A multi-modal, pan-cancer atlas of tumor-immune states across primary and metastatic disease using a large, real-world database

Prerna Jain[1], Michelle M. Stein[1], Paul Fields[1], Bolesław Osinski[1], Luca Lonini[1], Ariane Lozac'hmeur[1], Rohan Joshi[1], Halla Nimeiri[1], Martin C. Stumpe[1], Kate Sasser[1], Catherine Igartua[1], Justin Guinney[1], Mary Nora Disis[2]

[1]Tempus Labs, Chicago, IL
[2]School of Medicine, University of Washington, Seattle

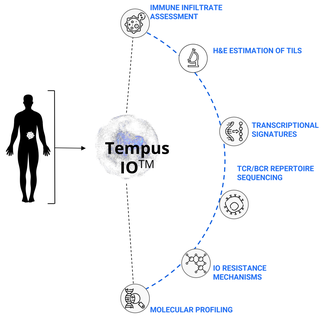
INTRODUCTION

Immuno-oncology (IO) therapies have demonstrated effective and durable benefits in multiple cancer indications but responses are variable. Discovery and validation of better biomarkers of treatment response, ability to modulate immunological states, selection of optimal drug combinations, and identification of new IO targets are top priorities to maximize the clinical impacts of immunotherapy.

While the immune and tumor microenvironment have been well characterized in primary tumors, large-scale assessments in metastatic disease are lacking. Here, we conducted a multi-modal, pan-cancer analysis comparing immune states across primary and metastatic disease using a real-world database.

METHODS

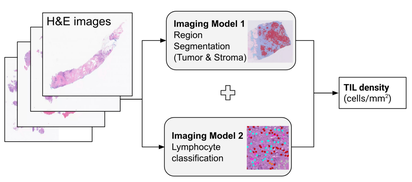
Analysis was conducted using Tempus IO™, an immunogenomics platform built on a large, real-world patient database.



Tempus IO comprises de-identified records with pre-computed immunophenotypes across dozens of cancer types, many treated with IO therapy. Somatic DNA alterations and whole-exome transcriptomes were profiled using the Tempus xT and xR NGS assays, respectively, with optimized probes for TCR/BCR profiling.

For assessment of immune cell fraction, TCR clonality, and IO biomarkers in solid tumors, 70K samples were selected from the Tempus Clinicogenomic Database. NSCLC cohorts were used to assess patient survival in relation to IO biomarkers and intratumoral TIL density from H&E images.

Imaging-based TIL density computation



H&E images are fed to two models, a tumor & stroma segmentation model and a lymphocyte classification model. Classified lymphocytes within the segmented areas are counted per mm² to give intra-tumoral and stromal TIL densities.

Acknowledgments: We thank Matthew Kase for data visualization guidelines and poster review.

SUMMARY

- A landscape, multi-modal comparison of tumor-immune states was performed on de-identified patient records.
- Bulk tumor RNA showed liver metastases had significantly lower immune infiltration, higher macrophage fraction, and lower TCR diversity compared to primary tumors and lung metastases.
- TIL quantification from digitized NSCLC H&E slides revealed a significant correlation between intratumoral TIL density and cytotoxic T-cell score, and confirmed lower intratumoral TIL density in liver metastases versus primary lung tumors.

RESULTS

Immune cell states vary across indications and primary versus metastatic sites

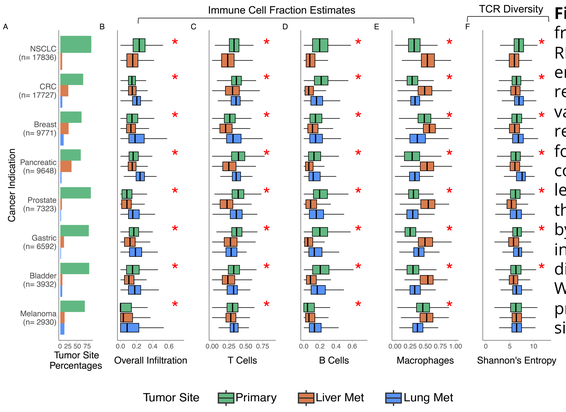


Figure 1. Immune cell fraction estimates from RNA-seq and Shannon's entropy of TCRβ repertoires (higher values = more diverse repertoire) by tumor site for the top 8 most common cancers. The left-most panel shows the percent distribution by tumor site. Asterisks indicate significant differences (pairwise Wilcoxon p < 0.001) in primary vs metastatic sites.

NGS-based measures of immune activity are associated with survival in IO-treated patients and vary across indications and primary versus metastatic sites

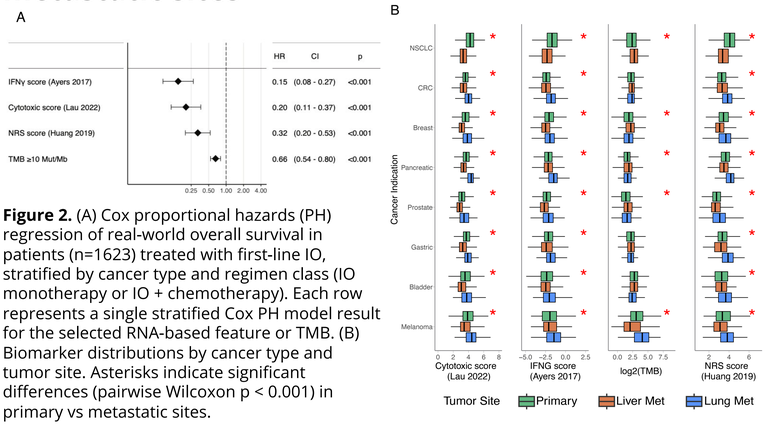


Figure 2. (A) Cox proportional hazards (PH) regression of real-world overall survival in patients (n=1623) treated with first-line IO, stratified by cancer type and regimen class (IO monotherapy or IO + chemotherapy). Each row represents a single stratified Cox PH model result for the selected RNA-based feature or TMB. (B) Biomarker distributions by cancer type and tumor site. Asterisks indicate significant differences (pairwise Wilcoxon p < 0.001) in primary vs metastatic sites.

Intratumoral TIL density computed from NSCLC H&E images varies across tissue sites

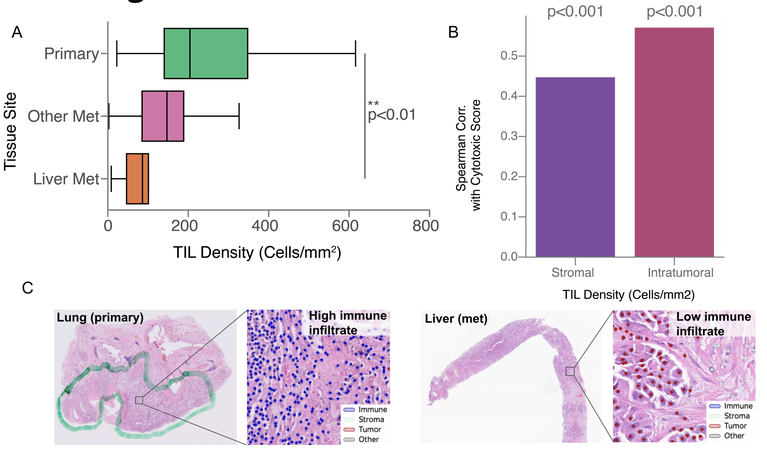


Figure 3. (A) Distribution of intra-tumoral TIL density in NSCLC by tumor site (N=104). (B) Cytotoxic score correlates more strongly with intra-tumoral TIL density than stromal TIL density, reflecting the higher density of cytotoxic T cells in tumor areas. (C) Examples of cell classification model outputs for NSCLC in lung (primary) and liver (metastatic) tissues.