1082P: Improved response prediction to immune checkpoint inhibitors by combining TMB and WGS-driven genomic features in NSCLC

INTRODUCTION

- Lung cancer is the second most commonly diagnosed cancer, among which non-small cell lung cancer (NSCLC) is the most prevalent subtype.
- In NSCLC patient treatment, the preferred regimen is the administration of immune checkpoint inhibitors (ICIs), such as programmed cell death protein 1 (PD-1) inhibitors.
- Recent findings indicate that tumor mutational burden (TMB) is a clinical biomarker that may improve response prediction to ICIs in many cancer types. Recent studies on TMB show that detailed analyses of NSCLC genomics and, consequently, the discovery of novel predictive biomarkers can help select patients benefitting from ICIs.
- The present study aims to identify genomic features that may serve as biomarkers associated with the response to ICIs in lung cancer patients based on whole genome sequencing (WGS) data analyses.

RESULTS

- Out of ~300 WGS-based genomic features, the Random Forest classifier has selected top 15 predictive biomarkers via Recursive Feature Elimination using SHAP importance (Fig.1).
- In addition to TMB, the model has revealed specific context-dependent features that are associated with a particular biological mechanism. The most overrepresented features, such as single base substitutions (indicated as SBS) in particular nucleotide context (C>A and C>T), represent mutations typical for COSMIC signatures 2 (APOBEC-related), 4 (smoking) and 7 (UV-related). Moreover, C>T mutations on the untranscribed strand (indicated as uccdt) and C>A mutations on the transcribed strand (indicated as tcc2ca) distinguish responders from non-responders. Importantly, short frameshift mutations that can lead to the generation of neoantigens (tumor-specific antigens) is another feature selected to predict response.
- In ten repetitions of 2-fold cross-validation (10x2 CV), Random Forest utilizing the proposed 15 genomic features achieved the best performance, with the Area Under the Receiver Operating Characteristic curve (AUC ROC) of 0.88, recall of 0.85, and precision of 0.82. The hold-out test results also confirmed the predictive power of the algorithm by showing AUC ROC, recall and precision of 0.79, 0.73 and 0.80, respectively.
- To compare the predictive power of the proposed approach with the currently known biomarkers, we trained two separate Random Forest models based on a single feature – TMB and Tumor Neoantigen Burden (TNB) respectively. The experiment confirmed that the proposed combination of biomarkers outperforms existing methods (Fig.2).

METHODS

- 57 metastatic NSCLC patients treated with ICIs inhibitors - nivolumab or pembrolizumab were randomized into training (n=38) and hold-out (n=19) sets.
- Patients treated with one of the two most common ICIs therapeutic - nivolumab or pembrolizumab - were labeled as responders (n=22) and non-responders (n=35) based on clinical metadata provided by the Hartwig Medical Foundation. Responders were defined as patients who achieved a complete response (CR) or partial response (PR), while non-responders as those who showed disease progression.
- Model was built using the Random Forest classifier.

ACKNOWLEDGEMENTS

Data was acquired from the Hartwig Medical Foundation under data request no. DR-369. This work was supported by MNM Diagnostics.

Disclosure statement: The authors declare no conflict of interest.

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