CD274 (PD-L1) gene expression and the 27-gene immuno-oncology (IO) assay are associated with efficacy to immune checkpoint inhibitor treated patients with non-small cell lung cancer

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Background

- Immune checkpoint inhibitors (ICIs) have become standard of care in NSCLC.
- Programmed death ligand-1 (PD-L1) as measured by immunohistochemistry (IHC) is an accepted biomarker for predicting response but has many limitations.
- PD-L1 IHC is intrinsically subjective due to the spatial and temporal heterogeneity within the tumor immune microenvironment (TIME) and lacks standardized scoring criteria.[1]
- The 27-gene IO assay (IO Score) is a gene expression panel which has recently been described as a classifier of the tumor immune microenvironment (TIME) and has demonstrated ability to predict response to immune checkpoint inhibitors (ICIs) across multiple indications.[2,3]

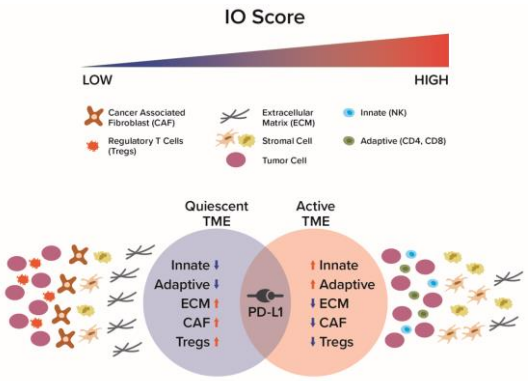


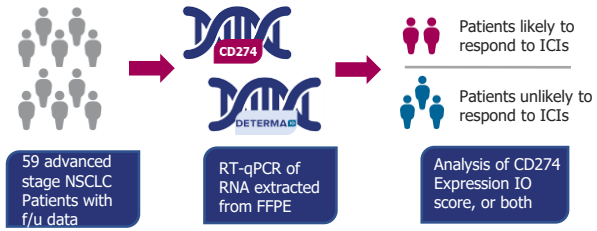
Figure 1 The IO score is a measure of both the quiescent and active states of the tumor immune microenvironment (TIME)

Aim

We sought to explore the utility of CD274 mRNA expression as a biomarker through the quantification of its association with ICI efficacy.

Methods

- Fifty-nine late-stage NSCLC FFPE specimens were obtained with 1-year PFS and PD-L1 IHC TPS (22C3) status.



- A generalized linear model was created using CD274 mRNA expression and PD-L1 IHC positivity (≥1%), then plotted to measure AUC.
- The threshold for CD274 mRNA expression was derived by maximizing specificity to PD-L1 IHC (CD274 High).
- Cox proportional hazard ratios (HRs) were calculated for IO score, PD-L1 IHC, and binary CD274 expression.
- A model combining IO score and CD274 at the 100% specificity threshold was also analyzed (CD274 High).

Cohort Demographics

Characteristic	Patients, n (%)	Characteristic	Patients, n (%)
Age at IO Therapy (years)		Type of Therapy	
≤50	2 (8%)	ICI Monotherapy	50 (85%)
51-60	11 (21%)	ICI + Chemotherapy	9 (15%)
61-70	20 (31%)	ICI therapy received	
> 70	26 (40%)	Nivolumab	26 (49%)
Sex		Pembrolizumab	31 (48%)
Female	27 (46%)	Nivo/Pembro	1 (1%)
Male	32 (54%)	Atezolizumab	1 (1%)
Race		IO Score	
African American	19 (30%)	Positive	32 (54%)
Caucasian	40 (70%)	Negative	27 (46%)
Disease Stage		PD-L1 TPS (≥1%)	
Stage 2[T]	2 (3%)	Positive	45 (67%)
Stage 3	8 (13%)	Negative	14 (21%)
Stage 4	49 (84%)		
Response Status			
Response (CR, PR)	37 (63%)		
Non-Response (PD, SD)	22 (37%)		

Results

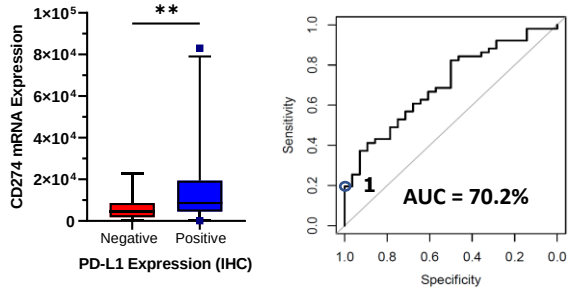


Figure 2: A) CD274 mRNA expression categorized by PD-L1 IHC positive (≥1%) or negative. CD274 measured by qPCR translated to expression by $2^{(40-Ct)}$. **p<0.005 **B)** ROC plot of generalized linear model of CD274 vs. PD-L1 IHC positivity. 1) The point of maximal specificity of CD274 expression to PD-L1 IHC (CD274 mRNA).

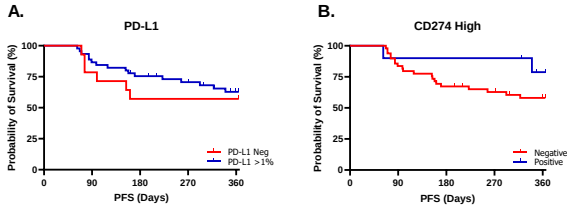


Figure 3: K-M plots estimating probability of 1-yr PFS. A) PD-L1 IHC HR=0.76; p=0.6; 45/59 positive, B) CD274-High HR=0.41; p=0.2; 10/59 positive.

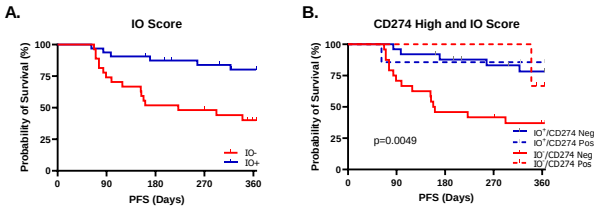


Figure 4: K-M plots estimating probably of PFS. A) IO Score HR=0.24; p=0.001; 32/59 positive B) Bivariate model of IO Score and CD274 High (IO Score HR=0.24; p=0.003; CD274 High HR=0.45; p=0.28; logrank for model p=0.0049). These data show independence of IO score from CD274 High.

Results

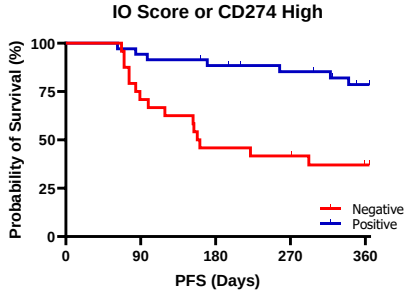


Figure 4: K-M plot estimating probability of PFS up to one year for IO Score or CD274-High HR=0.22; p=0.0003; 35/59 positives.

Conclusion

- Quantification of CD274 mRNA expression is correlated with PD-L1 IHC expression.
- The CD274 High mRNA expression threshold found a modest improvement over PD-L1 IHC alone but did not reach significance.
- Combining IO Score with highly specific CD274 mRNA expression threshold (super expressors) led to modest improvement in its association with one-year PFS.
  - There is a subgroup of 3 patients who were CD274 High but IO score negative and responded to ICI therapy. These data may suggest biological subgroup with checkpoint inhibition.
- Together these data demonstrate that measuring CD274 mRNA may help to better inform clinical decision making when paired with IO Score compared to PD-L1 IHC alone.

References

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2. Nielsen, T.J.; et. al. A novel immuno-oncology algorithm measuring tumor microenvironment to predict response to immunotherapies. *Heliyon*. 2021.
3. Iwase, T; et. al. A Novel Immunomodulatory 27-Gene Signature to Predict Response to Neoadjuvant Immunochemotherapy for Primary Triple-Negative Breast Cancer. *Cancers*. 2021.