Validation of an integrative pan-solid tumor predictor of pembrolizumab monotherapy benefit

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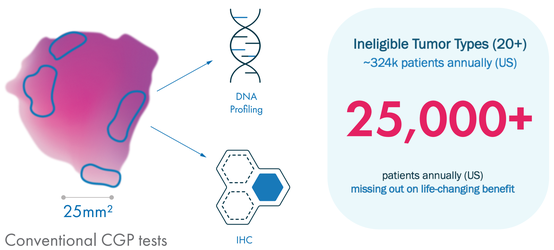
Purpose

Strata previously reported the development and validation of an integrative Immunotherapy Response Score (IRS) algorithm, which integrates tumor mutation burden (TMB) and quantitative gene expression of PD-L1, PD-1, ADAM12 and TOP2A, to predict PD-1 or PD-L1 (together PD-[L]1) monotherapy (mono)benefit across solid tumors from routine formalin fixed paraffin embedded samples[1]. Herein, we evaluated IRS performance for predicting pembrolizumab (pembro)mono benefit in a second, independent validation cohort.

Figure 1. Rationale for expression based biomarker



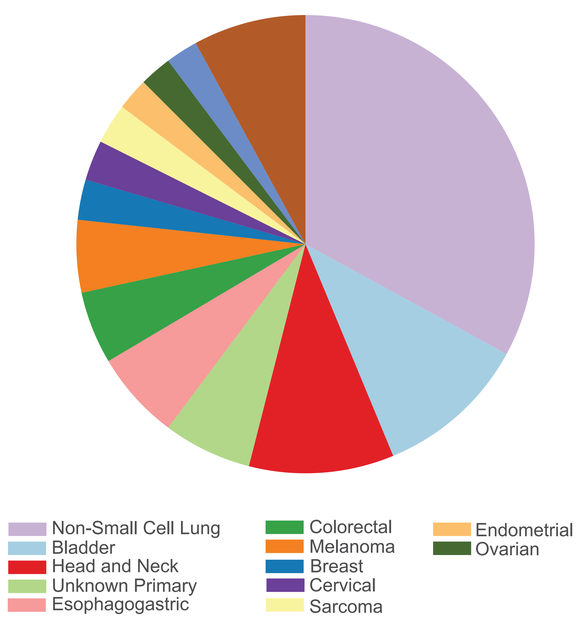
TMB misses responders

- Studies have consistently shown 5-10%+ response rates outside of approved indications, including TMB Low (6%) (e.g. Keynote-158)

PD-L1 is not pan tumor

- IHC is a tumor type specific biomarker
- Utilizes multiple antibodies, scoring systems and cut points and is subjective

Figure 2. Population by cancer type



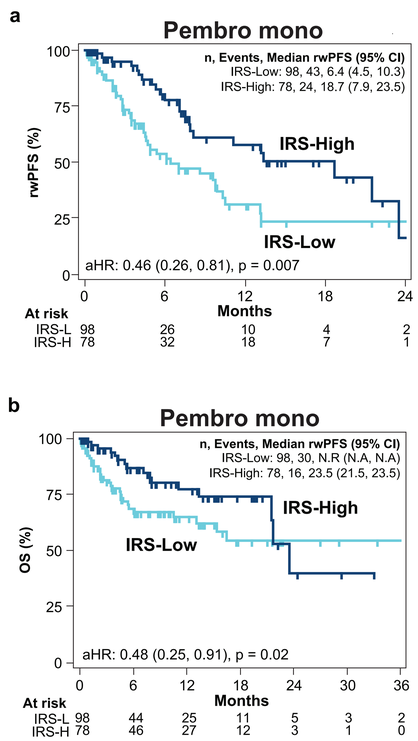
Methods

Inclusion/exclusion criteria for this validation cohort were the same as the original discovery cohort: 1) reportable TMB measurements from StrataNGS testing (including meeting the overall 20% tumor content requirement), 2) reportable immune gene expression quantification from an investigative multiplex PCR based transcriptomic profiling test, 3) treatment with a systemic pembro monotherapy line of therapy, 4) the tested tissue specimen was collected prior to the pembro monotherapy start date, and 5) the subject had had no prior anti-PD-(L)1 or CTLA4 blockade therapy prior to the pembro monotherapy line start date. Additionally, patients included in the original discovery or validation cohorts were excluded.

Adjusted real world progression free survival (rwPFS) and overall survival (OS) analyses were performed to compare group outcomes (by adjusted hazard ratios [aHR] and two-sided p-values) using Cox proportional hazard models unless otherwise specified. Covariate adjustments shared between all models included age and gender, IRS status (or TMB status for the TMB analysis), PD-(L)1 monotherapy indicated (MSI-H, TMB-H, or approved tumor types) vs. notindicated, and line of systemic therapy (continuous).

For the predictive analysis using the case-control internal comparator cohort considering rwPFS on the immediately preceding systemic therapy vs. subsequent pembro monotherapy, adjusted Cox proportional hazards models were utilized to examine the interaction between pembrolizumab vs. prior therapy rwPFS within the same patient and IRS status (IRS-High vs. Low) using a likelihood ratio test (LRT).

Figure 3. Kaplan Meier plots of pembrolizumab monotherapy treatment outcome (rwPFS and OS) stratified by IRS group



Purpose

Of the 176 patients in this independent validation cohort (from 25 tumor types [Fig. 2]), 78 (44%) patients were IRS-H, while 40 (23%) were TMB-H. Pembro mono rwPFS was significantly longer in IRS-H vs. IRS-L patients (median rwPFS 18.7 vs. 6.4 months, aHR 0.46, p=0.007 [Fig. 3a]), similarly in OS (aHR 0.48, p=0.02 [Fig. 3b], while PD-(L)1 mono indicated status was not associated with pembro mono rwPFS (indicated vs. not indicated aHR 1.47, p=0.26). In the case cross-over analysis of 55 (31%) patients treated with systemic therapy prior to pembro mono, pembro rwPFS was significantly longer than preceding therapy in IRS-H patients (median 18.7 vs. 5.5 months [Fig. 4b]) but not IRS-L patients (median 4.9 vs. 5.4 months [Fig.4a]); the LRT for interaction between IRS status and pembro/prior therapy was significant (p=0.046 [Fig. 4b]); results in the TMBL/non-MSI-H subset (n=45) of patients was similar (LRT p=0.025 [Fig. 4d]).

Additional Information

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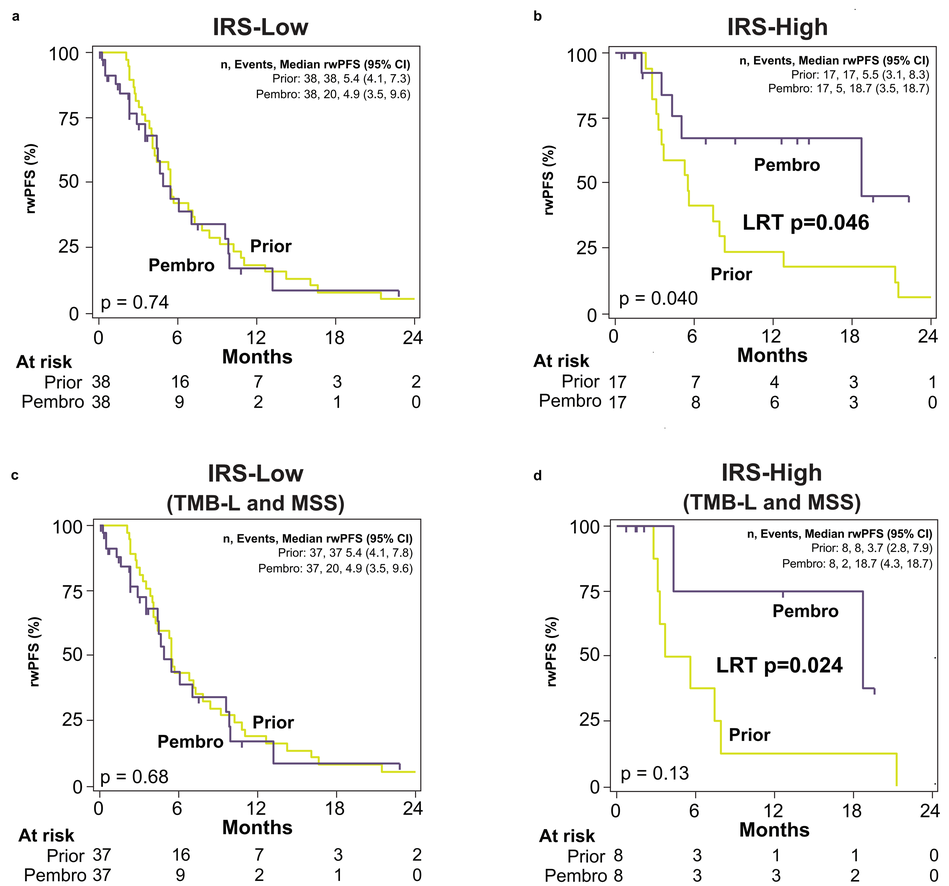
Summary

Here we demonstrate the IRS is predictive of pembro monotherapy rwPFS and OS in a cohort of 176 patients from 25 tumor types. The predictive nature of IRS was confirmed in a case cross-over analysis of 55 patients treated with pembro in the >1st line. Taken together with our previous validation cohort (248 patients from 24 tumor types treated with other PD-(L)1 monotherapy[1], we clearly demonstrate the pan-solid tumor nature of IRS-H status for predicting prolonged PD-(L)1 monotherapy benefit across tumor types and TMB status.

References

1. Tomlins, S.A., Khazanov, N.A., Bulen, B.J. et al. Development and validation of an integrative pan-solid tumor predictor of PD-1/PD-L1 blockade benefit. Commun Med 3, 14 (2023). https://doi.org/10.1038/s43856-023-00243-7 PMID: 36750617

Figure 4. Kaplan Meier plots of pembrolizumab monotherapy vs. prior therapy (case-crossover study design)



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