Association between LAG3 expression and immune checkpoint inhibitor (ICI) efficacy in advanced melanoma

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AACR American Association for Cancer Research

Abstract Presentation #

INTRODUCTION

- Combinations of CTLA4/PD-1, LAG3/PD-1, and triplet of LAG3/PD-1/CTLA4 targeted therapies are showing efficacy without true predictive markers of response.[1-3]
- LAG3 staining showed clear progression-free survival (PFS) benefits following single-agent PD-1 and LAG3/PD-1 combination therapies.[4,5]
- Patients with ≥1% LAG3-positive cells in their tumors had significantly longer PFS compared to patients with <1% LAG3 expression ($P = 0.0037$). The importance of overall survival (OS) is unclear.[6]
- Here, we evaluated the utility of LAG3 and PD-L1 in relation to outcomes for single agent and combination IO therapy in a real-world cohort of advanced melanoma patients.

METHODS

Real-world retrospective cohort selection

De-identified next-generation sequencing data from patients (pts; N=367) with stage III-IV (advanced) cutaneous melanoma in the Tempus Database were selected for analysis (Tempus AI, Inc., Chicago, IL). The Tempus Database contains data from geographically diverse oncology practices, including integrated delivery networks, academic institutions, and community practices.

Treatment data

Pts were treated with 1L ICIs, aCTLA4/PD-1 (n=222), or aPD-1 (n=145). Pts treated with 1L aLAG-3/PD1 were limited and not included.

Molecular Characteristics

Tissue was collected prior to 1L and sequenced with xT DNA (648-gene panel) and xR RNA assays. LAG3 high (LAG3-H) and low (LAG3-L) expressors were defined by median LAG3 RNA transcripts per million. PD-L1 was determined by IHC. QuanTIseq was used to estimate immune cell proportions.

Real-world Outcomes

Real-world OS (rwOS) was calculated from treatment start to death from any cause. Rw objective response rate (rwORR) was defined as the proportion of pts with a documented complete or partial response within 90 days of treatment start.

Statistics

Hazard ratio (HR) was calculated using a Cox proportional hazards (CoxPH) model and p-values using the Wald test.

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RESULTS

Table 1. Overview of the Cohort

Characteristic	LAG3-L, aPD-1 mono (n=68)	LAG3-H, aPD-1 mono (n=77)	LAG3-L, aPD-1/ CTLA4 combo (n=113)	LAG3-H, aPD-1/ CTLA4 combo (n=109)	P-value
Age at Biopsy (years), median (IQR)	68 (60, 77)	71 (64, 78)	60 (52, 68)	62 (52, 70)	<0.001
Sex, n (%)					0.255
Male	38 (56%)	54 (70%)	73 (65%)	64 (59%)	
Female	30 (44%)	23 (30%)	40 (35%)	45 (41%)	
Metastasis Prior to 1L Therapy, n (%)					0.035
Liver	8 (12%)	6 (7.8%)	27 (24%)	26 (24%)	
Other	45 (66%)	55 (71%)	65 (58%)	68 (62%)	
Unknown	15 (22%)	16 (21%)	21 (19%)	15 (14%)	
Number of Metastases Prior to 1L Therapy, n (%)					<0.001
1	28 (41%)	47 (61%)	34 (30%)	47 (43%)	
2	15 (22%)	6 (7.8%)	26 (23%)	17 (16%)	
3+	10 (15%)	8 (10%)	32 (28%)	30 (28%)	
Unknown	15 (22%)	16 (21%)	21 (19%)	15 (14%)	
Somatic alt					
BRAF	20 (34%)	34 (45%)	47 (42%)	54 (50%)	0.230
NRAS	20 (30%)	21 (28%)	30 (27%)	22 (20%)	0.488
NF1	13 (19%)	19 (25%)	24 (21%)	19 (18%)	0.660

Significant associations between LAG3 status and immune biomarkers

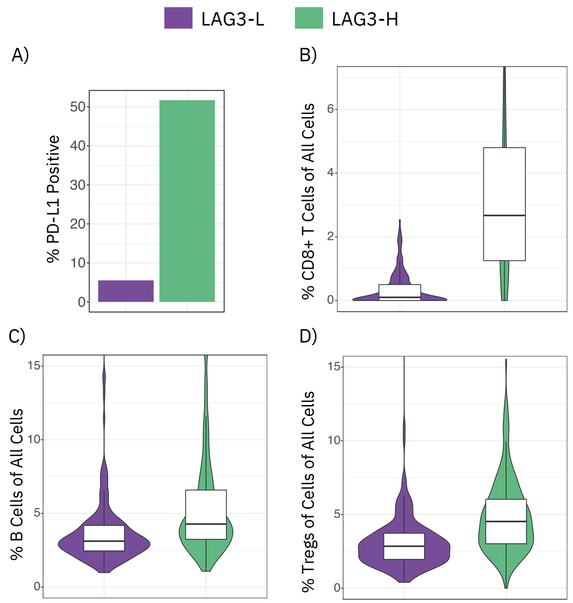

Figure 1. LAG3-H was associated with PD-L1+ status (LAG3-H 52% vs LAG3-L 5.5%) and higher proportions of adaptive immune cells, including CD8+ (2.7% vs 0.1%), B (4.3% vs 3.1%), and inhibitory Treg cells (4.5% vs 2.9%; p<0.001 for all). Innate immune cells (M1, M2 macrophages, NK cells, and neutrophils) were higher in pts with LAG3–H vs LAG3-L (p<0.001). Monocytes were higher in pts with LAG3-L vs LAG3-H (p<0.001).

rwORR in patients with LAG3-L vs. LAG3-H tumors treated with monotherapy and combination therapy

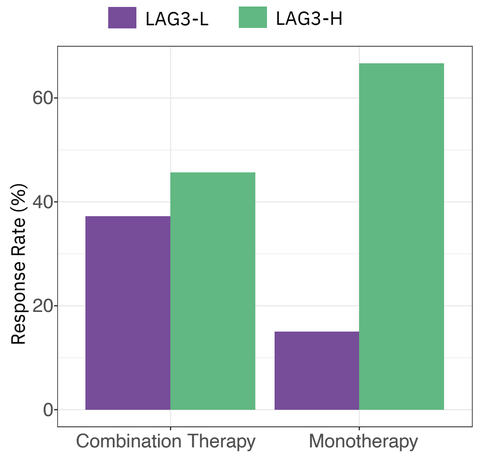

Figure 2. In the aPD1 cohort, LAG3-H (n=77) had higher rwORR vs LAG3-L (n=68; 67% vs 15%, p=0.002). In the aCTLA4/PD1 cohort, LAG3-H (n=109) had similar rwORR vs LAG3-L (n=113; 46% vs 37%, p=0.42).

rwOS following monotherapy vs combination therapy in patients with LAG3-L and LAG3-H tumors

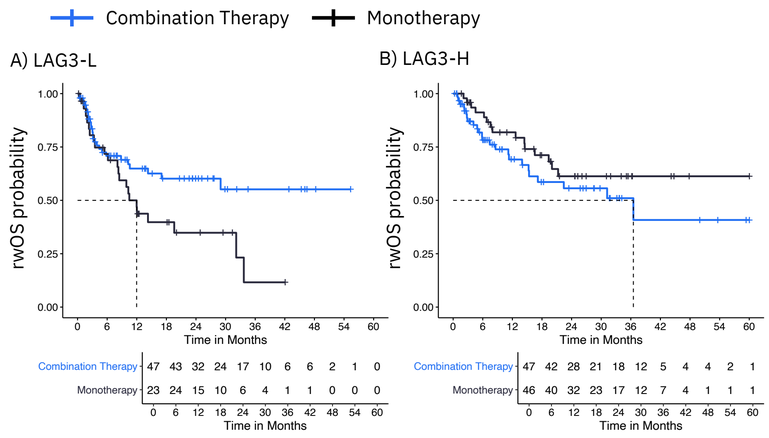

Figure 3. CoxPH analysis found a significant interaction between LAG3 and 1L ICIs on rwOS (p=0.02), suggesting the ICI effect on rwOS differs between LAG3-L and LAG3-H (p=0.02). In the LAG3-L group, pts treated with aPD1 had reduced rwOS compared to the aCTLA4/PD1 cohort (HR, 1.88, p=0.03), while in the LAG3-H group pts treated with aPD1 had numerically higher rwOS compared to the aCTLA4/PD1 cohort (HR, 0.67, p=0.2).

SUMMARY

- In this study, rwORR response rates were similar in LAG3-L and LAG3-H patients treated with anti-CTLA4 + anti-PD-1 combination therapy.
- In patients receiving anti-PD-1 monotherapy, LAG3-H patients had a higher rwORR than LAG3-low patients, pointing to the potential utility of LAG-3 as a biomarker in guiding therapy decisions.
- Our preliminary rwOS data indicate a greater benefit for combination anti-CTLA4 + anti-PD-1 therapy compared to anti-PD1 monotherapy in metastatic patients with low LAG3 expression.
- Prospective studies should validate these findings to confirm the optimal ICI regimens for LAG3-L vs. LAG3-H patients.

References

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