LAG-3 Expression and Outcome of Metastatic Melanoma Patients Treated with Combination Anti-LAG-3 + Anti-PD-1 Immunotherapies

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BACKGROUND

Lymphocyte-activation gene-3 (LAG-3), an immune checkpoint receptor, negatively regulates T-cell function and facilitates immune escape of tumors[1].

Dual inhibition of LAG-3 and programmed cell death receptor-1 (PD-1) significantly improved progression-free survival (PFS) in metastatic melanoma patients compared to anti-PD-1 therapy alone[2].

Investigating the utility of LAG-3 expression as a biomarker of response to anti-LAG-3 + anti-PD-1 immunotherapy is of great clinical relevance.

OBJECTIVES

To evaluate the association between baseline LAG-3 expression and clinical outcomes following anti-LAG-3 immunotherapy in metastatic melanoma

METHODS

- LAG-3 immunohistochemistry (clone D2G4O) was performed on pre-treatment formalin-fixed paraffin-embedded metastatic melanoma specimens from 53 patients treated with combination anti-LAG-3 + anti-PD-1-based therapies
- Patients were categorized as responders (CR or PR; n=37) or non-responders (SD or PD; n=16) based on RECIST
- Tumor-infiltrating lymphocytes (TILs) were scored on hematoxylin and eosin-stained sections using a four tier TIL grading scheme
- LAG-3 was evaluated on lymphocytes expressing punctate, cytoplasmic, or membranous LAG-3 as described previously[3]
- Samples were classified as LAG-3 positive if the number of LAG-3+ lymphocytes was ≥1% of all cells

RESULTS

LAG-3 Expression in Melanoma

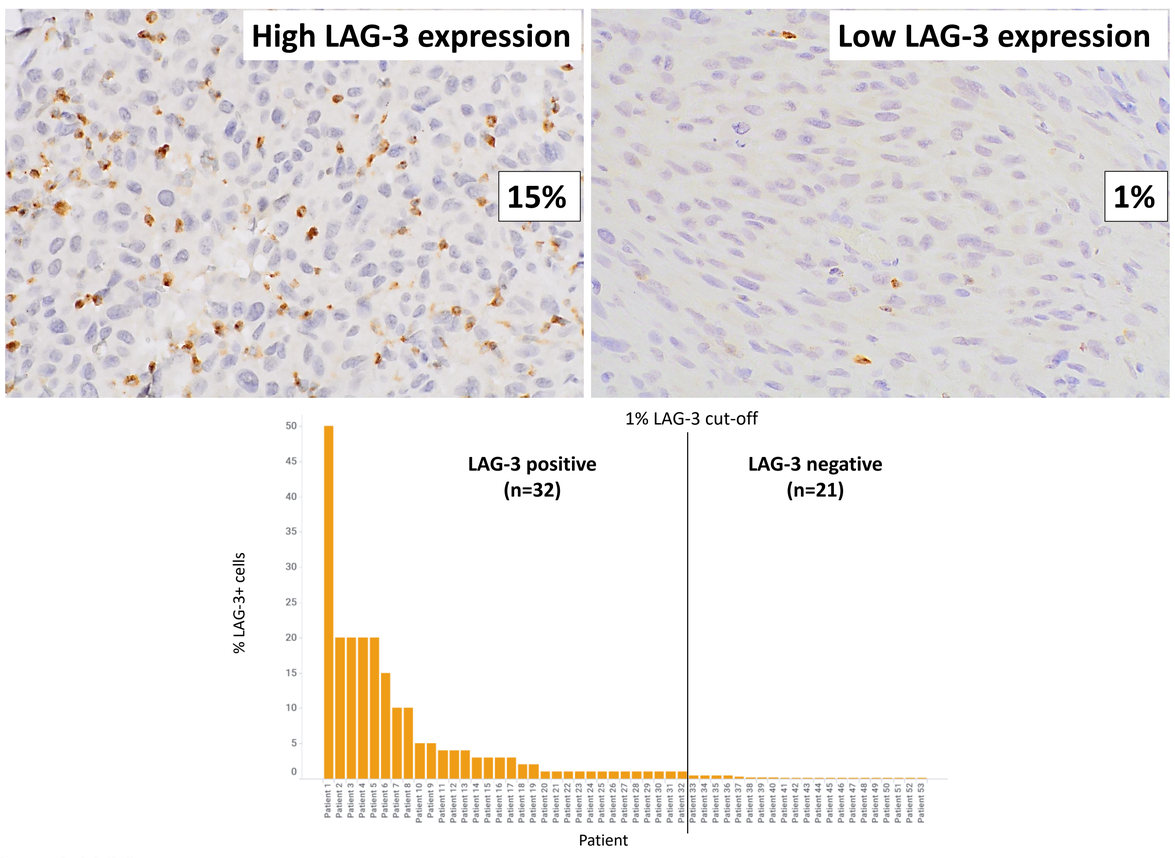


Figure 1. LAG-3 expression in melanoma.

LAG-3 Expression in Different Sites of Metastasis

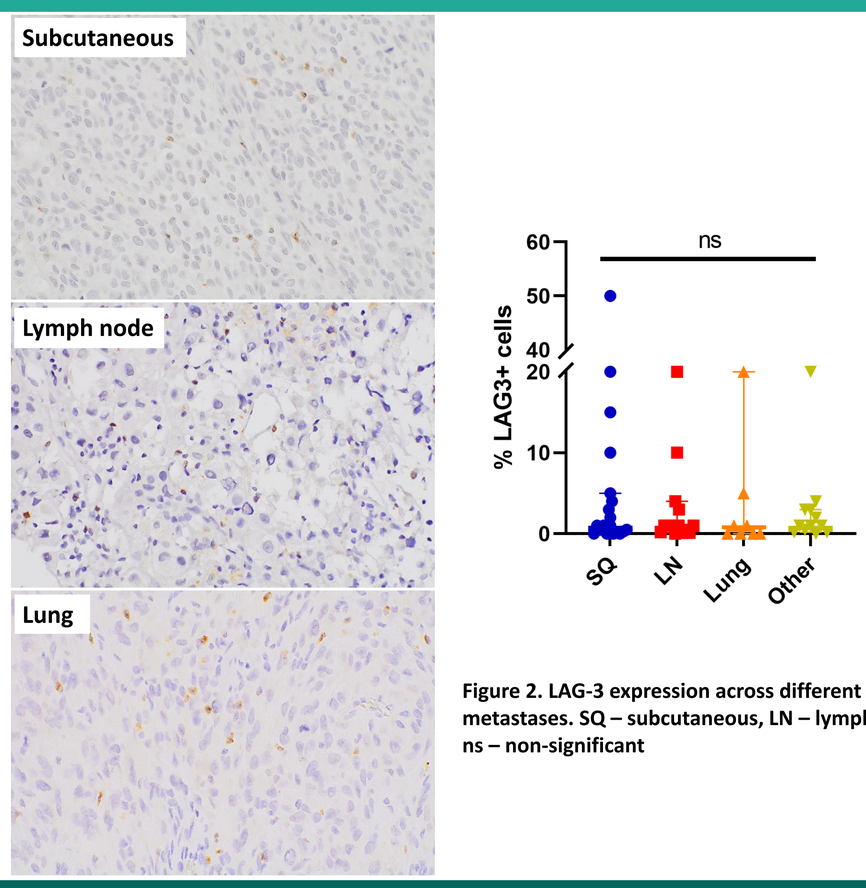
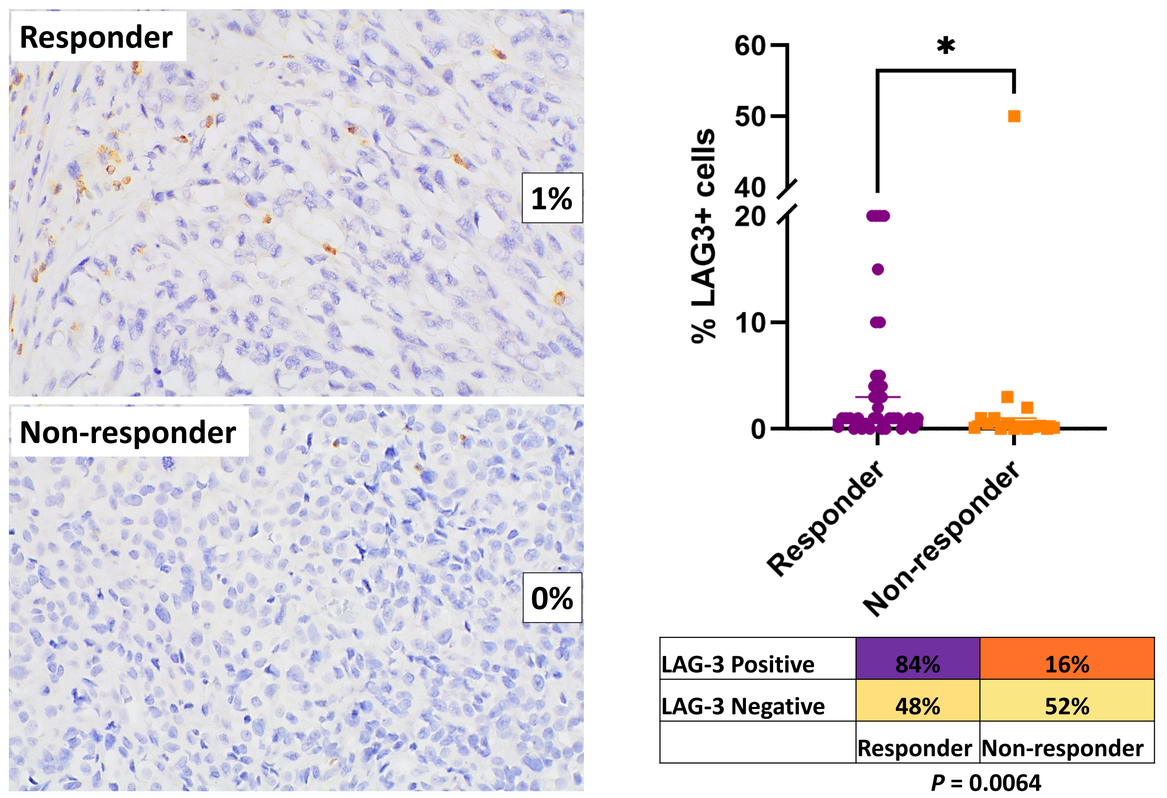


Figure 2. LAG-3 expression across different sites of metastases. SQ – subcutaneous, LN – lymph node, ns – non-significant

LAG-3 Expression is Associated with Response



LAG-3 Positive	84%	16%
LAG-3 Negative	48%	52%
	Responder	Non-responder

P = 0.0064

Figure 3. Association between LAG-3 expression and response to anti-LAG-3 + anti-PD-1-based immunotherapy. **P* < 0.05

LAG-3 Expression is Associated with PFS

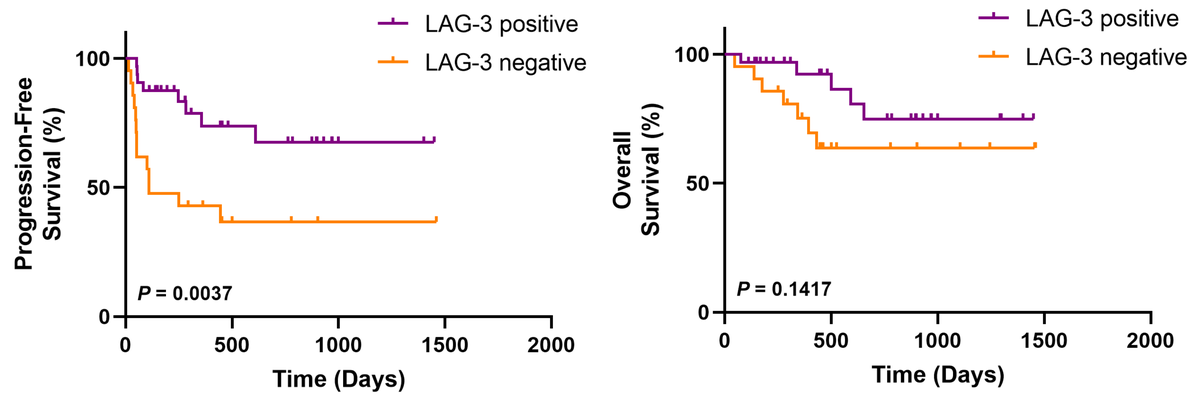


Figure 4. Association between LAG-3 status and progression-free and overall survival.

LAG-3 Expression in Anti-PD-1 Refractory Patients

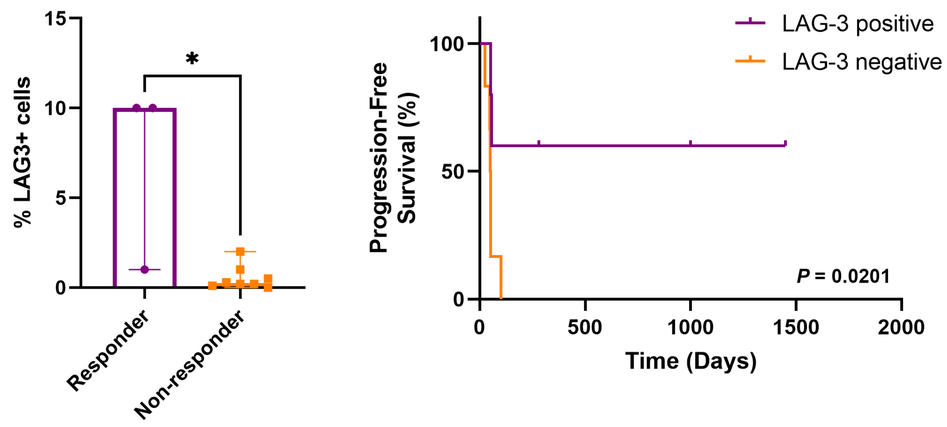


Figure 5. Association between LAG-3 expression, response and PFS in anti-PD-1 refractory cohort. **P* < 0.05

CONCLUSIONS

- LAG-3 expression is associated with response to combination anti-LAG-3 and anti-PD-1-based immunotherapy
- Patients with LAG-3 positive tumours have significantly longer PFS compared to those with LAG-3 negative tumours
- Assessment of LAG-3 expression via IHC warrants further evaluation to determine its predictive value in metastatic melanoma

References

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3. Johnson et al. Development of a LAG-3 immunohistochemistry assay for melanoma. J Clin Pathol 2022;0:1-8

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