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PD-L1 By Next Generation RNA-sequencing: Comparison with PD-L1 IHC 22C3 and Association with Survival Benefit from Pembrolizumab With or Without Chemotherapy in Non-small Cell Lung Cancer.

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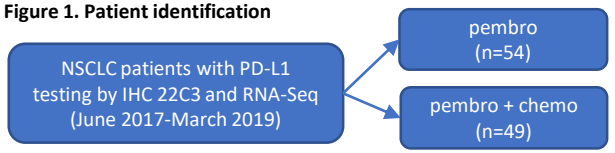
INTRODUCTION

PD-L1 testing by immunohistochemistry (IHC) is critical for checkpoint inhibition treatment selection in NSCLC, yet suboptimal for predicting patient clinical benefit from these therapies. To date, PD-L1 liquid biopsy lacks clinical validity and sensitivity. Alternatively, PD-L1 testing by next generation RNA-sequencing potentially offers a more robust, tissue-efficient, scalable clinical solution to identifying NSCLC patients who are likely to benefit from checkpoint blockade [1].

METHODS

NSCLC patients whose tumors underwent simultaneous PD-L1 testing by both IHC and RNA-seq as part of a comprehensive immune profiling panel and treated by pembrolizumab monotherapy or in combination with chemotherapy post-test. All testing was performed in a CAP and CLIA certified laboratory as part of standard care.

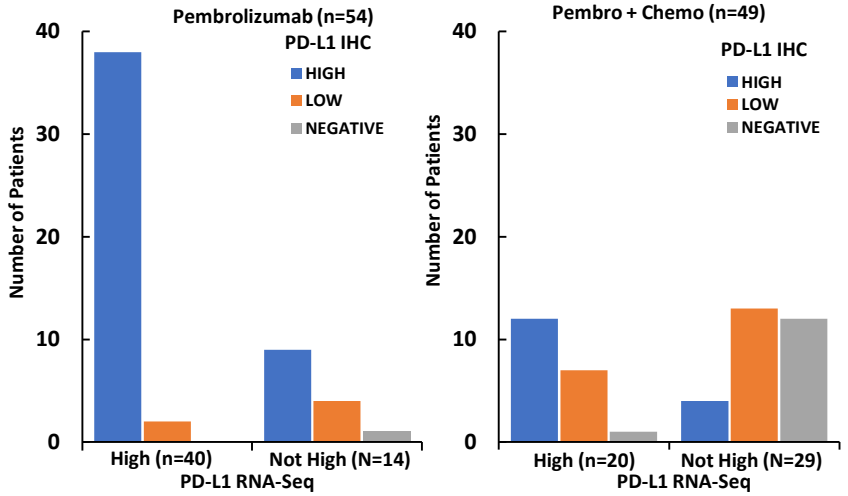
Figure 1. Patient identification



- PD-L1 IHC 22C3 companion diagnostic testing was assessed following scoring guidelines for tumor proportional score (TPS) clinical cutoffs: ≥50% (high); 1-49% (low), 0% (negative)
- PD-L1 by RNA-seq, was measured as a percentile rank relative to a reference population and normalized to a continuous value of 1-100, and categorically: ≥75 (high); <75 (not high)

Figure 2: Concordance of PD-L1 RNA-Seq to IHC 22C3 at Clinical Cut Offs

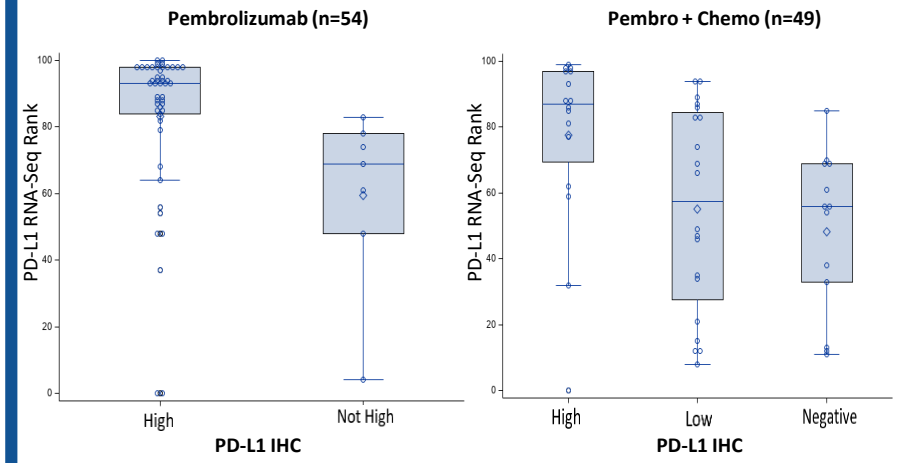
A. PD-L1 RNA-Seq as a Categorical Variable



Proportion analysis using Fisher exact test comparing IHC versus RNA-seq, and Bonferroni pairwise post-hoc analysis of IHC with RNA-seq.

- More than 75% of IHC high cases were also classified as high by RNA-Seq for both treatment groups (p<0.001).

B. PD-L1 RNA-Seq as a Continuous Variable



Kruskal Wallis test performed to assess whether PD-L1 RNA rank distributions differed by PD-L1 IHC cut-off

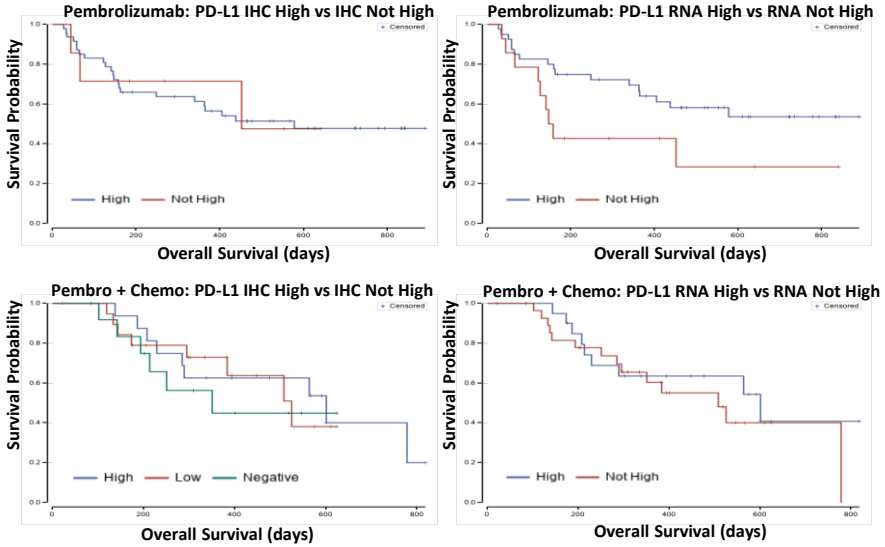
- Median PD-L1 measured by RNA-seq was significantly different between PD-L1 IHC high versus not high status (p<0.001).

Figure 3: NSCLC Patient Survival By Treatment and Marker Status

A. Hazard Ratios by Treatment and Marker Status

Therapy	Marker	HR (95%CI)	P-Value
Pembrolizumab	PD-L1 IHC High vs IHC Not High	0.66 (0.13-3.47)	0.63
	PD-L1 RNA High vs RNA Not High	0.25 (0.08-0.82)	0.02
Pembro + Chemo	PD-L1 IHC High vs IHC Low	0.71 (0.04-11.7)	0.81
	PD-L1 IHC High vs IHC Negative	0.11 (0.01-4.30)	0.24
	PD-L1 IHC Low vs IHC Negative	0.15 (0.05-4.11)	0.10
	PD-L1 RNA High vs RNA Not High	0.77 (0.15-4.06)	0.76

B. Kaplan Meier Survival Curves by Treatment and Marker Status



Cox regression analysis was performed for treatment HR prediction by PD-L1 IHC or PD-L1 RNA-Seq status, controlling for potential covariates: age, sex, smoking comorbidity index, performance status, treatment line, prior treatment types, and co-occurring genomic alterations. No covariates were significant.

Pembrolizumab monotherapy: PD-L1 RNA-seq high versus not high status was associated with improved overall survival (p=.02), however, PD-L1 IHC high versus RNA not high status showed no association with survival benefit.
Pembrolizumab + chemotherapy: Neither IHC (high versus low), nor RNA-seq (high versus not high) status was associated with survival benefit

CONCLUSIONS:

Measurement of PD-L1 status by RNA-seq and IHC appear to be comparable. Unlike PD-L1 IHC however, PD-L1 RNA-seq high status versus not high status is associated with greater survival benefit, indicating PD-L1 by RNA-seq may have utility for pembrolizumab selection.

REFERENCES:

1. Conroy et al. PMID: 30678715