INTRODUCTION

Tums often do not respond to PD-1/PD-L1 axis inhibitors due to immune escape mechanisms present in the tumor microenvironment. Bi-functional antibody-based immunotherapies that simultaneously target immune checkpoints and immunosuppressive cells are being developed to slow tumor growth.

Anti-PD-L1/TGF-β trap fusion proteins are one approach being developed to counter the traditional immune checkpoint inhibition via PD-1/PD-L1 axes and simultaneously inhibit the pro-tumor/anti-inflammatory effects of TGF-β. In this study, we not only describe the tumor immune microenvironment of tumors expressing PD-L1 and TGF-β, but also describe potential patient selection strategies based on gene expression measurements of these tumor immune microenvironments in clinical samples.

METHODS

RNA-seq was performed for 395 immune transcripts on 1323 FFPE tumors of diverse histologies. To find true TGF-β high expressing tumors, TGFβ1 gene expression was normalized by a tumor inflammatory score (average expression rank of 161 inflammation genes derived from a co-expression signature of >1000 tumors spanning 35 histologies). Proportion of PD-L1 IHC positive, inflamed, tumor mutational burden (TMB) high and cell proliferation2 categories was estimated for TGFβ1 high expressing tumors. Inclusion and exclusion criteria were developed based on PD-L1 and normalized TGFβ1 expression.

CONCLUSION

- Evaluation of a 1323 patient cohort suggests an immune phenotype of potentially PD-L1/TGF-β trap responsive tumors exists across multiple histologies.
- PD-L1/TGF-β high tumors have distinct immune profiles compared to PD-L1/TGF-β low tumors.
- A clinical immune gene expression assay described in this study could not only improve patient selection for anti-PD-L1/TGF-β trap treatment, but for other bispecific fusion protein-based immunotherapies.

REFERENCES