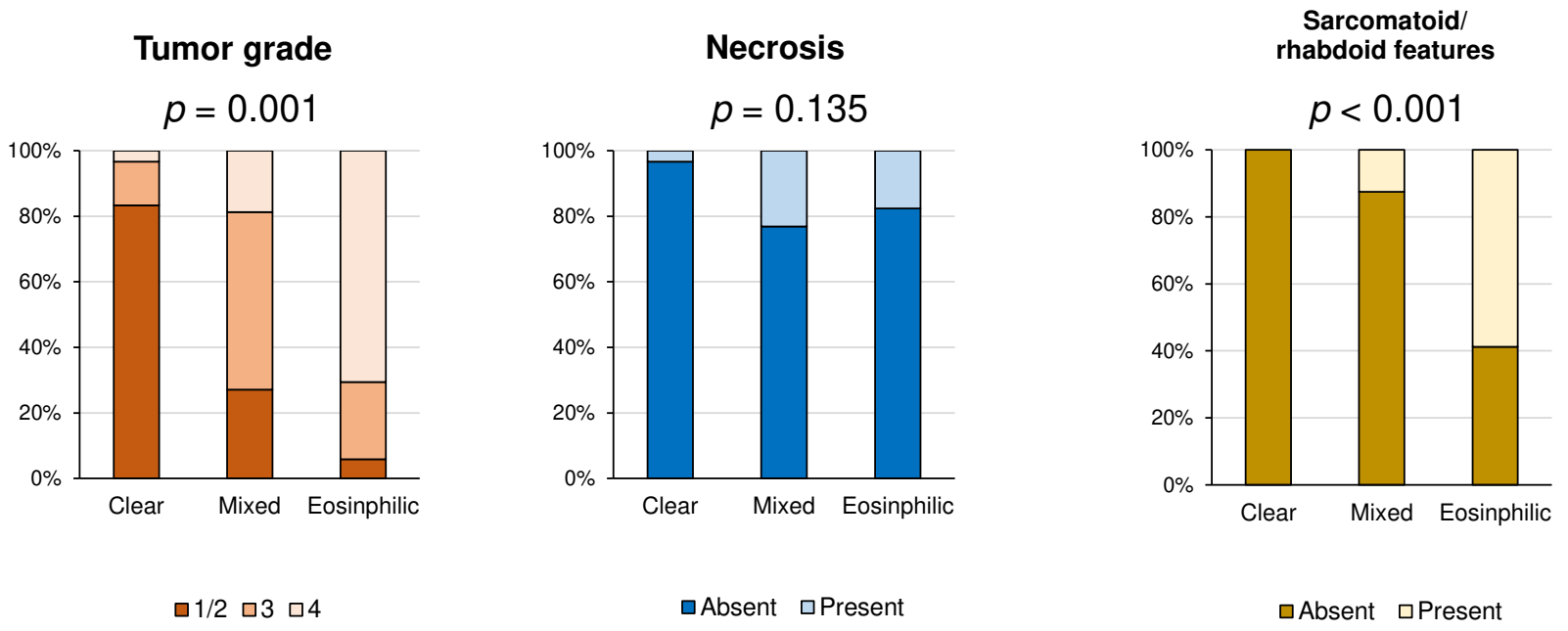


Fig. S4. Hierarchical cluster analysis using the 34-gene set. The color bar on the bottom and second tiers of the heatmap represen ts the clusters for molecular subtyping and histological phenotype, respectively.

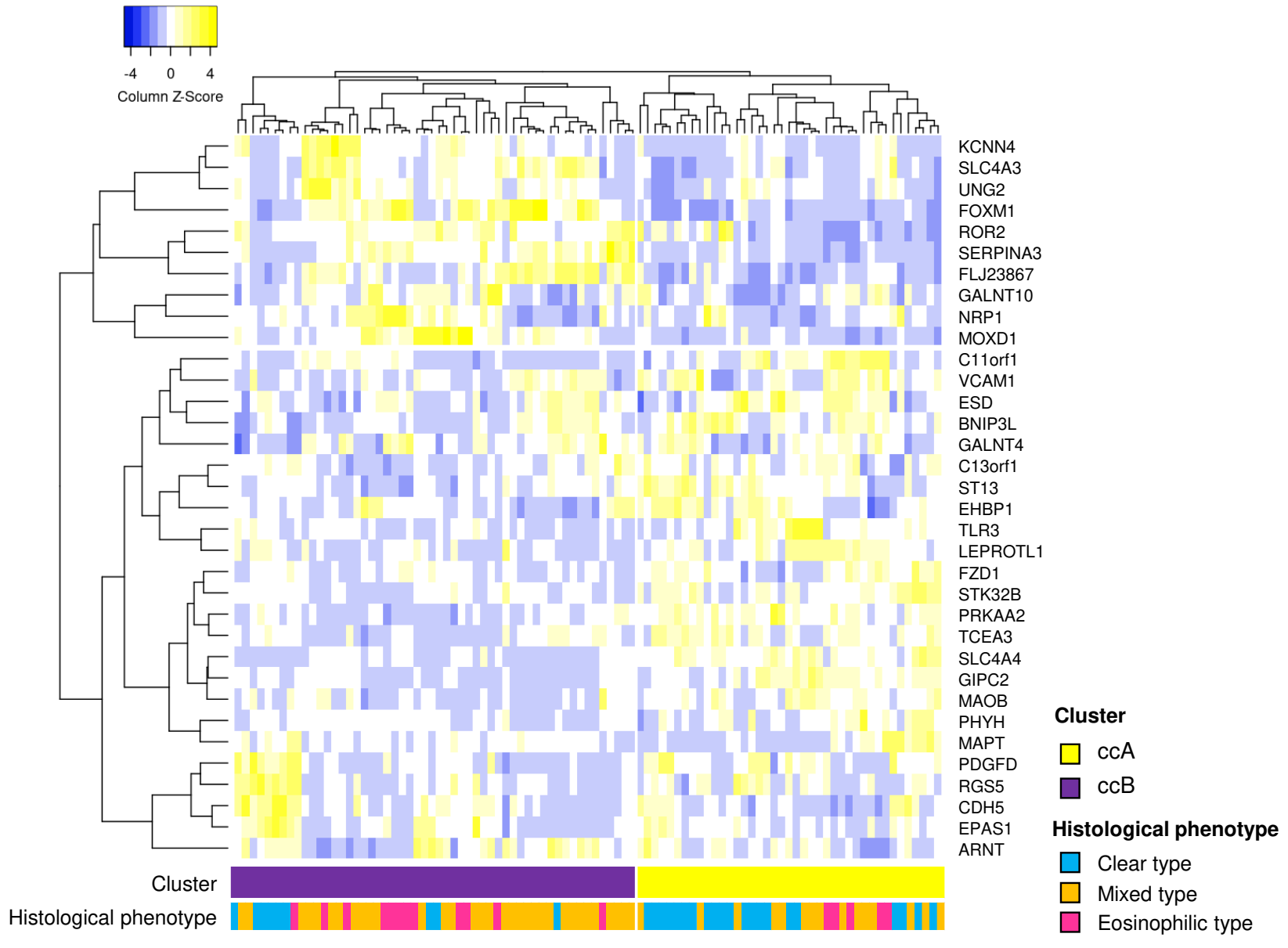


Table S2. Pathological and molecular factors in the 95 ccRCC samples.

Factor	Group	Total	Cluster1	Cluster2	*p* value*
No. of cases		95	42	53	
ClearCode34 molecular subtype, n, (%)	ccA	41 (43.1)	17 (40.5)	24 (45.3)	0.681
	ccB	54 (56.9)	25 (59.5)	29 (54.7)	
Histological phenotype, n, (%)	Clear type	30 (31.6)	20 (47.6)	10 (18.9)	0.001
	Mixed type	48 (50.4)	20 (47.6)	28 (52.8)	
	Eosinophilic type	17 (17.9)	2 (4.8)	15 (28.3)	
Necrosis, n, (%)	Absent	82 (86.3)	36 (85.7)	46 (86.8)	1
	Present	13 (13.7)	6 (14.3)	7 (13.2)	
Sarcomatoid rhabdoid features, n, (%)	Absent	79 (83.2)	40 (95.2)	39 (73.6)	0.005
	Present	16 (16.8)	2 (4.8)	14 (26.4)	
WHO/ISUP grade, n, (%)	1	7 (7.4)	5 (11.9)	2 (3.8)	0.171
	2	32 (33.7)	16 (38.1)	16 (30.2)	
	3	34 (35.8)	15 (35.7)	19 (35.8)	
	4	22 (23.1)	6 (14.3)	16 (30.2)	

ccRCC, clear cell renal cell carcinoma; WHO, World Health Organization; ISUP, International Society of Urological Pathology
* Chi-square test.

Fig. S5. Association between gene signature scores and clusters divided by IMmotion 150 gene panel. Mann–Whitney U test was used for statistical analysis. Angio, Angiogenesis; Teff, T-effector.

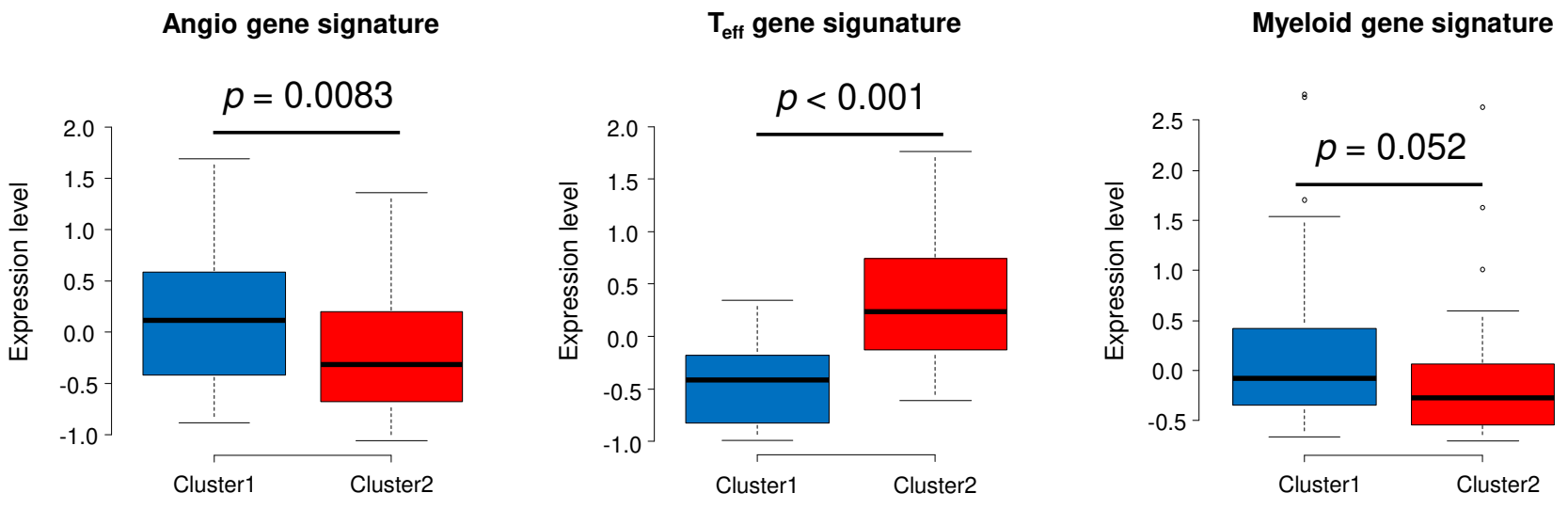
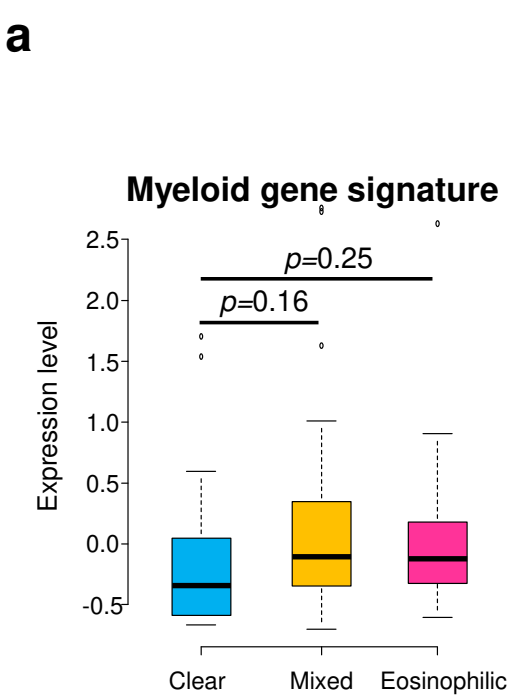


Fig. S6. Association between histological phenotypes and molecular factors. (a) Comparison of myeloid gene signature scores ; Kruskal-Wallis test with Holm's method. (C) Representative immunohistochemical (IHC) stains of PD-L1; TC, tumor cell; IC, tumor-infiltrating immune cells.



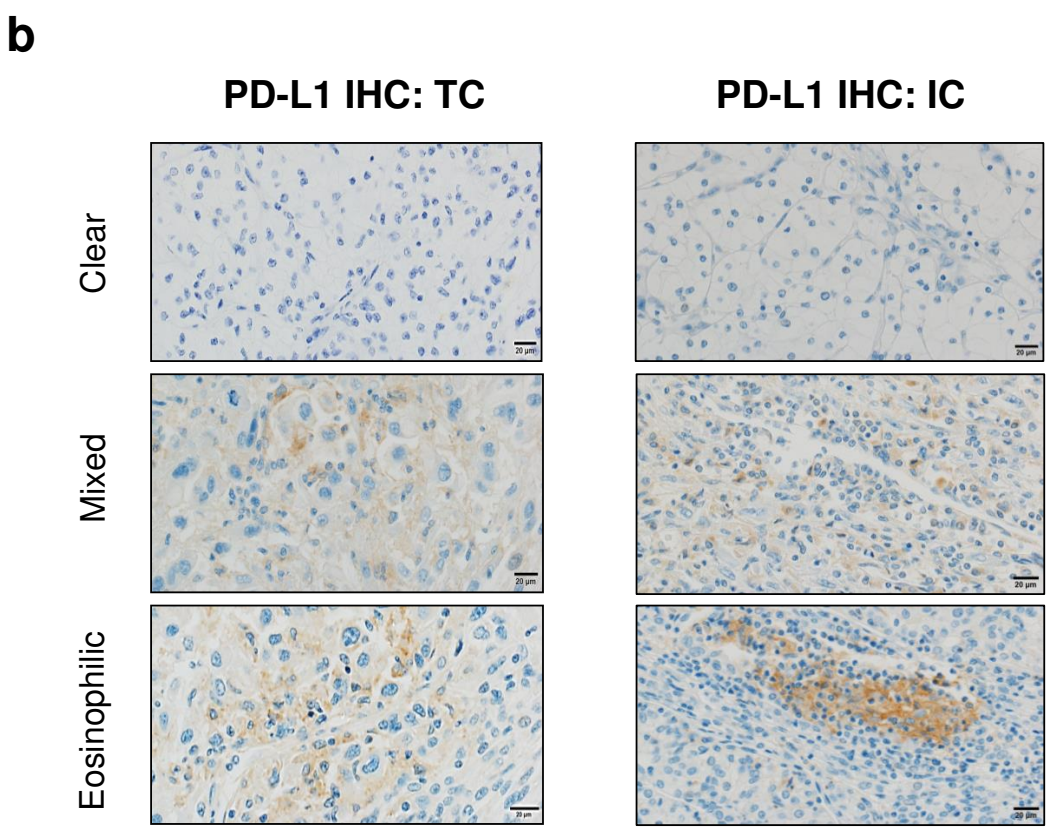


Fig. S7. Survival curves for overall survival (OS) stratified by WHO/ISUP (World Health Organization/ International Society of Urological Pathology) in the metastatic clear cell renal cell carcinoma (cohort 2). Kaplan-Meier method with the log-rank test was used for statistical analysis.

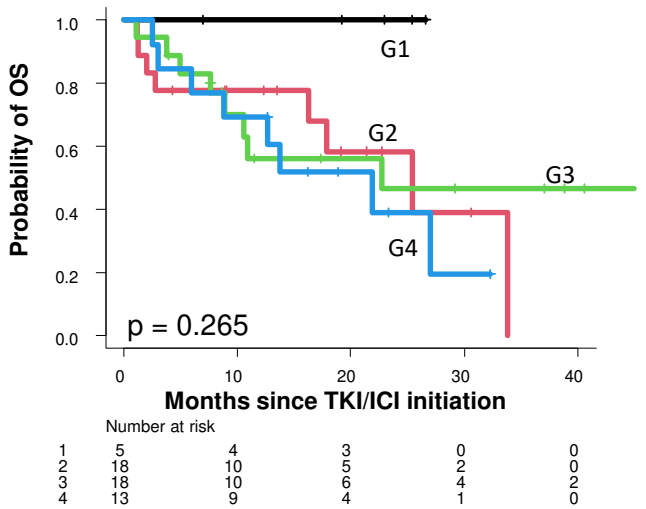
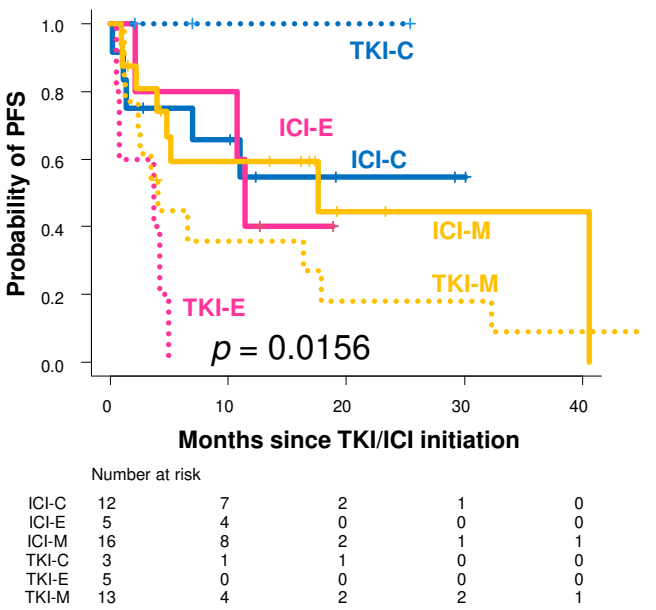


Fig. S8. Kaplan–Meier curves of progression-free survival (PFS) stratified by the therapeutic group combined with histological phenotypes; e.g., TKI-C = clear type treated with TKI, ICI-M = mixed type treated with ICI and TKI-M/E = mixed and eosinophilic types treated with TKI. The log-rank test with Holm's method was used for statistics. TKI, tyrosine-kinase inhibitors; ICI, immune checkpoint inhibitors.



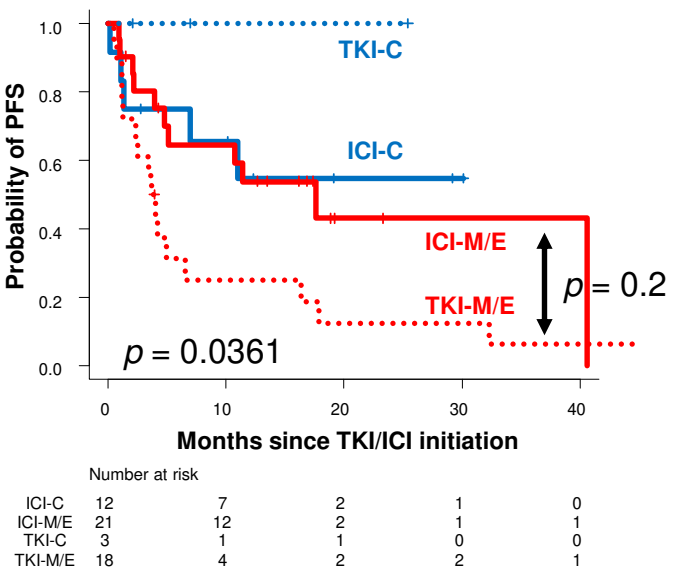


Table S3. Target lesions for TKI/ICI treatment in the metastatic ccRCC cohort.

Target lesions	TKI therapy group	ICI therapy group	*p* value*
No. of cases	21	33	
Adrenal	0 (0.0)	1 (3.0)	0.987
Bone	4 (19.0)	6 (18.2)	
Brain	0 (0.0)	2 (6.1)	
Intraperitoneal	0 (0.0)	1 (3.0)	
Kidney	1 (4.8)	1 (3.0)	
Liver	1 (4.8)	3 (9.1)	
Lung	13 (61.9)	15 (45.5)	
Lymph node	1 (4.8)	1 (3.0)	
Muscle	1 (4.8)	1 (3.0)	
Pancreas	0 (0.0)	1 (3.0)	
Retroperitoneal	0 (0.0)	1 (3.0)	

ccRCC, clear cell renal cell carcinoma; ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor. * Chi-square test.

Table S4. Best overall response of systemic treatment in the metastatic ccRCC cohort stratified by histological phenotypes.

Response	TKI therapy group			ICI therapy group			*p* value*
	Clear (n = 3)	Mixed (n = 13)	Eosinophilic (n = 5)	Clear (n = 12)	Mixed (n = 16)	Eosinophilic (n = 5)	
CR	1 (33.3)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	0.024
PR	0 (0.0)	3 (23.1)	0 (0.0)	4 (33.3)	2 (12.5)	3 (60.0)	
SD	2 (66.7)	5 (38.5)	1 (20.0)	5 (41.7)	11 (68.8)	2 (40.0)	
PD	0 (0.0)	5 (38.5)	4 (80.0)	2 (16.7)	3 (18.8)	0 (0.0)	

ccRCC, clear cell renal cell carcinoma; ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor; CR, complete response; PR, partial response; SD, stable disease; and PD, progression disease. * Chi-square test.