Poster 181

Associations between multimodal immune biomarkers and clinical outcomes in a real-world non-small cell lung cancer cohort

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INTRODUCTION

Established biomarkers of immune checkpoint inhibitor (ICI) response in metastatic non-small cell lung cancer (mNSCLC), such as PD-L1 and tumor mutational burden (TMB), do not identify all patients with durable response. While biomarkers spanning multiple data modalities have been proposed to address this unmet need, additional evidence is required for use in the clinic. Here, we performed a comparative study assessing the association between previously described biomarkers of ICI response and outcomes in a real-world mNSCLC cohort.

METHODS

Cohort generation

Using the Tempus Database, de-identified records of non-squamous *EGFR*-negative and *ALK* fusion-negative mNSCLC patients treated with first-line ICI regimens and profiled with targeted-panel DNA-seq and whole-exome-capture RNA-seq were selected for analysis.

ICI biomarker selection and implementation

ICI-related biomarkers were calculated following published methods using the Tempus IO™ platform (Table 1).

Table 1. ICI-related biomarkers assessed using the Tempus IO™ platform.

Biomarker	Data Source	Reference
APOBEC SBS 2, SBS 13	DNA	Alexandrov, Nature 2013
Smoking SBS 4	DNA	Alexandrov, Nature 2013
TLS	RNA	Andersson, Nat Comms 2021
IMPRES score	RNA	Auslander, Nat Med 2018
IFNgamma TIS	RNA	Ayers, JCI 2017
IFN gamma score	RNA	Beaubier, Nat Biotech 2019
STK11, *KEAP1* mutations	DNA	Biton Clin Cancer Res 2018, Skoulidis Cancer Disc 2018
TLS	RNA	Cabrita, Nature 2020
HLA-LOH	DNA	Chowell, Science 2018
TLS Chemokine	RNA	Coppola, Am J Pathol 2011
Angiogenesis	RNA	Cristescu, Clin Cancer Res 2022
gMDSC	RNA	Cristescu, Clin Cancer Res 2022
mMDSC	RNA	Cristescu, Clin Cancer Res 2022
Glycolysis	RNA	Cristescu, Clin Cancer Res 2022
Hypoxia	RNA	Cristescu, Clin Cancer Res 2022
Proliferation	RNA	Cristescu, Clin Cancer Res 2022
Stroma	RNA	Cristescu, Clin Cancer Res 2022
NRS Score	RNA	Huang, Nat Med 2019
Immune resistance program	RNA	Jerby-Arnon, Cell 2018
Cytotoxic Score	RNA	Lau, Nat Comms 2022
CXCL9	RNA	Litchfield, Cell 2021
HLA Promiscuity score	DNA	Manczinger, Nat Cancer 2021
Immune Score	RNA	Roh, Sci Trans Med 2017
Cytolytic Index	RNA	Rooney, Cell 2015
T cell exhaustion score	RNA	Sade-Feldman, Cell 2018
MIRACLE score	RNA	Turan, BJC 2020
APM score	RNA	Thompson, J Immunother Cancer 2020
IRS model	RNA+DNA	Tomlins, Commun Med 2023
T cell resilience	RNA	Zhang, Nat Med 2022

Outcomes analysis

Real-world time to progression (rwTTP) was defined as the interval from ICI start to the first progression event, censored on last known physician encounter. Cox proportional hazards (Cox PH) models were fitted to evaluate the relationship between each biomarker and rwTTP as a single feature. A second, multivariable Cox PH model included TMB status and PD-L1 IHC. To facilitate direct comparison of HR, all biomarkers were min-max scaled prior to Cox PH regression.

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SUMMARY

- RNA-based immune signatures are significantly associated with improved progression outcomes and may supplement well-established ICI biomarkers (TMB, PD-L1 IHC) in therapy selection, following prospective validation in future studies.
- Many RNA signatures are well correlated, suggesting a shared or overlapping immune inflammatory signal in bulk RNA-seq from mNSCLC tumors.

RESULTS

Overview of a real-world metastatic NSCLC cohort

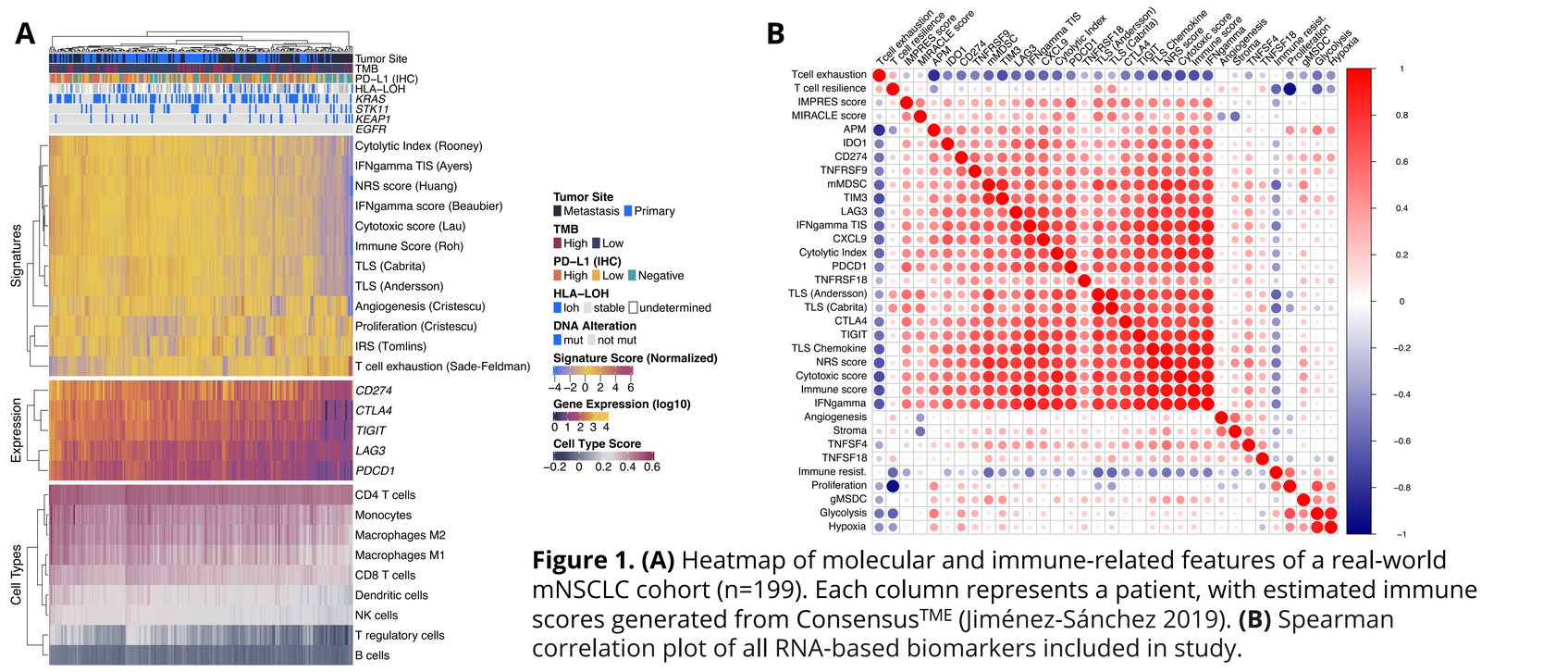

Figure 1. (A) Heatmap of molecular and immune-related features of a real-world mNSCLC cohort (n=199). Each column represents a patient, with estimated immune scores generated from Consensus™ (Jiménez-Sánchez 2019). **(B)** Spearman correlation plot of all RNA-based biomarkers included in study.

RNA-based signatures and immune checkpoint genes are frequently associated with patient outcomes

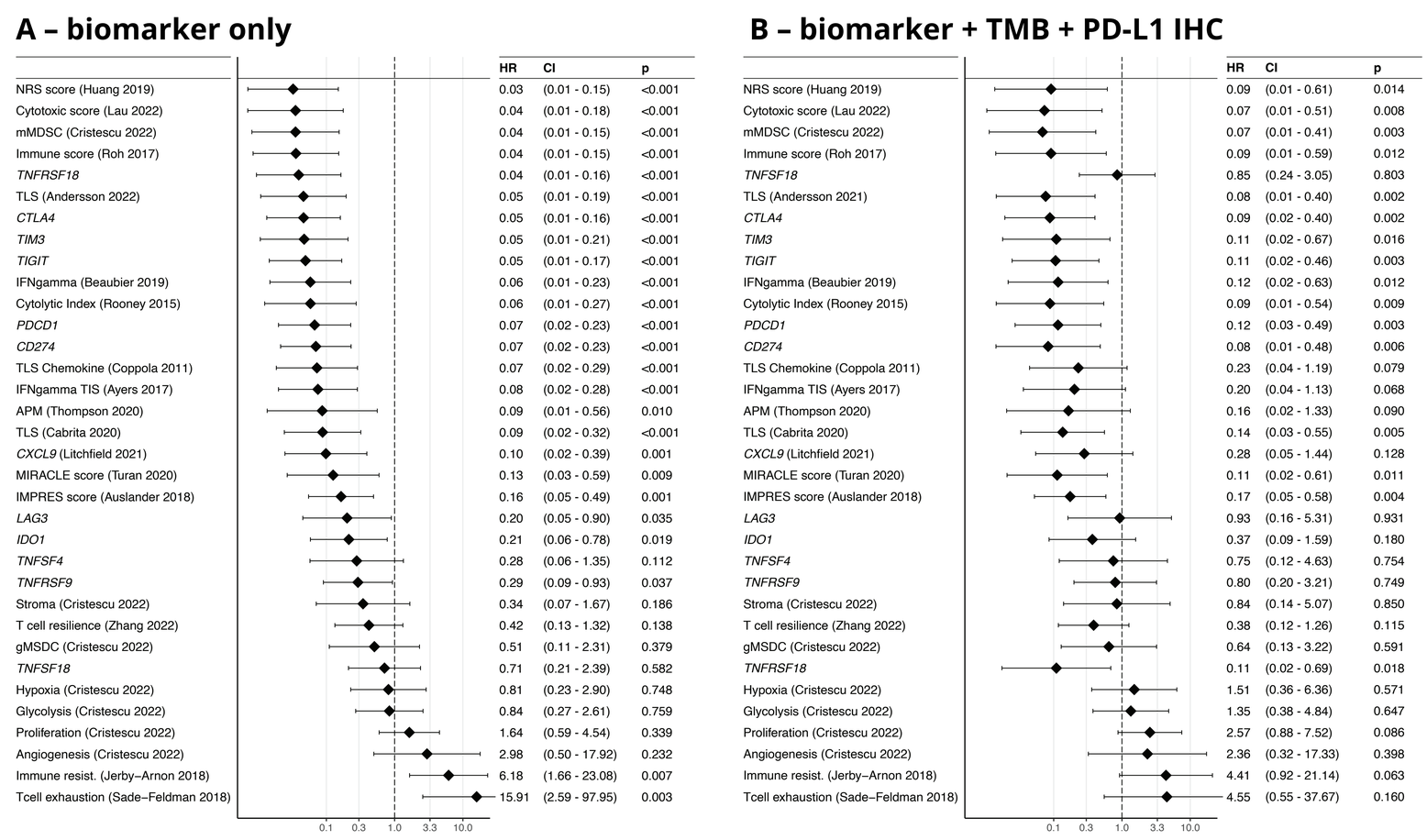

Figure 2. (A) Forest plot of RNA-based ICI-associated biomarkers of rwTTP. Each row represents the results of a single univariate Cox PH regression of each feature as a continuous variable. **(B)** Forest plot of RNA-based biomarkers in a multivariable Cox PH regression model that includes TMB (high/low) and PD-L1 IHC (<1% TPS/1-49% TPS/<50% TPS).

Non-RNA and multimodal features are generally not associated with outcomes in this cohort

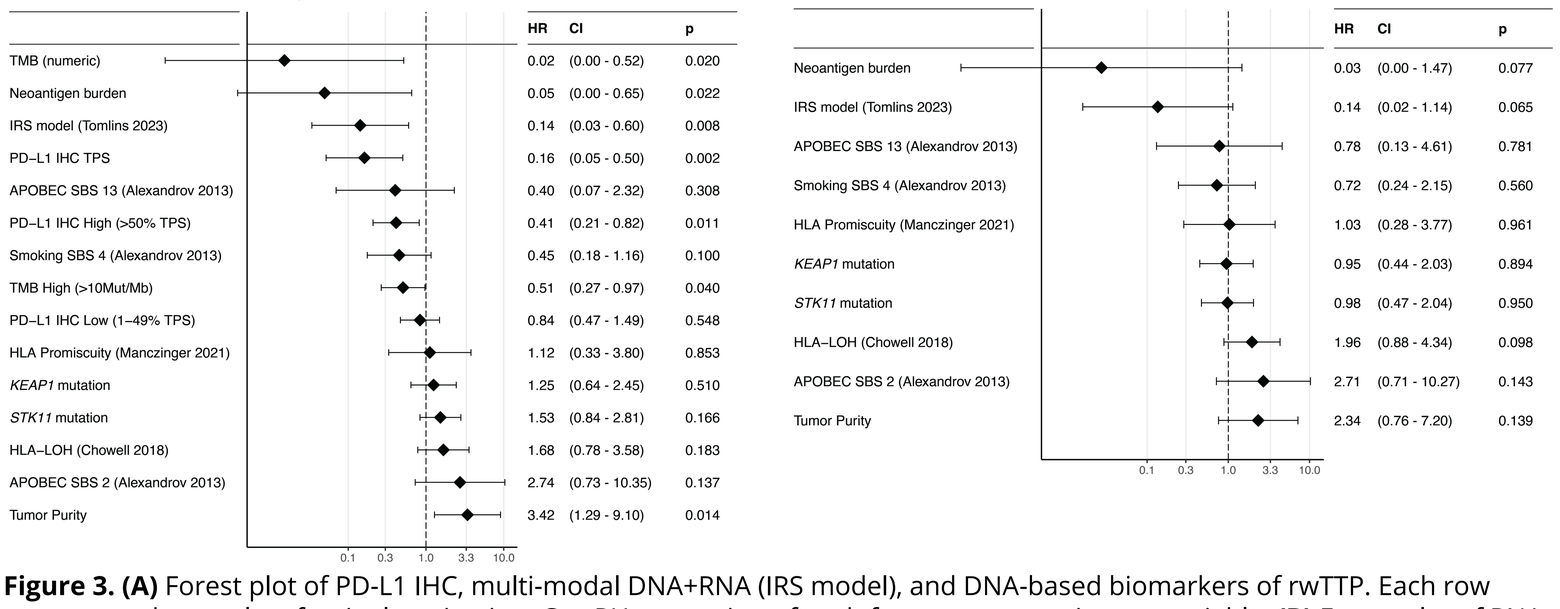

Figure 3. (A) Forest plot of PD-L1 IHC, multi-modal DNA+RNA (IRS model), and DNA-based biomarkers of rwTTP. Each row represents the results of a single univariate Cox PH regression of each feature as a continuous variable. **(B)** Forest plot of RNA-based biomarkers in a multivariable Cox PH regression model that includes TMB (high/low) and PD-L1 IHC (<1% TPS/1-49% TPS/<50% TPS).