Development of a novel RNA-based immune checkpoint inhibitor response signature (ICI-PRS) that avoids standard-of-care (SOC) prognostic signal for use in patients with urothelial cancer (UC)

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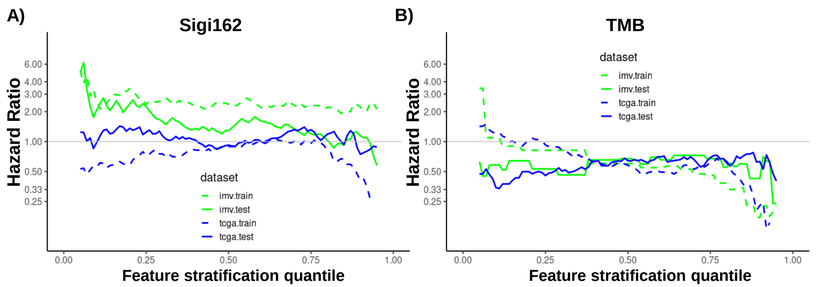
BACKGROUND

- Immune checkpoint inhibitors (ICIs) show durable responses in a portion of urothelial carcinoma patients[1], making predictive biomarkers beneficial
- Elevated PD-L1 or total mutation burden (TMB) are associated with ICI response[1], but also with response to chemotherapy[2,3] in bladder cancer
- Confirmatory trials of ICIs within PD-L1 biomarker positive patients have failed, leading to withdrawal of atezolizumab and durvalumab in bladder cancer
- Better biomarkers, that distinguish ICI-response from non-ICI standard-of-care (SOC) are needed

METHODS

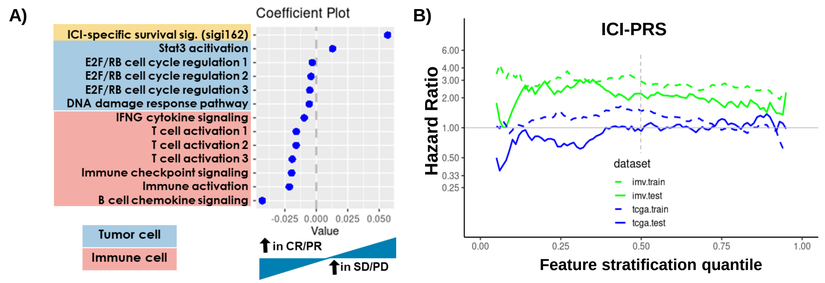
- RNA expression data from the IMvigor210 trial[1] (n=298) and from the Cancer Genome Atlas (TCGA) bladder cancer cohort[4] (n=405) were combined, with 2/3 used to identify treatment-agnostic and ICI-specific prognostic genes (training set)
- Candidate ICI-specific genes were developed into an ICI-specific survival signature (sigi162) and applied to the withheld 1/3 of IMvigor210 and TCGA (test set)
- A novel composite ICI predictive response signature (ICI-PRS), featuring sigi162 and other selected signatures reflective of both tumor and immune microenvironment was developed in the same training sets and tested in IMvigor210 and TCGA test sets and two independent ICI-treated bladder cancer datasets: UNC-106 (BACI; n=84 receiving ICI>3 weeks)[5] and BCAN UC-GENOME (BCAN; n=105)[6]

Figure 1: Prognostic Value of Sigi162 Signature (A) and TMB (B) in ICI-treated IMvigor210 and SOC-treated TCGA BLCA



- Sigi162 signature was trained to be prognostic for ICI-treated patients (e.g., IMvigor210, green lines) but not non-ICI treated patients (e.g., TCGA BLCA, blue lines). Note separation of green vs blue lines, with blue lines near 1 for Hazard Ratio of Cox Proportional Hazard models of overall survival when data is stratified at given quantile in Figure 1A
- TMB is prognostic in both ICI- and non-ICI treated patients. Note overlapping green and blue lines in Figure 1B
- Sigi162 signature was not clearly prognostic for ICI treatment in IMvigor210 test set (solid green line in Figure 1A), thus necessitating improvement with the addition of other features

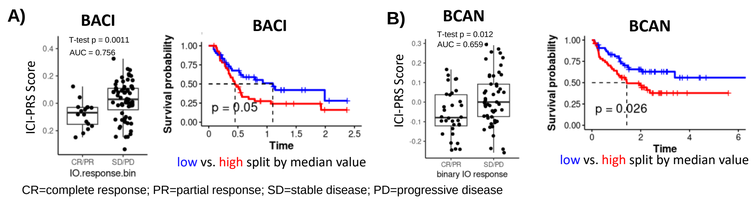
Figure 2: ICI Predictive Response Signature (ICI-PRS) Combines Sigi162 with Tumor Cell and Immune Microenvironment Features



CR=complete response; PR=partial response;
SD=stable disease; PD=progressive disease

- A new ICI-PRS, incorporating sigi162 with select RNA features reflective of tumor cells and the immune microenvironment (Figure 2A), was trained in the IMvigor210 training set, where it was associated with response and survival for ICI-treated patients, but was still not associated with survival in non-ICI treated TCGA BLCA training (Figure 2C)
- In the separate testing dataset, the ICI-PRS signature was significantly associated with response and survival for ICI-treated patients only (e.g., IMvigor210) but not in non-ICI treated patients (e.g., TCGA BLCA) (Figure 2D)

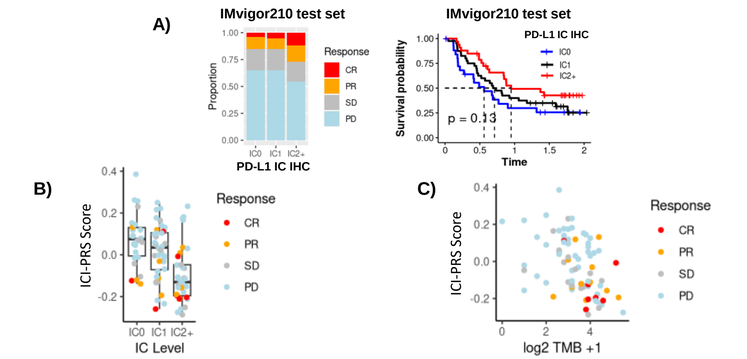
Figure 3: ICI-PRS Signature Status is Associated with Response and Survival in Independent Cohorts of ICI-treated BLCA Patients



CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease

- When applied to independent cohorts of patients treated with ICI therapy (BACI (A) and BCAN (B)), ICI-PRS status is associated with both clinical response and overall survival

Figure 4: PD-L1 and TMB are Complimentary to ICI-PRS Signature



IMvigor test dataset	
Model	**LR p.val**
OS: IC	(base model)
OS: IC + ICI-PRS	**0.00714**

IMvigor test dataset	
model	**LR p.val**
OS ~ TMB	(base model)
OS ~ TMB + ICI-PRS	**0.00911**

- PD-L1 IHC levels in peritumoral immune cells (IC) have been associated with clinical response and survival in ICI-treated patients (IMvigor210 test set shown in Figure 4A)
- ICI-PRS appears to improve both PD-L1 IHC and TMB predictive strength in IMvigor210 training (data not shown) and testing data (Fig. 4B-C). LR = likelihood ratio.
- PD-L1 and/or TMB may be complimentary to ICI-PRS use

SUMMARY AND CONCLUSIONS

- Herein we describe the development of a novel ICI-PRS and initial demonstration that it provides ICI-treatment specific prognostic value for bladder cancer patients
- ICI-PRS status was associated with extended survival in patients treated with ICI but not those treated with non-ICI SOC therapy
- These results support the further evaluation of the ICI-PRS and potential development as a diagnostic test for selecting UC patients most likely to benefit from ICI therapy

References

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