Characterization of PDLIM2 in Non-Small Cell Lung Cancer

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Introduction

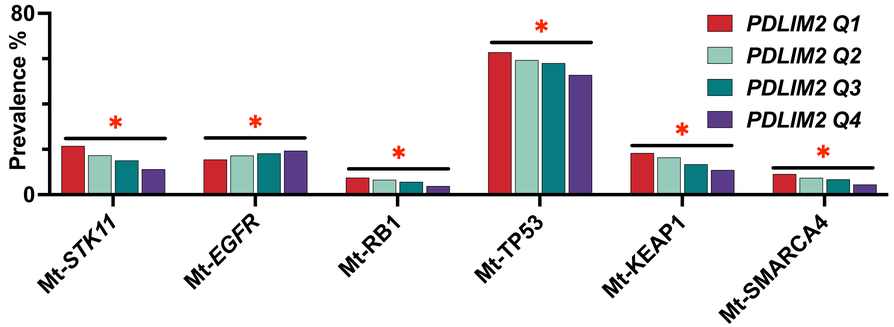
- PDZ and LIM domain protein 2 (PDLIM2) acts as tumor suppressor by downregulating NF-kB and STAT3 signaling, modulating inflammation, immune response, and cell survival.
- Mouse models have demonstrated that downregulation of *PDLIM2* leads to PD-1 immune blockade and chemotherapy resistance.
- We characterized the genomic and immunological landscape of *PDLIM2* expression in Adenocarcinoma non-small cell lung cancer (NSCLC).

Methods

- NextGen sequencing of DNA (whole exome)/RNA (whole transcriptome) was performed for NSCLC (Total N = 29126; Adenocarcinoma [-A, N = 15765]) patient tumors submitted to Caris Life Sciences (Phoenix, AZ).
- Mutations were defined as pathogenic SNVs/indels. Samples were stratified by *PDLIM2* expression quartiles (in transcripts per million [TPM]) for all NSCLC tumors (Q4: ^{H}, Q1: ^{L}).
- PD-L1 expression [22C3; Positive (+): tumor proportion score (TPS) ≥1%]was assessed by IHC.
- High tumor mutational burden (TMB-high) set as >=10 mutations per Mb. Cell infiltration in the tumor microenvironment was estimated by QuantiSEQ.
- Gene expression profiles were analyzed for transcriptional signatures predictive of response to immunotherapy (T cell-inflamed).
- Real-world overall survival was assessed from insurance claims data and Kaplan-Meier estimates were calculated for molecularly defined subpopulations.
- Mann-Whitney U and X^2/Fisher-Exact tests were applied where appropriate, with P-values adjusted for multiple comparisons ($p < 0.05$).

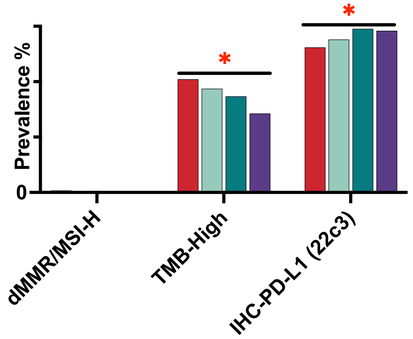
Results

Figure 1: NSCLC-Adenocarcinoma Mutational Profile by PDLIM2



PDLIM2-A^{L} had a lower prevalence of *EGFR* mutations than *PDLIM2*-A^{H} (15.5% vs 19.4%, $p < 0.01$), but the opposite pattern was observed for *STK11* (21.5% vs 11.2%), *RB1* (7.5% vs 3.8%), *TP53* (62.9% vs 52.8%), *KEAP1* (18.4% vs 10.9%), and *SMARCA4* (9.15 vs 4.5%) alterations (all $p < 0.001$).

Figure 2: NSCLC-Adenocarcinoma TMB/PD-L1

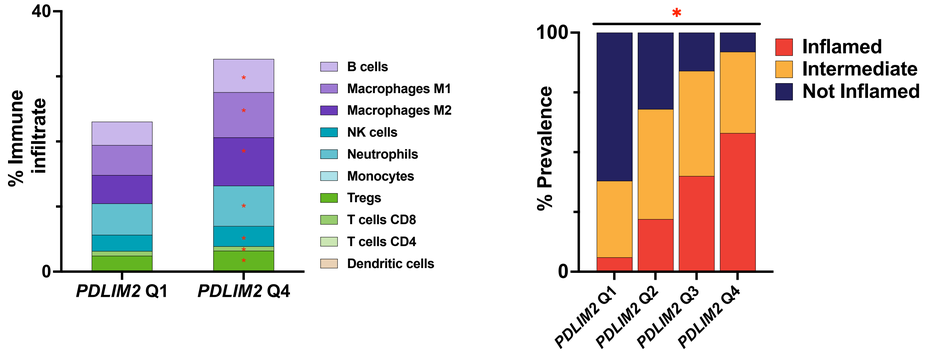


PDLIM2-A^{L} tumors had decreased PD-L1+ (L: 52.4% vs H: 58.4% $p < 0.001$) but increased TMB-High status (L: 40.9% vs H: 28.5%, $p < 0.001$).

CONCLUSIONS

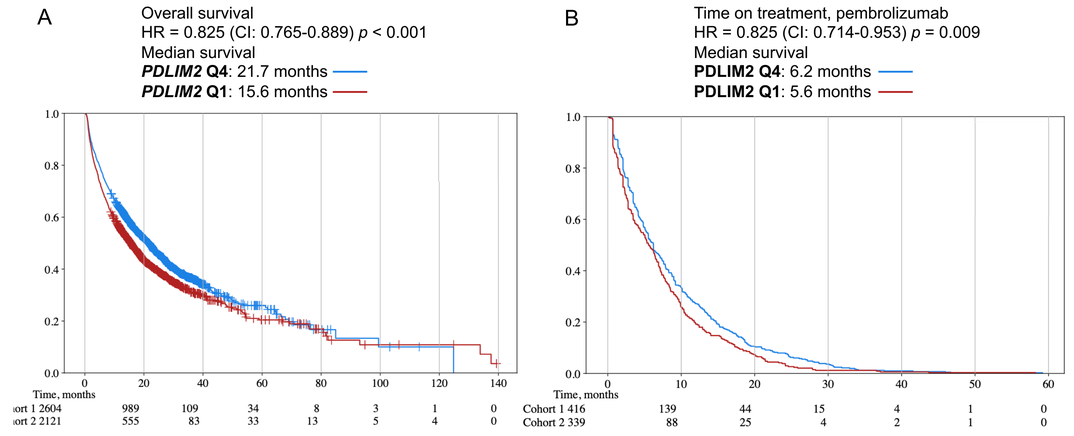
- **NSCLC-A with high PDLIM2 expression have a unique mutational profile, increased immune cell infiltration and favorable OS.**
- **Therapeutic strategies for targeting PDLIM2 to modulate NF-kB and STAT3 signaling should be further explored.**

Figure 4: NSCLC-Adenocarcinoma Immune cell infiltration & T-cell inflamed score



In both NSCLC-A, *PDLIM2*^{H} had increased infiltration of NK cells, macrophages, dendritic cells, T cells, neutrophils, monocytes, and B cells compared to PDLIM2^{L} (all $p < 0.05$, red asterisk indicates statistical significance and which quartile had a higher % infiltrate), in addition to increased T cell-inflamed score ($p < 0.001$).

Figure 5: NSCLC-Adenocarcinoma A) OS and B) Time on Treatment with Pembrolizumab



PDLIM2-A^{H} was associated with improved overall survival (OS) (median 21.7 vs L: 15.6 months; $p < 0.001$; Hazard ratio [HR] = 0.825, 95% Confidence Interval [CI] 0.765 – 0.889) and time on pembrolizumab treatment (median 6.2 vs L: 5.6 months; $p = 0.009$; HR = 0.825 95% CI 0.714 – 0.953).