PREVALENCE OF SECONDARY IMMUNOTHERAPEUTIC TARGETS IN THE ABSENCE OF ESTABLISHED IMMUNE BIOMARKERS IN SOLID TUMORS

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Background Immune checkpoint inhibitor-based therapies have achieved impressive success in the treatment of several cancer types. Predictive immune biomarkers, including PD-L1, MSI and TMB are well established as surrogate markers for immune evasion and tumor-specific neoantigens across many tumors. Positive detection across cancer types varies, but overall ~50% of patients test negative for these primary immune markers. In this study, we investigated the prevalence of secondary immune biomarkers outside of PD-L1, TMB and MSI.

Methods Comprehensive genomic and immune profiling, including PD-L1 IHC, TMB, MSI and gene expression of 395 immune related genes was performed on 6078 FFPE tumors representing 34 cancer types, predominantly composed of lung cancer (36.7%), colorectal cancer (11.9%) and breast cancer (8.5%). Expression levels by RNA-seq of 36 genes targeted by immunotherapies in solid tumor clinical trials, identified as secondary immune biomarkers, were ranked against a reference population. Genes with a rank value ≥75th percentile were considered high and values were associated with PD-L1 (positive ≥1%), MSI (MSI-H or MSS) and TMB (high ≥10 Mut/Mb) status. Additionally, secondary immune biomarker status was segmented by tumor type and cancer immune cycle roles.

Results In total, 41.0% of cases were PD-L1+, 6.4% TMB+, and 0.1% MSI-H. 12.6% of cases were positive for ≥2 of these markers while 39.9% were triple negative (PD-L1-/TMB-/MSS). Of the PD-L1-/TMB-/MSS cases, 89.1% were high for at least one secondary immune biomarker, with 69.3% having ≥3 markers. Of these PD-L1-/TMB-/MSS tumor types with ≥50% prevalence of high secondary immune biomarkers included brain, prostate, kidney, sarcoma, gallbladder, breast, colorectal, and liver cancer. High expression of cancer testis antigen secondary immune biomarkers (e.g., NY-ESO-1, LAGE-1A, MAGE-A4) was most commonly observed in bladder, ovarian, sarcoma, liver, and prostate cancer (≥15%). Tumors demonstrating T-cell priming (e.g., CD40, OX40, CD137), trafficking (e.g., TGFB1, TLR9, TNF) and/or recognition (e.g., CTLA4, LAG3, TIGIT) secondary immune biomarkers were most represented by kidney, gallbladder, and sarcoma (≥40%), with melanoma, esophageal, head & neck, cervical, stomach, and lung cancer least represented (≥15%).

Conclusions Our studies show comprehensive tumor profiling that includes gene expression can detect secondary immune biomarkers targeted by investigational therapies in ~90% of PD-L1-/TMB-/MSS cases. While genomic profiling could also provide therapeutic choices for a percentage of these patients, detection of secondary immune biomarkers by RNA-seq provides additional options for patients without a clear therapeutic path as determined by PD-L1 testing and genomic profiling alone.

REFERENCE


http://dx.doi.org/10.1136/jitc-2021-SITC2021.077