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Lymphocyte activation gene-3 expression patterns and immunotherapy response in metastatic renal cell carcinoma

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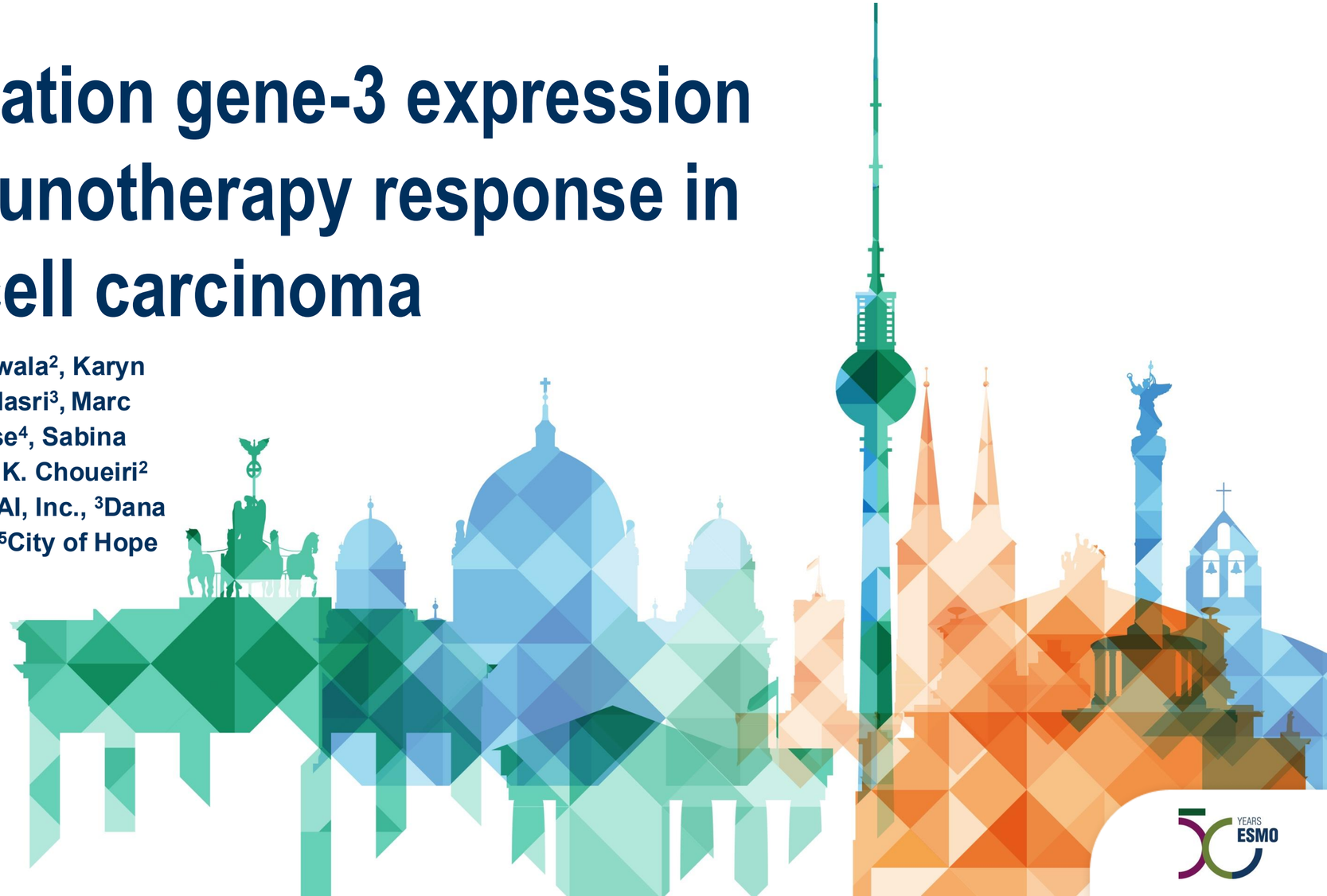

XX October 2025

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Declarations of Interest

- Consulting/advisor with Ambrx, Arcus, AstraZeneca, Aveo, Bayer, Blue Earth Diagnostics, Bristol-Myers Squibb, Calithera, Caris, Daiichi Sankyo, Dendreon, Exelixis, Johnson & Johnson, Lilly, Merck, Myovant, Neomorph, Nimbus, Novartis, Pfizer, Sanofi, SeaGen, Sorrento Therapeutics, Telix, Tempus.

- Institutional research funding from Artera AI, AstraZeneca, Bayer, Bristol-Myers Squibb, Exelixis, Oncternal, Tempus.

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Background

Immunotherapy combinations are the new frontline treatment in RCC

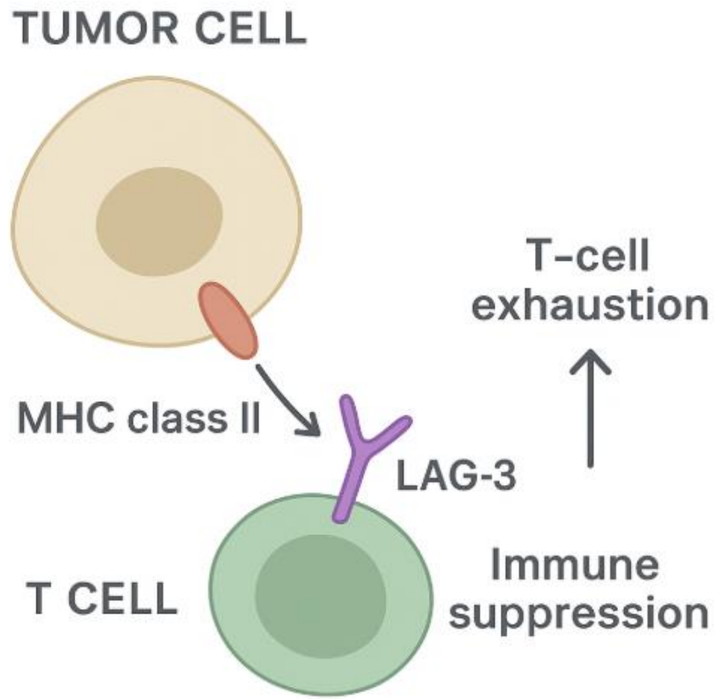
Outcomes to treatment are heterogenous

A wide range of biomarkers have been investigated in RCC, but none are used clinically

LAG-3 is an inhibitor receptor on T-cells that suppresses T-cell activation and promotes exhaustion

LAG-3 expression (alone or combined with PD-1/PD-L1 and other immune exhaustion markers) has been linked to an inflamed TME

The purpose of this work was to investigate LAG3 RNA expression as a biomarker in RCC patients receiving frontline immunotherapy



RCC=Renal cell carcinoma; LAG3=Lymphocyte activation gene 3; TME=Tumor microenvironment.
.Saleh et al Front Oncol, 2019; Li et al, Aging, 2024; Lee et al, Int J Immunopathol Pharmacol, 2022.

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Methods

De-identified DNA-NGS (xT) and RNA-NGS (xR) data from patients with RCC within Tempus multimodal database

Eligibility:
- Received 1L IO treatment*
- Tissue collected within 365 days before and up to 15 days after treatment start

Stratified into quartiles by LAG-3 RNA expression

Checkpoint Gene Expression
-CLTA-4, TIM-3, TIGIT
-PD-L1, PD-1, PD-2

Immunotherapy Markers
-Tumor Mutation burden
-Microsatellite Instability
-PD-L1 IHC Status (22C3 clone)

Immune Cell Proportions
-Estimated from RNA (quanTIseq)

DNA Alterations
-Single nucleotide variants
-Insertions/deletions
-Copy number alterations

Objective Response Rate#

Overall Survival##

*Eligible patients received 1) nivolumab + ipilimumab, 2) pembrolizumab + axitinib, 3) nivolumab + cabozantinib, or 4) pembrolizumab + lenvatinib.
**RNA-seq data were normalized by computing transcripts per million (TPM) for all protein-coding transcripts and then transforming them by $log_2(TPM + 1)$.
#Objective response rate was calculated as best response occurring at least 15 days after and within 180 days of treatment initiation as extracted from the medical record.
##Overall survival was defined as the time from 1L immunotherapy start to death, lost to follow-up, or 5 years after 1L and analyzed using Cox proportional hazard models and p values (Wald test).
NGS=Next-generation, sequencing; RCC=Renal cell carcinoma; 1L=First-line; IO=Immuno-oncology; IHC=Immunohistochemistry.

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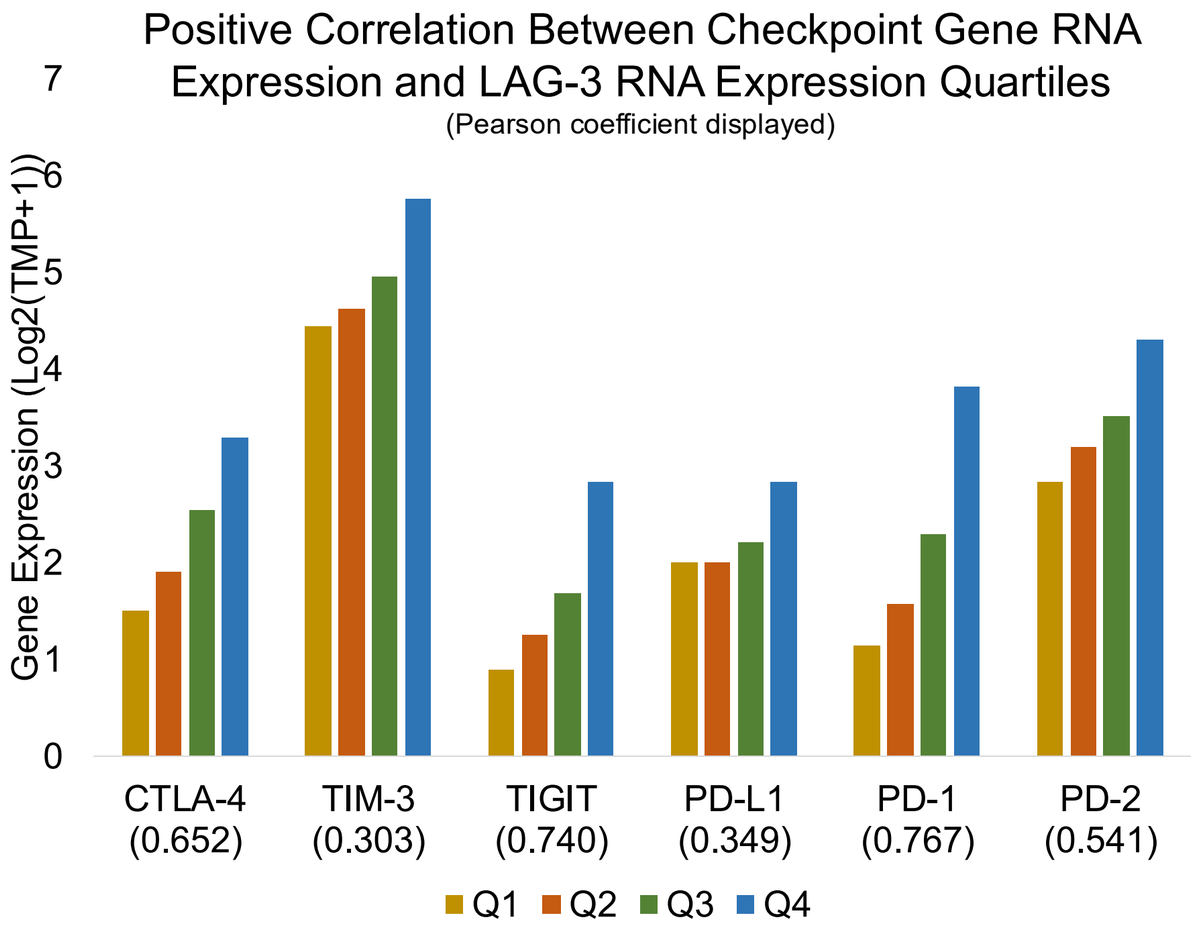
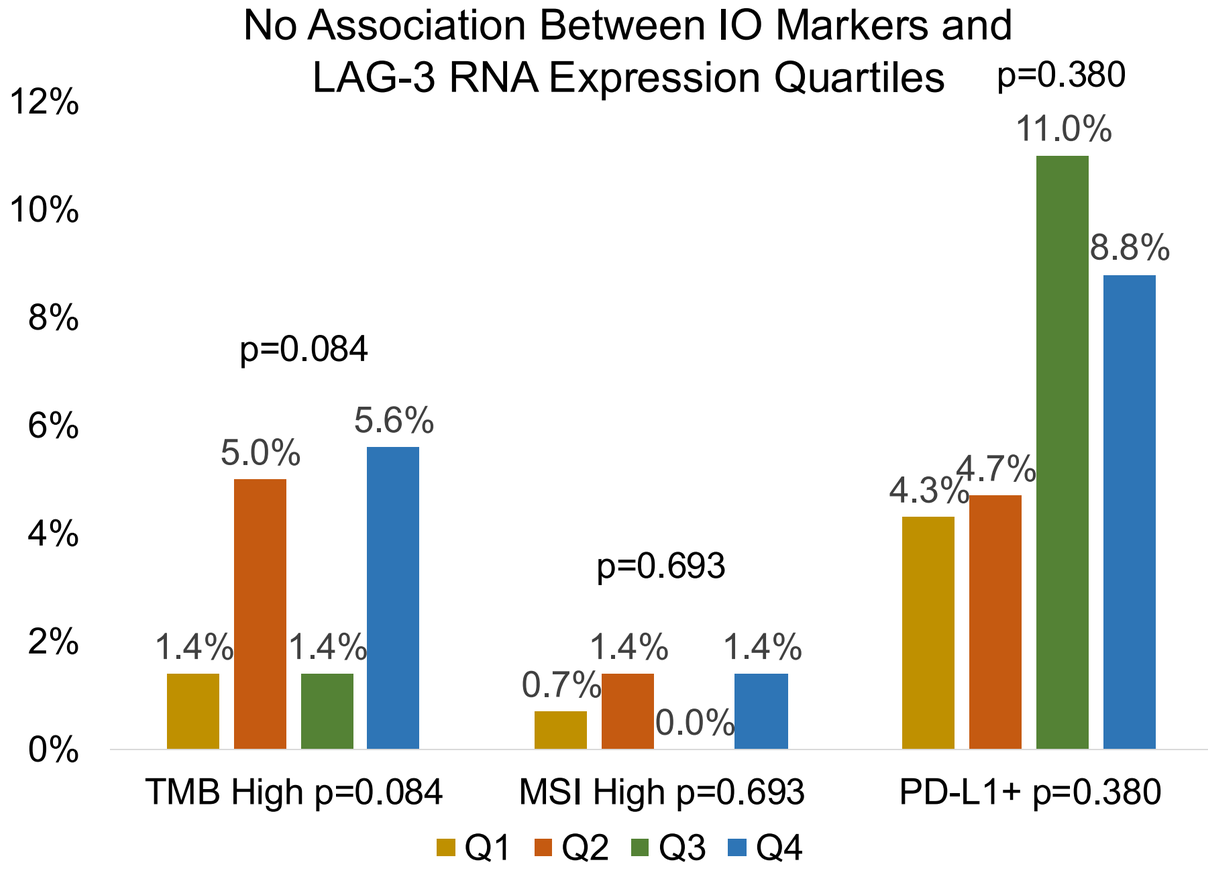
Baseline Characteristics

Variable		Overall (n=566)	Q1 (n=142)	Q2 (n=141)	Q3 (n=141)	Q4 (n=142)	P-value
Median age, years		61	61	61	61	61	0.571
Male		409 (72%)	98 (69%)	109 (77%)	96 (68%)	106 (75%)	0.244
Non-White Race		89 (21%)	22 (21%)	27 (27%)	20 (17%)	20 (20%)	0.352
Hispanic		65 (21%)	19 (23%)	11 (14%)	21 (26%)	14 (19%)	0.316
Former/Current Smoker		241 (43%)	58 (41%)	63 (45%)	65 (46%)	55 (39%)	0.572
Prior Nephrectomy		285 (50%)	69 (49%)	60 (43%)	76 (54%)	80 (56%)	0.096
Stage IV at Collection		489 (94%)	126 (95%)	126 (94%)	116 (94%)	121 (95%)	0.997
Bone Metastases		95 (17%)	19 (13%)	26 (18%)	27 (19%)	23 (16%)	0.561
Liver Metastases		**68 (12%)**	**26 (18%)**	**19 (13%)**	**13 (9%)**	**10 (7%)**	**0.019**
Brain Metastases		48 (9%)	12 (8.5%)	9 (7%)	10 (7%)	17 (12%)	0.337
Brain Metastases		48 (9%)	12 (9%)	9 (6%)	10 (7%)	17 (12%)	0.337
First-line Therapy	Nivolumab + Ipilimumab	268 (47%)	56 (39%)	67 (48%)	70 (50%)	75 (53%)	0.285
	Pembrolizumab + Axitinib	178 (31%)	44 (31%)	48 (34%)	43 (30%)	43 (30%)	
	Nivolumab + Cabozantinib	71 (13%)	27 (19%)	14 (10%)	16 (11%)	14 (10%)	
	Pembrolizumab + Lenvatinib	49 (9%)	15 (11%)	12 (9%)	12 (9%)	10 (7%)	

Checkpoint Gene Expression and IO Markers





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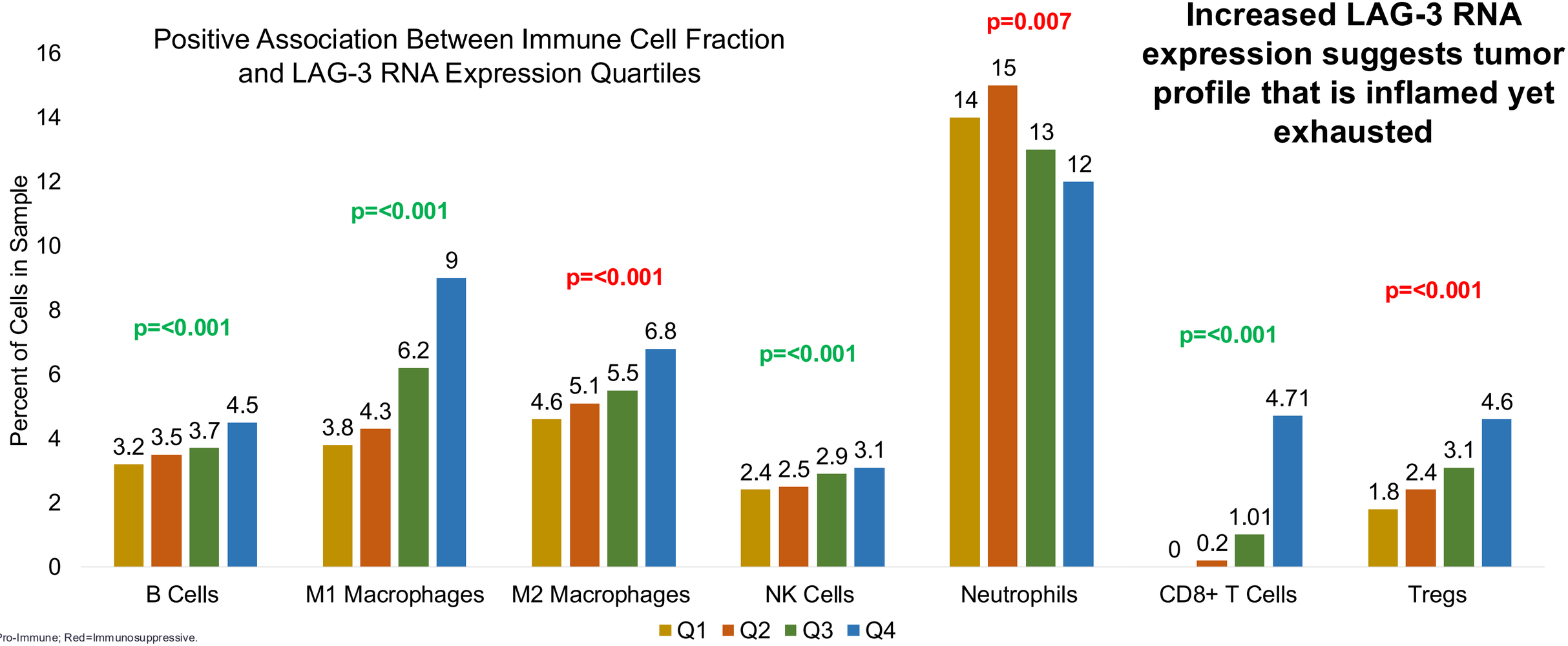
Associations with Immune Cell Fraction



Increased LAG-3 RNA expression suggests tumor profile that is inflamed yet exhausted

Green=Pro-Immune; Red=Immunosuppressive.

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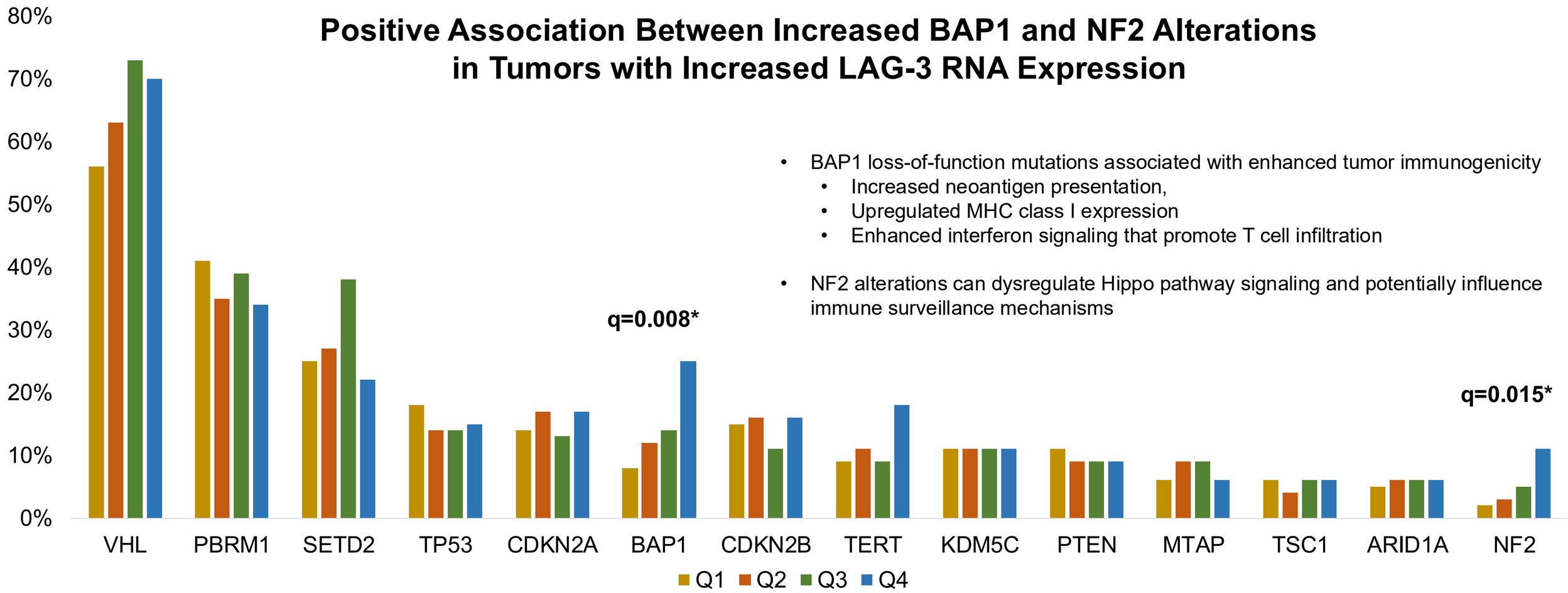
Associations with Somatic Alterations



- BAP1 loss-of-function mutations associated with enhanced tumor immunogenicity
  - Increased neoantigen presentation,
  - Upregulated MHC class I expression
  - Enhanced interferon signaling that promote T cell infiltration
- NF2 alterations can dysregulate Hippo pathway signaling and potentially influence immune surveillance mechanisms

*Q values adjusted for multiplicity testing. Only statistically significant q values are presented.

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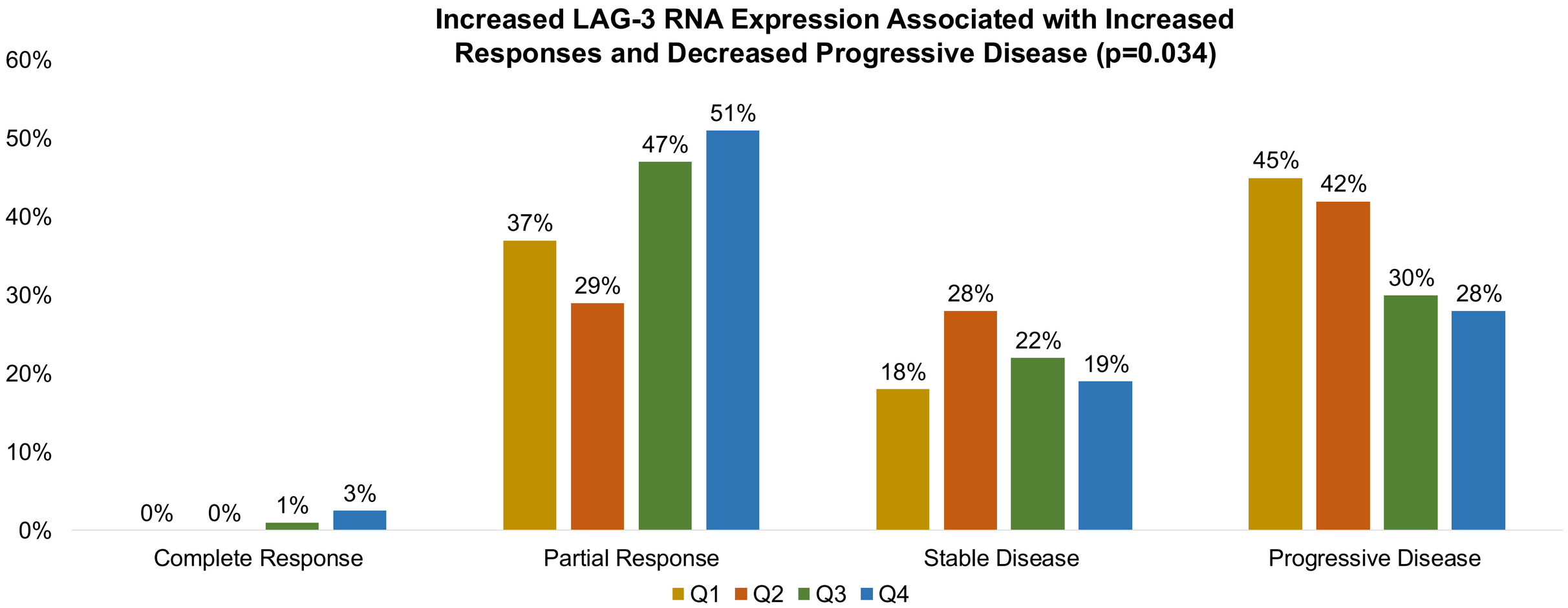
LAG-3 Expression Associated with ORR



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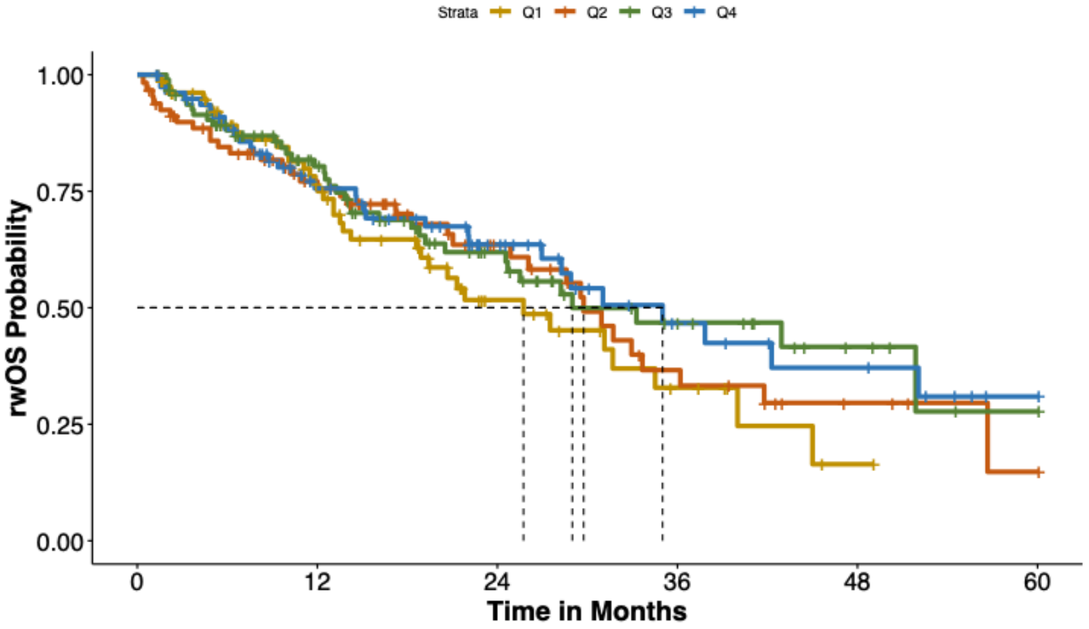
No Association Between LAG-3 Expression and OS



LAG-3 Quartile (n=339)	Median Overall Survival	HR	95% CI	P-Value
Q1	25.7 (18.9, 45.0)	-	-	-
Q2	29.8 (24.9, 41.8	0.85	0.53, 1.36	0.5
Q3	29.0 (24.6, NA)	0.75	0.48, 1.20	0.2
Q4	35.0 (27.0, NA)	0.74	0.46, 1.18	0.2

rwOS=Real world overall survival; HR=Hazard ratio; CI=Confidence interval.

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Conclusions

Tumors with higher LAG-3 expression demonstrated a decreased proportion of liver metastases.

LAG-3 RNA expression positively correlated with other checkpoint genes, suggesting severe T cell dysfunction and adaptive immune resistance.

Tumors with high LAG3 expression exhibited a complex immunological phenotype characterized by robust effector cell infiltration (CD8+ T cells, NK cells, M1 macrophages, B cells) alongside concurrent immunosuppressive mechanisms (M2 macrophages, Tregs), indicating an adaptive resistance state.

Tumors with high LAG3 expression exhibited increased BAP1 and NF2 alterations, which are associated with enhanced tumor immunogenicity.

Greater responses were observed among tumors with increased LAG-3 expression, however overall survival was similar across LAG-3 RNA expression quartiles.

High LAG3 expression identifies RCC tumors with enhanced immunogenicity and greater therapeutic responses despite adaptive resistance mechanisms; however, further data and protein correlation are needed to validate these findings.

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