Abstract #8531: PD-L1 and alternative immune checkpoints (AICs) in non-small cell lung cancer (NSCLC): Insights into the tumor immune microenvironment (TIME) and immunotherapy (IO) outcomes

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Background:

- We previously showed that HHLA2 is expressed in ~2/3 NSCLC and associated with EGFR mutation status (1), and that the majority of PD-L1 neg NSLCC express B7x and HHLA2 (2)
- We sought to explore patterns of PD-L1 and AICs within the TIME and impact on IO outcomes

Methods:

- 27,636 NSCLC samples analyzed (Caris Life Sciences) with NGS on DNA/RNA
- Gene expression profiles analyzed for IFN-γ score and QuantiSEQ used to assess the TIME
- Real-world overall survival (rwOS: from time of biopsy to last contact), time on treatment [TOT: from the first pembrolizumab (pembro) treatment to the last], and OS on pembro (OSpem: from pembro start to last contact) calculated
- Mann-Whitney U, X2/Fisher-Exact, and log-rank tests applied

Results:

- PD-L1 IHC+ and high PD-L1 RNA expressing NSCLC had higher IFN-γ score (Figure 1) and immune cell fractions (Figure 2) vs PD-L1 IHC- and low expressing NSCLC, respectively (p<0.0001 for all)
- PD-L1 IHC+ NSCLC was associated with higher median transcript levels (TPM) of PD-L1 and B7-H3, while PD-L1 IHC- NSCLC was associated with higher TPM of HHLA2 and B7x (p <0.0001 for all) (Figure 4)
- AIC expression varied significantly by molecular subtype (Figure 5)
- IO outcomes varied significantly by PD-L1 IHC/RNA and AIC RNA expression (Table 2, Figures 6)

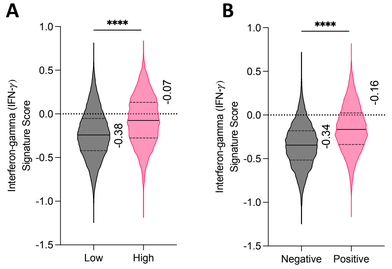
Table 1. Study demographics and AIC gene expression by site

Category	Samples
NSCLC samples, n	27636
Median Age, n (range)	69 (21- >89)
Sex	
Female, n (%)	13676 (49.5%)
Male, n (%)	13960 (50.5%)
Specimen Sites	**Count (n)**
Lung	16048 (58.1%)
Lymph node	3486 (12.6%)
Brain	1610 (5.8%)
Liver	1306 (4.7%)
Bone	1290 (4.7%)
Adrenal Gland	388 (1.4%)
Other metastatic sites*	3506 (12.7%)

*including but not limited to, kidney, breast, soft tissue, GI, Peritoneum, Retroperitoneum, Peritoneal Cavity, etc.

The unique expression profiles of alternative immune checkpoints identified in our study may represent *key subtypes that play a role in mediating the response to immunotherapy* in NSCLC.

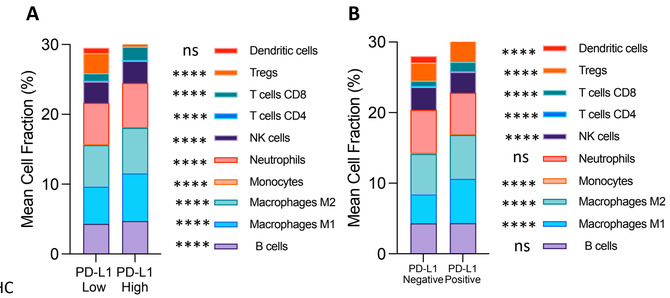
Figure 1. Interferon-gamma (IFN-γ) Signature Score



PD-L1 RNA expression (TPM)
Low: <0.25th percentile TPM
High: >0.75th percentile TPM

PD-L1 protein expression by IHC
Negative TPS <1%
Positive TPS ≥1%

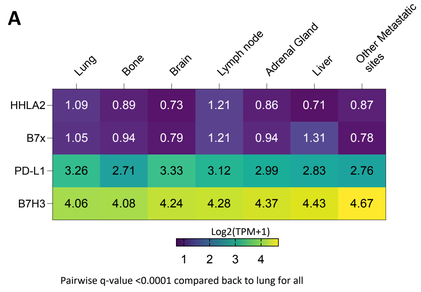
Figure 2. The immune cell microenvironment in PD-L1 expression by IHC and by whole transcriptomic sequencing



By WTS (RNA)

By IHC (Protein)

Figure 3. Gene expression analysis by specimen site



Pairwise q-value <0.0001 compared back to lung for all

Figure 4. AIC Expression by PD-L1 IHC status (22c3)

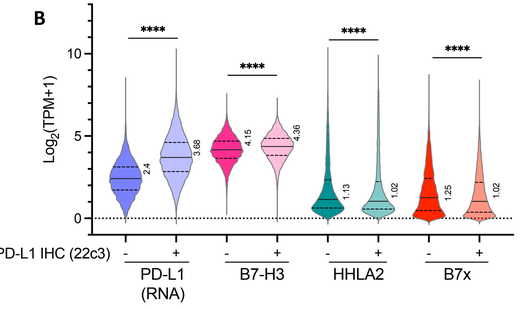


Figure 5. AIC Expression by Molecular Subtype

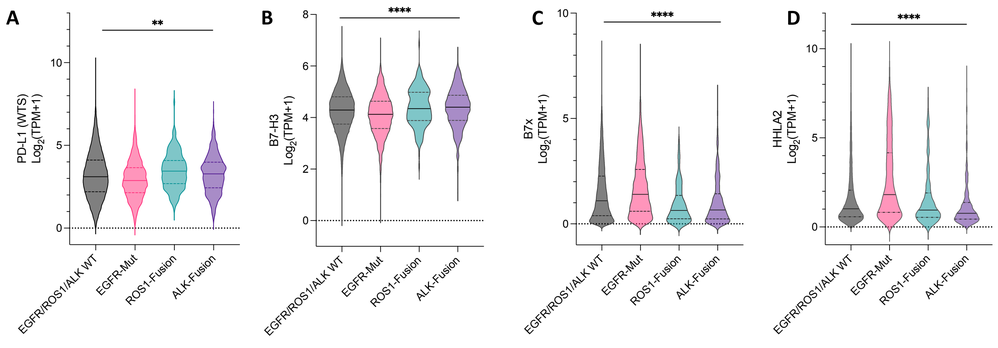


Table 2. IO Outcomes by PD-L1 and AIC Expression

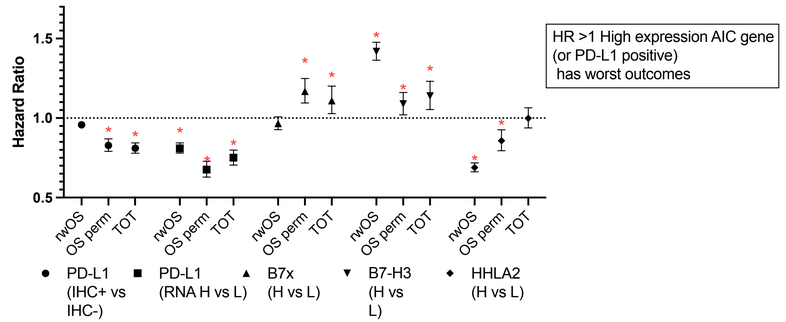
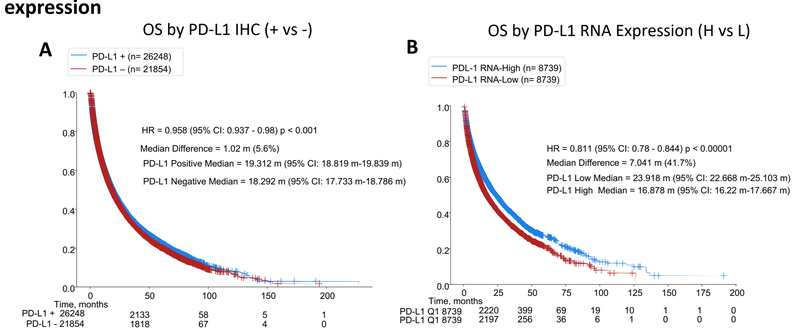


Figure 6. Overall survival from biopsy to last contact by PD-L1 IHC and RNA expression



Conclusions:

- Both PD-L1 IHC+ and high PD-L1 RNA NSCLC cases are associated with more inflammatory TIME, superior survival, and IO outcomes
- Consistent with our prior HHLA2 IHC work (1,2), HHLA2 RNA expression significantly higher in PD-L1 IHC- and EGFR mutant cases
- These findings support the potential utility of transcriptomics, along with protein expression, for assessing novel predictive biomarkers for IO

References:

1. Cheng H, et al. HHLA2, a New Immune Checkpoint Member of the B7 Family, Is Widely Expressed in Human Lung Cancer and Associated with EGFR Mutational Status. Clin Cancer Res. Feb 01 2017;23(3):825-832.
2. Cheng H, et al. Wide Expression and Significance of Alternative Immune Checkpoint Molecules, B7x and HHLA2, in PD-L1-Negative Human Lung Cancers. Clin Cancer Res. Apr 15 2018;24(8):1954-1964.

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