From Smoke to Signaling: Linking Tobacco Exposure to Tumor Immunogenicity in Black Patients with Non Small Cell Lung Cancer (NSCLC)

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Introduction

- Commercial tobacco use remains the leading cause of preventable death in the United States
- Despite national declines, Michigan continues to have one of the highest adult smoking rates (18.9%)
- From 1985-2018, 142,000 Michigan residents were diagnosed with non-small cell lung cancer (NSCLC), highlighting the ongoing public health burden of tobacco exposure in the state
  - Smoking induces distinct molecular alterations in lung tumors contributing to biologically and histologically distinct NSCLC subtypes
  - Modern NSCLC management relies on immunologic and molecular biomarkers to guide therapy
    - Programmed death-ligand 1 (PD-L1) expression and tumor mutational burden (TMB) play central roles in predicting response to immune checkpoint inhibitors such as pembrolizumab
- Elevated TMB* is associated with increased neoantigen formation and enhanced tumor immunogenicity, particularly when PD-L1 expression is low or equivocal (Fig.1)
- High PD-L1** expression (≥50%) supports first-line pembrolizumab monotherapy, while intermediate expression (1–49%) may guide combination regimens (Fig.2)

- Understanding how smoking history influences biomarkers may refine treatment selection, improve prognostication, and reduce unnecessary toxicity.
- The relationship between smoking intensity + duration and immunotherapy-relevant biomarkers remains underexplored in Black patients with NSCLC, a population historically underrepresented in molecular oncology research.
- Exploration may support precision oncology, inform biomarker-guided treatment strategies, and guide the development of tailored smoking cessation interventions for lung cancer patients.

* TMB represents the total number of somatic mutations within a tumor genome. Higher TMB increases neoantigen formation, enhancing tumor immunogenicity and response to immune checkpoint inhibitors. TMB is particularly informative when PD-L1 expression is low or intermediate and serves as a complementary biomarker for immunotherapy selection.

** PD-L1 is an immune regulatory protein expressed on tumor and immune cells that suppresses T-cell activation through PD-1 signaling, enabling immune evasion. Immune checkpoint inhibitors (e.g., pembrolizumab) block this pathway and restore antitumor immunity. Higher PD-L1 expression is associated with improved response to PD-1/PD-L1–targeted therapies and guides treatment selection in NSCLC.

We hypothesize that greater smoking exposure is associated with higher tumor mutational burden and altered PD-L1 expression in Black patients with NSCLC, with increasing smoking intensity and duration correlating with more immunogenic tumor profiles.

Primary Aim

To evaluate the association between smoking status and tumor mutational burden (TMB) and PD-L1 expression in Black patients with NSCLC.

Secondary Objectives

1). To assess the impact of smoking intensity (pack-years) and duration on molecular tumor characteristics

2). To explore how smoking-related biomarker profiles may inform immunotherapy selection and prognostication

3). To establish preliminary data for future prospective studies examining smoking-driven resistance mechanisms and therapeutic response

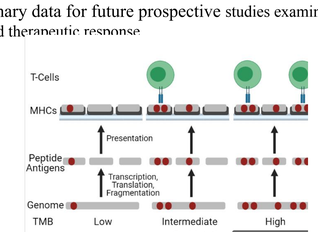

Figure 1: High TMB association with greater T-cell recognition via neoantigens

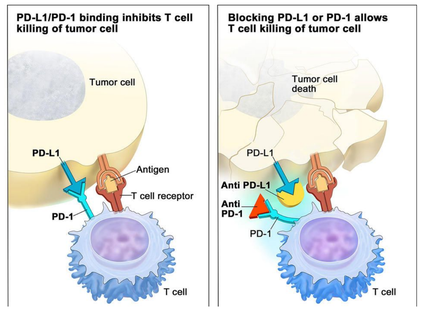

Figure 2: PD-L1 and T-cell tumor interactions

Methods

Retrospective cohort study of patients with NSCLC evaluated at Corewell Health Royal Oak Hospital. Clinical, pathologic, and molecular data were extracted from the EMR.

Patient inclusion:

- ❑ Self-identified as African American/Black
- ❑ Confirmed diagnosis of NSCLC by pathology and/or molecular testing
- ❑ Evaluated between June 2019 and June 2023
  Had available smoking history and next-generation sequencing (NGS) results

Variables collected:

- ❑ Demographics: date of birth, sex, race
- ❑ Smoking history: smoking status (current, former, never), packs per day (PPD), pack-years
- ❑ Tumor characteristics: histology, grade, stage, primary tumor location
  Molecular markers: PD-L1 expression, tumor mutational burden (TMB; mutations/Mb), microsatellite instability (MSI %), and NGS mutation categories

Demographic baseline:

- Sample size (n) = 33 (17 female, 16 male)
- 6 current smokers, 24 former smokers, 3 never smokers (~10%)
- Average pack years for smokers ~ 31 years
- Most prevalent histology was adenocarcinoma (90%), followed by squamous cell carcinoma (6.1%)
- Most common locations were RUL (33.3%) and LUL (30.3%)
- 50% of cases were Stage IV, followed by Stage IIIA; few Stage II

Results

- **Stage IV NSCLC patients demonstrated a significant positive association between smoking exposure and TMB (***Spearman ρ = 0.58, p = 0.02)***
  - This relationship was **not observed** in Stage I–III disease or in the overall cohort
- **No significant association** between pack-years and PD-L1 expression
  - Across all stages, sexes, and smoking categories

Both correlation and linear regression analyses were non-significant

- **Inverse relationship between pack-years and MSI**
  - Higher smoking exposure correlated with **lower MSI percentages**
  - Strongest effect observed in **male patients**

Figure 3: TMB vs. Pack Years by Stage

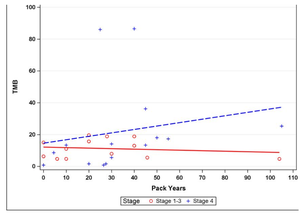

Figure 4: TMB vs. Pack Years (Stage 4)

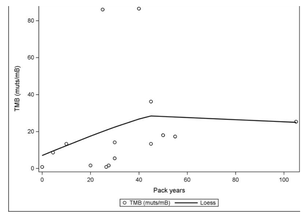

Figure 5: PD-1 vs. Pack Years by Stage

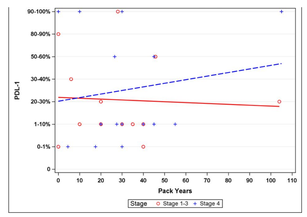

Figure 6: PDL-1 vs Pack Years by Sex

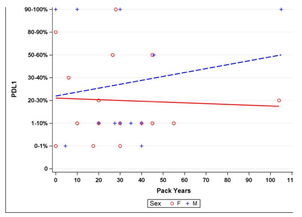

Figure 7: MSI vs. Pack Years by Stage

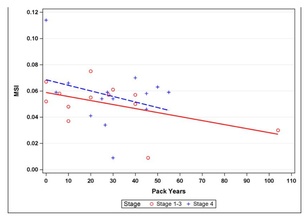

Figure 8: MSI vs. Pack Years by Sex

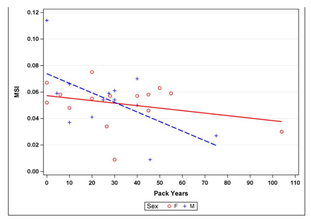

Table 1: Relationship Between TMB and Pack Years

Group	Spearman ρ (p-value)	Linear β per 10 pack-years (95% CI, p-value)
Overall	0.27 (0.16)	0.76 (-2.05 – 3.57, p = 0.60)
Stage 1-3	0.03 (0.93)	-0.32 (-1.47 – 0.82, p = 0.58)
Stage 4	0.58 (0.02)	2.15 (-3.30 – 7.60, p = 0.44)
Females	0.21 (0.45)	0.30 (-1.36 – 1.97, p = 0.72)
Males	0.34 (0.24)	1.15 (-4.19 – 6.50, p = 0.67)

Conclusions

In summary, among Stage IV patients, there was a moderate positive monotonic association between TMB and smoking exposure (Spearman ρ = 0.58, p = 0.02).

In linear regression, the estimated mean increase in TMB per 10 pack-years was 2.15 (95% CI: −3.3 to 7.6, p = 0.44). The discrepancy suggests that the relationship may be non-linear or influenced by a few extreme observations rather than a consistent linear increase across the full range of pack-years.

Interpretation:

TMB may increase with smoking intensity, driven by tumor evolution and genomic instability

Relationship may reflect threshold effects or outlier exposures

Biomarker insights:

Tobacco-related tumors show high TMB without corresponding MSI elevation & Variable PD-L1 expression highlights need for multimodal biomarker assessment MSI alone may underestimate immunotherapy potential

Clinical relevance:

- Smoking history may help contextualize TMB, especially when PD-L1 is low/intermediate
- May serve as a clinical surrogate for immunogenicity when genomic testing is delayed
- Aligns with CheckMate 227 and KEYNOTE-042, showing immunotherapy benefit with high TMB despite modest PD-L1

Equity & future directions:

Highlights need to expand molecular testing access in underserved populations Supports investigation of serial genomic profiling and dynamic biomarkers in advanced NSCLC

Limitations of incomplete molecular data availability for all patients and a geographically restricted sample group

References

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