

Multi-omic characterization of RCC1 expression and its association with molecular alterations, immune phenotypes, and cancer outcomes

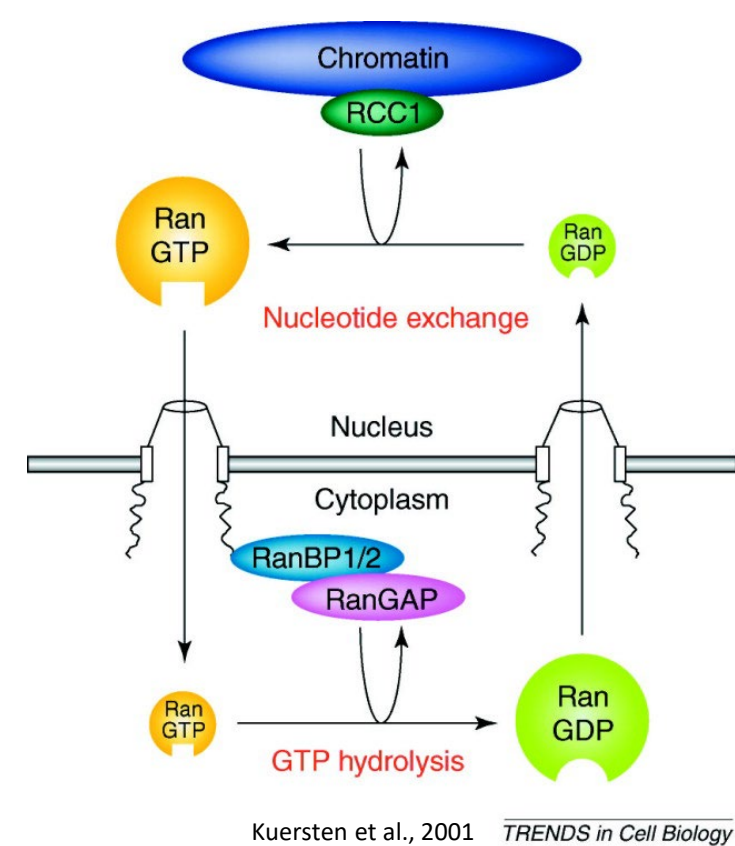
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Background

- Regulator of Chromosome Condensation 1 (RCC1) is the only identified guanine nucleotide exchange factor for the Ras-related nuclear protein Ran and it functions in nuclear transport, cell cycle and DNA damage response.



- Overexpressed in several cancer types, RCC1 is associated with poor outcomes.
- We aim to investigate the role of aberrant RCC1 co-alterations and association with immune phenotypes and cancer outcomes.

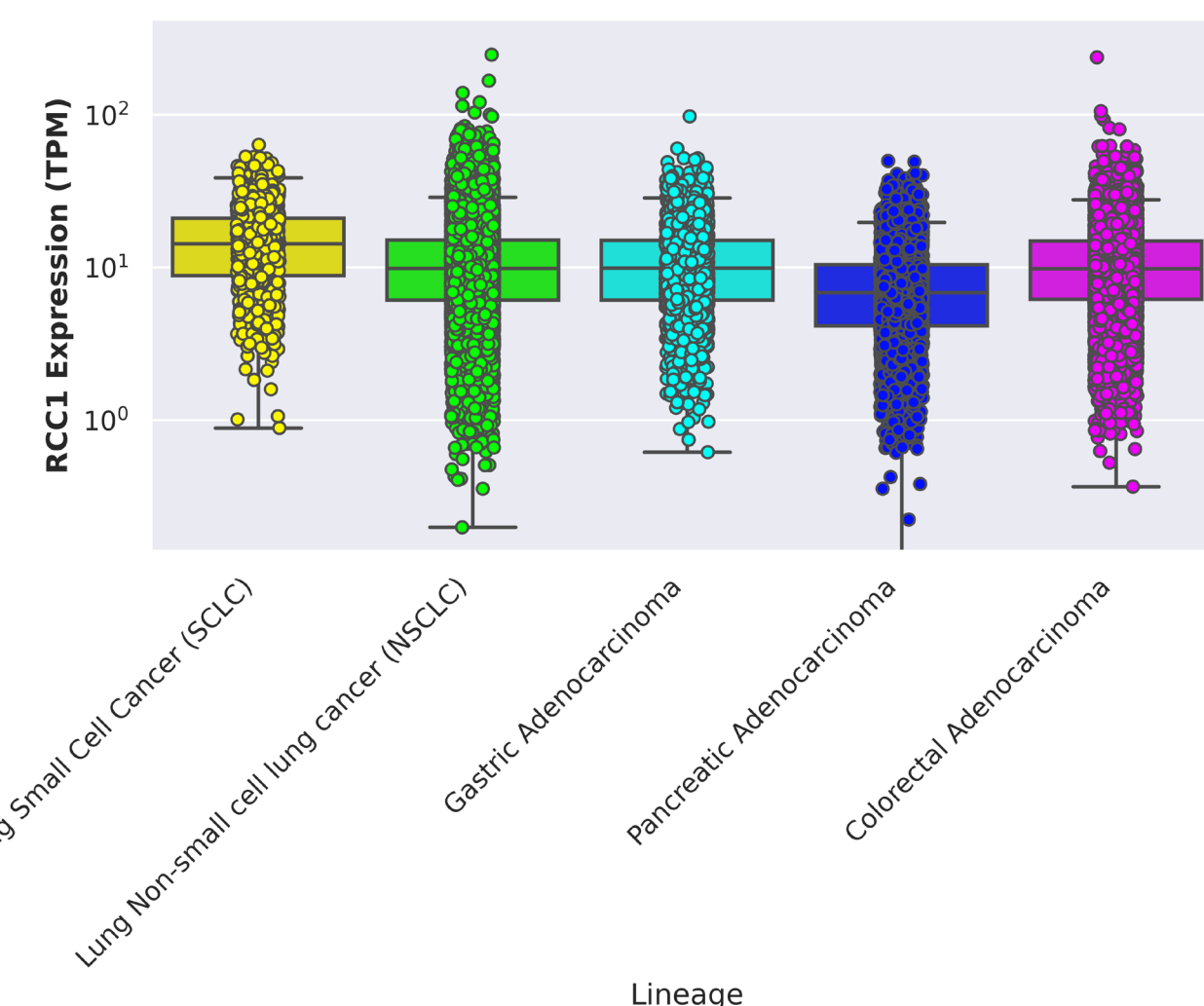
Methods

- DNA (592-gene or whole exome) and RNA (whole transcriptome) sequencing was performed at Caris Life Sciences (Phoenix, AZ).
- Samples were stratified by RCC1 expression quartile thresholds (Q1:low, Q4:high) for multiple cancers:
 - Small cell lung (SCLC, n = 876)
 - Non-small cell lung (NSCLC, n = 21603)
 - Gastric (GC, n = 1908)
 - Pancreatic (PC, n = 5071)
 - Colorectal (CRC, n = 14892)
- PD-L1+ expression was tested by IHC.
 - 22c3: ≥1%
 - SP142: ≥2+, 5%
- TMB-High was defined as ≥10 mutations/MB.
- Tumor microenvironment immune cell fractions were estimated by RNA deconvolution using quanTIseq².
- Overall survival (OS) was calculated using Kaplan-Meier estimate.
- Statistical significance was determined using chi-square and Wilcoxon rank sum test and adjusted for multiple comparisons (*P < 0.05).

Results

RCC1 expression across cancer types

Figure 1. Box-and-whisker plot of RCC1 expression by cancer type lineage. Median RCC1 expression highest in SCLC (14.3 TPM), followed by GC (9.9), NSCLC (9.9), CRC (9.8), and PC (6.9)



Genomic alterations associated with RCC1 expression

Table 1 and 2. Relative frequency of biomarker alterations between RCC1 Q4 and RCC1 Q1 expression subgroups. Positive values in red indicate higher frequency in RCC1 Q4, and negative values in blue indicates higher frequency in RCC Q1.

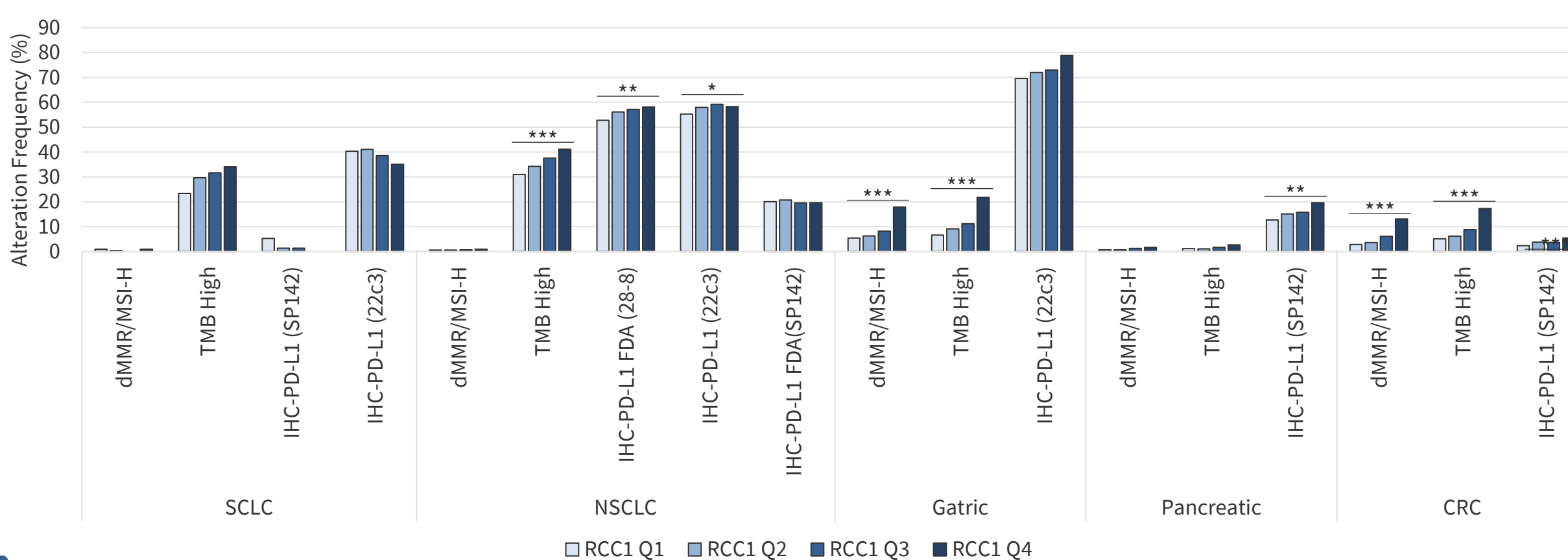
- In PC, TP53 mutations (Q1-Q4 range: 70-85%*) and MYC amplifications (1-4%*) were more frequent among RCC1 Q4, whereas ATM mutations were less frequent (6-3%).
- In CRC, TP53 (Q1-Q4 range: 70-81%*) and APC (72-81%*) mutations were more frequent in RCC1 Q4, while GNAS mutations were less frequent (4-2%*).

Feature	SCLC			NSCLC			Gastric-MSS			Gastric-MSI			Pancreatic			CRC-MSS			CRC-MSI		
	Q4 % - Q1%	p-value	q-value	Q4 % - Q1%	p-value	q-value	Q4 % - Q1%	p-value	q-value	Q4 % - Q1%	p-value	q-value	Q4 % - Q1%	p-value	q-value	Q4 % - Q1%	p-value	q-value	Q4 % - Q1%	p-value	q-value
NGS-RB1	12.7	0.03	1	6.6	0	0	4.9	0	0.02	-4.4	0.88	1	0.08	0.65	1	0.67	0.06	0.57	4.23	0.43	1
NGS-TP53	12.3	0	0.04	20	0	0	11.3	0	0.49	17.8	0.02	0.69	1.29	0.08	0.97	9.51	0	0	12.1	0.02	0.96
CNA-CSF3R	4.36	0.04	1	-0.1	0.7	0.93	0.24	0.88	1	32	0	0.69	0.16	0.76	1	0.32	0	0.08	5.12	0.57	1
CNA-IL21R	2.7	0.04	1	0.06	0.23	0.73	0.23	0.91	1	2.33	0.03	0.69	0.42	0.32	1	0.42	0	0.05	-0.4	1	1
NGS-PRKDC	2.49	0.04	1	0.19	0.66	0.92	0.12	1	-6.1	0.03	0.69	0.09	0.3	1	0.24	0.39	0.83	-1.3	0.86	1	
CNA-LCK	1.86	0.03	1	0.02	0.83	0.97	0.3	0.23	1	0	0.04	0.69	0.33	0.48	1	0	0.45	0.86	1.68	0.42	1
NGS-BRCA2	0.47	0.04	1	-0.3	0.59	0.89	0.7	0.08	0.97	6.67	0.05	0.69	0.16	0.36	1	0.12	0.53	0.87	10.5	0.05	1
CNA-NTRK1	-2.4	0.03	1	0.08	0.43	0.84	0.21	0.24	1	20	0.05	0.69	0.79	0.06	0.96	-0.8	0.11	0.64	1.67	0.72	1
NGS-HOXB13	-2.5	0.03	1	0.07	0.88	0.99	0.15	0.64	1	-4.2	0.89	1	7.27	0	0	2.93	0.09	0.64	-0.2	0.89	1
CNA-CCND1	-2.8	0.01	0.61	0.1	0.27	0.74	-1.4	0.56	1	8.89	0.05	0.69	-2.8	0	0.01	-1.7	0	0.06	2.51	0.45	1
CNA-FGF3	-3	0.01	0.61	0.12	0.97	1	0.5	1	1	-2.2	1	1	-0.2	0.01	0.5	-0.1	0.27	0.71	0	0.5	1
CNA-FGF19	-3.4	0	0.24	0.15	0.82	0.97	0.94	1	6.67	0.36	1	0.4	0.01	0.5	0.23	0.19	0.7	1.67	0.07	1	
CNA-FGF4	-4.2	0	0.06	0.21	0.71	0.93	0.1	1	1.07	0.02	0.79	0.86	0	0.1	-6.8	0.28	1	-6.8	0.28	1	
NGS-LOH	-4.8	0.35	1	7.11	0	0	0.24	0.88	1	0.84	1	0.72	0.03	0.83	0.67	0.01	0.24	-2.3	0.25	1	
NGS-EGFR	-2.3	0.08	1	5.23	0	0	0.25	0.81	1	1.68	0.54	1	1.07	0.02	0.79	0.86	0	0.1	-6.8	0.28	1
CNA-MYC	3.24	0.15	1	2.12	0	0	0.25	1	1.63	0	0	0	0	0	0	0	0	0	0	0	
CNA-FOXA1	0.91	0.74	1	1.76	0	0	0.25	1	1.63	0	0	0	0	0	0	0	0	0	0	0	
CNA-EGFR	0	0.25	1	1.63	0	0	-0.9	0.69	1	1.51	0	0	0	0	0	0	0	0	0	0	
NGS-ARID2	-0.9	0.69	1	1.51	0	0	-2.8	0.38	1	1.33	0	0	0	0	0	0	0	0	0	0	
CNA-FGFR1	-2.8	0.38	1	1.33	0	0	-0.5	0.62	1	1.18	0	0	0	0	0	0	0	0	0	0	
CNA-MET	-0.5	0.62	1	1.18	0	0	0.06	1	1.08	0	0	0.01	0	0	0	0	0	0	0	0	
CNA-CDK4	0	0.06	1	1.08	0	0.01	0.46	0.86	1	1.02	0	0	0	0	0	0	0	0	0	0	
CNA-CNE1	0.46	0.86	1	1.02	0	0	0.25	1	0.97	0	0	0	0	0	0	0	0	0	0	0	
CNA-NFKBIA	0	0.25	1	0.97	0	0	0.32	1	0.47	0	0.01	0	0	0	0	0	0	0	0	0	
CNA-IL7R	0	0.32	1	0.47	0	0.01	N/A	N/A	N/A	0.46	0	0.01	0	0	0	0	0	0	0	0	
NGS-MLH3	N/A	N/A	N/A	0.46	0	0.01	-0.5	0.15	1	0.34	0	0	0	0	0	0	0	0	0	0	
CNA-PDCD1LG2	-0.5	0.15	1	0.34	0	0	-1.5	0.21	1	0.33	0	0.01	0	0	0	0	0	0	0	0	
CNA-CD274	-1.5	0.21	1	0.33	0	0.01	-0.6	0.81	1	0.32	0	0.03	0	0	0	0	0	0	0	0	
CNA-JAK2	-0.6	0.81	1	0.32	0	0.03	-0.5	0.13	1	0.23	0	0.03	0	0	0	0	0	0	0	0	
CNA-CDKN2A	-0.5	0.13	1	0.23	0	0.03	N/A	N/A	N/A	-0.4	0	0	0	0	0	0	0	0	0	0	
Fusion-NRG1	N/A	N/A	N/A	-0.23	0	0	0.5	1	1	-0.4	0	0.03	0.47	0.44	1	4.44	0.9	1	0.08	0.37	1
NGS-GNAS	-0.5	1	1	-0.4	0	0.03	0.77	0.18	1	4.62	0.8	1	-0.4	0.5	1	0.25	0.84	0.99	-1.5	0.03	0.96
NGS-NKX2-1	0.47	0.49	1	-0.5	0	0	0.24	0.95	1	6.67	0.73	1	0.72	0.35	1	0.7	0.01	0.24	7.23	0.03	0.96
CNA-KHLH6	0.45	0.64	1	-0.8	0	0	0.93	1	-1.8	0.31	1	0.08	1	1	-0.4	0.15	0.69	-4	0.03	0.96	
NGS-STK11	-1.4	0.41	1	-5.3	0	0	0	0.24	1	-2.7	0.35	1	-0.1	0.76	1	0.34	0.13	0.67	3.24	0.04	1
NGS-KRAS	-2.8	0.1	1	-13	0	0	0	0.24	1	-2.7	0.35	1	-0.1	0.76	1	0.34	0.13	0.67	3.24	0.04	1

Predictive biomarkers of response to immunotherapy

Figure 2. Frequency of immunotherapy-related biomarkers by cancer type

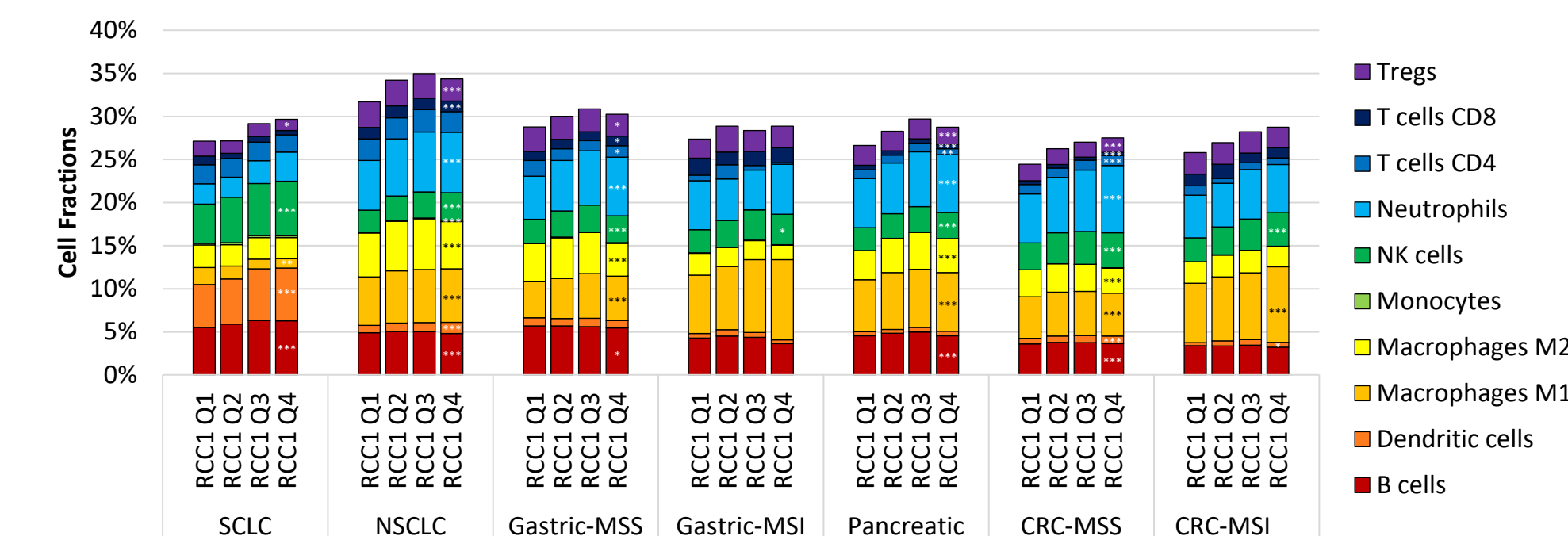
- TMB-high frequency increased progressively with RCC1 expression in NSCLC, GC, and CRC (3-13%*), consistent with dMMR/MSI-high rates in GC (5-18%*) and CRC (3-13%*). Similar trends were observed for PDL1+ rates in PC (Q1-Q4 range: 13-20%*), CRC (2-5%*) and NSCLC (55-58%*).
- In NSCLC, TP53 (Q1-Q4 range: 57-77%*), RB1 (7-13%*), and EGFR (10-15%*) mutations were seen more with higher RCC1 expression, while STK11 (15-10%*) and KRAS (33-21%*) mutations were seen less.



Tumor microenvironment composition

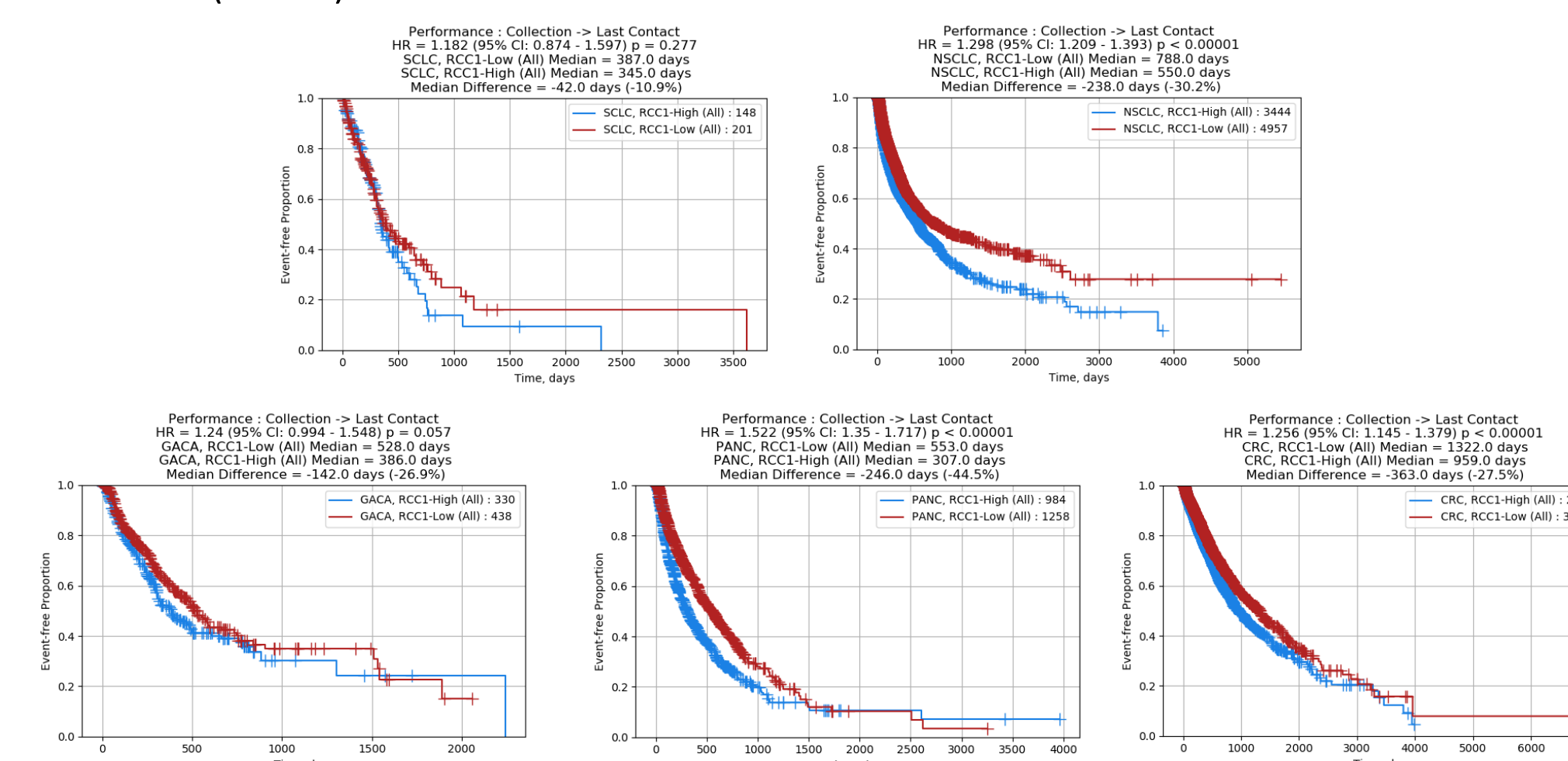
Figure 3. Estimation of infiltrating immune cell fractions by RCC1 expression quartiles. Asterisks reflect significant difference between RCC1 Q1 and RCC1 Q4 subgroups.

- In both SCLC and NSCLC, high RCC1 expression was associated with increased dendritic cell (5-6%* and .8-1.3%*, respectively) and NK cell fractions (5-6%* and 2.5-3.2%*) and decreased Treg fractions (1.8-1.3%* and 3.0-2.6%*).
- In pMMR/MSS CRC, high RCC1 expression was associated with increased dendritic cell (.6-.9%*), NK cell (3-4%*), neutrophil (6-8%*) and CD4 T cell fractions (1.1-1.2%*) and decreased CD8 T cell (.5-.4%*) and Treg fractions (1.9-1.7%*).



Clinical outcomes associated with RCC1 expression

Figure 4. High RCC1 expression was associated with worse OS in NSCLC (HR 1.3*), PC (HR 1.5*) and CRC (HR 1.3*), with a similar but not significant effect in SCLC (HR 1.2) and GC (HR 1.2).



Cancer Type	Prognostic	Chemotherapy	Immunotherapy
SCLC	HR 1.182, P=0.277	HR 1.11, P=0.669	HR 0.947, P=0.853
NSCLC	HR 1.298, P<0.0001	HR 1.395, P<0.0001	HR 1.224, P=0.013
Gastric	HR 1.24, P=0.057	HR 1.291, P=0.162	HR 1.539, P=0.282
Pancreatic	HR 1.522, P<0.00001	HR 1.494, P<0.0001	HR 1.979, P=0.252
CRC	HR 1.256, P<0.00001	HR 1.494, P<0.0001	HR 1.101, P=0.795

Conclusions

- RCC1 expression is a negative prognostic marker in NSCLC, PC, and CRC.
- Further studies to investigate this at the molecular level may be a potential opportunity for novel targeted drug development.

References

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