ImmunoDriver-1: Driver Alterations and their Immunological Implications in Early and Metastatic Non-Small Cell Lung Cancer (NSCLC)

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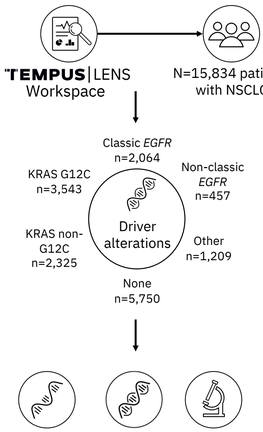
INTRODUCTION

NSCLC treatments and clinical trials include targeted agents and immunotherapy (IO) across stages, yet driver alterations and how they relate to the tumor immune microenvironment (TIME) are incompletely characterized in early NSCLC (eNSCLC; stage I-III) and metastatic NSCLC (mNSCLC; stage IV). Here, we evaluated the NSCLC TIME by driver alteration status to inform immunotherapy biomarker strategies.

METHODS



De-identified NSCLC samples sequenced by the Tempus xT DNA assay (eNSCLC n=5,535; mNSCLC n=10,299) were selected. A subset were also evaluated by Tempus xR whole-transcriptome analysis.

Driver alterations were evaluated across the cohort. Classic EGFR - L858R and exon 19 del; Other - *ALK*, *ROS1*, *RET*, *NTRK1-3* fusions, *ERBB2* alt, *MET*ex14.

Immune cell proportions were estimated by quanTIseq from RNA-seq, PD-L1 was evaluated by IHC, and tumor mutational burden (TMB; mut/Mb) was calculated from DNA-seq.

Analyses were stratified by driver alteration status and stage. Significance ($p<0.05$) was assessed using chi-squared or Wilcoxon/Kruskal- Wallis rank sum tests.

SUMMARY

- This real-world analysis demonstrated similar driver alteration prevalence across eNSCLC and mNSCLC, while the TIME was distinct across stages and driver alterations.
- TIMEs of *KRAS* G12C-altered tumors and tumors without driver alterations were similar, while *EGFR* tumors were the least immunogenic.
- These findings highlight immunological differences across stages and driver alterations that should be considered when developing immunotherapy strategies.

RESULTS

Cohort Overview

Characteristic	eNSCLC, n=5,535	metNSCLC, n=10,299
Age at diagnosis	69 (63, 75)	68 (61, 75)
Sex, n (%)		
Female	3,176 (57%)	5,332 (52%)
Male	2,359 (43%)	4,967 (48%)
Race, n (%)		
White	3,153 (57%)	5,366 (52%)
Unknown	1,613 (29%)	3,318 (32%)
Black or African American	412 (7.4%)	840 (8.2%)
Other Race	225 (4.1%)	444 (4.3%)
Asian	132 (2.4%)	331 (3.2%)
Ethnicity, n (%)		
Not Hispanic or Latino	2,703 (95%)	4,445 (93%)
Hispanic or Latino	144 (5.1%)	334 (7.0%)
Unknown	2,688	5,520
Smoking status, n (%)		
Ex-smoker	2,031 (37%)	3,192 (31%)
Unknown	1,491 (27%)	3,036 (29%)
Current-smoker	1,169 (21%)	2,393 (23%)
Never-smoker	844 (15%)	1,678 (16%)

Driver alterations in eNSCLC and metNSCLC

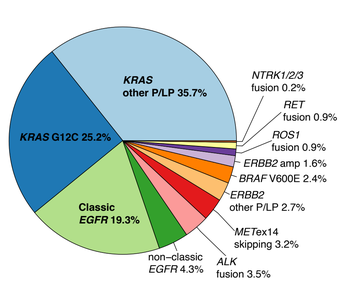


Figure 1. *KRAS* and *EGFR* driver alteration prevalences were similar across early and late-stage NSCLC.

CD8 T cell infiltration by stage

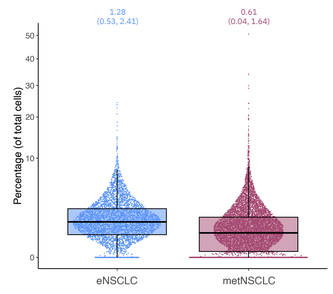


Figure 2. The proportion of CD8 T cells was higher in eNSCLC than mNSCLC ($p<0.001$). Median % (Q1, Q3) is shown above each column.

Immune infiltrate proportions by driver alteration status

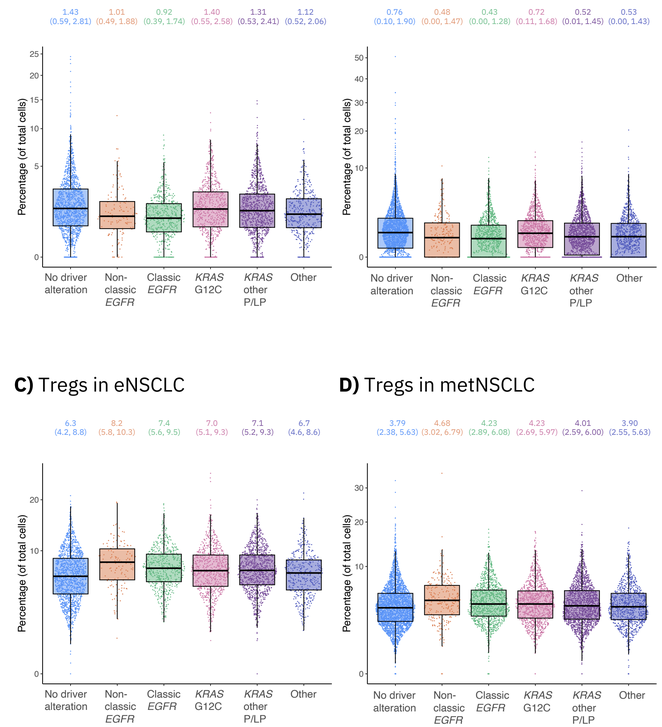


Figure 3. CD8 proportions in the *KRAS* G12C-altered cohort were nearly identical to the non-driver alteration cohort, while classical and non-classical *EGFR*-altered tumors exhibited the lowest proportion of CD8 T cells and highest proportion of Tregs. Median % (Q1, Q3) is shown above each column.

Common immunotherapy molecular markers by driver alteration status

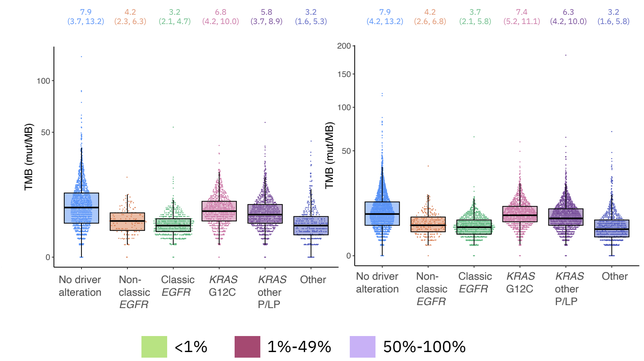


Figure 4. TMB (A,B) and PD-L1 (C,B) were similar between tumors with *KRAS* G12C alterations and tumors without driver alterations. TMB and PD-L1 were lowest among classical and non-classical *EGFR*-mutated tumors ($p<0.001$ for both). Median (Q1, Q3) TMB (mut/Mb) is shown above each column. Proportion of patients with the indicated TPS are shown within the bars for PD-L1.

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