Comprehensive genomic and immune profiling defines immunotherapy treatment in NSCLC patients with low PD-L1 IHC

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Background:

- There is highly unmet need for an immunotherapy predictive biomarker strategy that addresses the complexity of the tumor microenvironment and immune escape mechanisms in non-small cell lung cancer (NSCLC).
- Novel biomarkers for NSCLC : tumor inflammation (TIGS), cell proliferation (CP), and cancer testis antigen burden (CTAB) have previously been shown to provide independent measures of inflammation, proliferative capacity, and cancer testis antigen co-expression, respectively.
- Here, we applied a comprehensive genomic and immune profiling (CGIP) strategy that includes these novel markers to identify distinct NSCLC subgroups with potentially differential benefit for single agent or combination ICI treatment strategies.

Methods:

- A discovery cohort (DC) of 5450 tumors across 37 histologies were evaluated by comprehensive genomic and immune profiling of the tumor immune microenvironment[1] (Figure 1).
- Individual and combination biomarker assessment included PD-L1 IHC (% TPS), TMB[1], tumor inflammation (TIGS)[2], cell proliferation (CP)[2] and cancer testis antigen burden (CTAB)[3].
- Principle component analysis (PCA) and unsupervised clustering of the DC identified four sample phenotypes: Tumor Dominant, Proliferative, Inflamed, and Checkpoint (Figure 2).
- From the DC, combinations of molecular and immune biomarkers were identified and applied to a retrospective cohort (RC) of 225 metastatic NSCLC patients treated with pembrolizumab + chemotherapy or pembrolizumab alone to correlate with treatment response.
- Comparison of objective response rates (ORR) was performed using Chi-square test. Kaplan-Meir analysis was performed to test for differences in overall survival (OS) and 1-year OS (Figure 3 and 4).

References:

1. Conroy JM, Pabla S, Glenn ST, et al. Analytical validation of a next-generation sequencing assay to monitor immune responses in solid tumors. The Journal of Molecular Diagnostics. 2018;20(1):95.
2. Pabla S, Seager RJ, Van Roey E, et al. Integration of tumor inflammation, cell proliferation, and traditional biomarkers improves prediction of immunotherapy resistance and response. Biomark Res. 2021;9(1):56.
3. Pabla S, Seager R, Lee YH, et al, Cancer testis antigen burden: A novel predictive biomarker for immunotherapy in solid tumors. Journal for ImmunoTherapy of Cancer 2021;9:doi: 10.1136/jitc-2021-SITC2021.080

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Comprehensive genomic and immune profiling identify PD-L1 low NSCLC patients who benefit from single agent pembrolizumab.

- *PD-L1 low NSCLC patients with a proliferative phenotype may benefit from single agent pembrolizumab.*
- *Whereas PD-L1 low NSCLC cases with an inflamed phenotype may benefit from both single agent and combination pembrolizumab.*

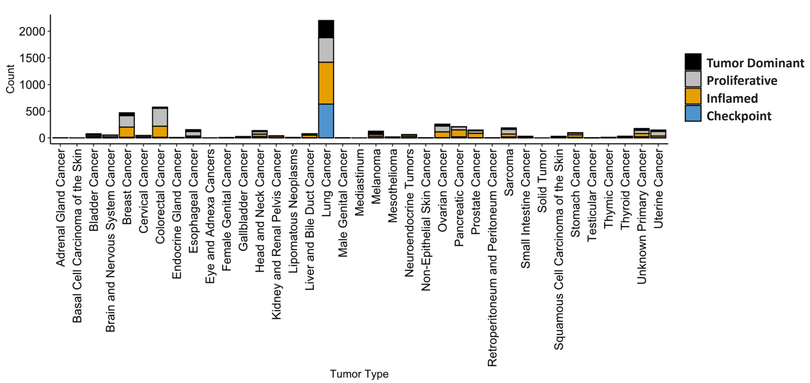

Figure 1. Distribution of Discovery Cohort phenotypes within tumor type.

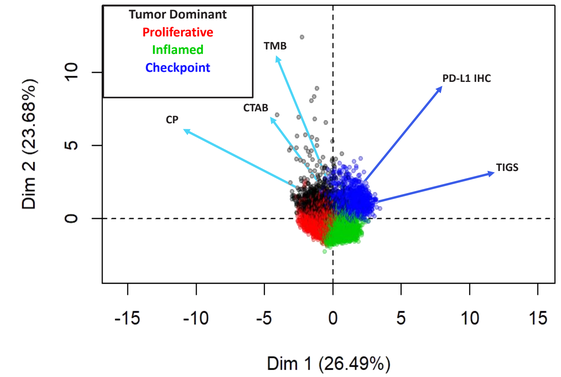

Figure 2. PCA individual and variable plot describing four unsupervised clusters of sample phenotypes from the discovery cohort and the variables driving the clusters include CP, CTAB, PD-L1 IHC, TMB, and TIGS

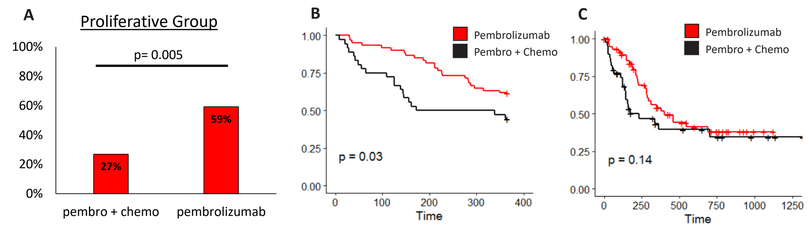

Figure 3. Patients in the proliferative group (35.1%, 79/225; median PD-L1 = 20% TPS) treated with single agent pembrolizumab showed **A.** significantly higher ORR (59%; 16/27) compared to pembrolizumab + chemo (27%; 14/52; p=0.005); **B.** significantly higher 1 year OS compared to pembrolizumab + chemo (p=0.03); **C.** trend towards higher OS compared to pembrolizumab + chemo (p=0.14)

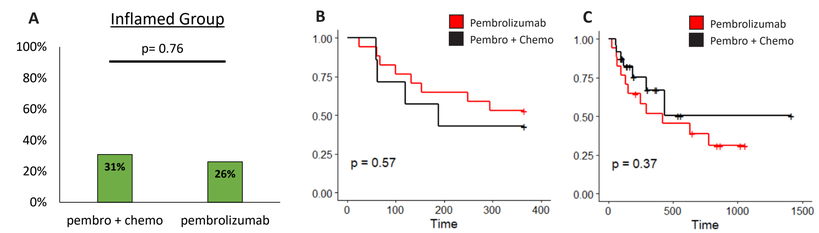

Figure 4. Patients in the inflamed group (16%, 36/225; median PD-L1 = 1% TPS), suggested that **A.** pembrolizumab + chemo (ORR 26.1%; 6/23) was not associated with ORR compared to pembrolizumab (ORR 31%; 4/13, p = 0.76); **B.** treatment selection was not associated with 1 year OS (p=0.57); **C.** group treatment selection was not associated with OS (p=0.37)

Future Directions:

Although further clinical validation of these predictive biomarker combinations is required, this data-driven approach demonstrates the potential of CGIP to provide treatment decision support when selecting an ICI therapeutic strategy in lung cancer.