CANCER TESTIS ANTIGEN BURDEN: A NOVEL PREDICTIVE BIOMARKER FOR IMMUNOTHERAPY IN SOLID TUMORS

Sarabjot Pabla*, RJ Seager, Yong Hee Lee, Erik Van Roey, Shuang Gao, Vincent Giamo, Blake Burgher, Paul DePietro, Mary Nesline, Sean Glenn, Shengle Zhang, Jeffrey Conroy. *OmnSeq, Inc., Buffalo, NY, USA*

Background When expressed in cancer cells, cancer testis antigens (CTAs) are highly immunogenic and have the capacity to elicit cancer-specific immune responses in diverse malignancies. With their expression limited to tumor cells, CTAs have become a prime target of natural T cell response, immune cell-based therapy, and cancer vaccines. In this study, we investigated CTA burden in real-world clinical tumors spanning multiple histologies, revealing a novel prognostic gene expression-based biomarker.

Methods Targeted RNA-seq was performed on 5450 FFPE tumors representing 39 histologic types, predominantly composed of lung cancer (40.4%) followed by colorectal cancer (10.6%) and breast cancer (8.6%). Using an amplicon-based NGS approach, expression levels of 17 CTA genes were ranked against a reference population. Cancer Testis Antigen Burden (CTAB) was calculated as the sum of the gene expression rank for each CTA gene. The median CTAB of ≥ 171 was used as cutoff for CTAB High versus Low classification. We estimated Pearson's correlation for all CTA genes to discover co-expression patterns between CTAs and histologies. Overall survival (OS) analysis was performed using CoxPh regression model whereas response analysis was performed using logistic regression model with p-values reported.

Results Within the tumor samples, CTAB values ranged from 0–1700, with kidney cancer demonstrating overall lowest mean CTAB (110) and melanoma the highest (550). NSCLC had an average CTAB of 283. In an immune checkpoint blockade treated retrospective cohort of 110 NSCLC patients, High CTAB showed better OS compared to Low CTA (HR: 0.55, $p=0.07$). Additionally, when combined with tumor inflammation and cell proliferation biomarkers, highly inflamed but poorly proliferative tumors with High CTAB had improved OS (HR: 0.27, $p=0.05$). No significant association with response was detected.

Conclusions Our studies show that co-expression of multiple CTA genes occurs in many tumor types and can be reliably detected using a targeted RNA-seq approach. Utilization of this co-expression pattern to calculate CTAB reveals tumor-type associated signatures, which in a small NSCLC cohort is associated with the overall survival. The findings suggest that these immunogenic antigens expose the tumor cells to natural or immunotherapy augmented cell-based immune response, and that CTAB is a potential predictive marker for therapeutic response to checkpoint inhibitors. Further studies are needed to establish the predictive value in other tumor types, as well as the role of CTAB in immune cell therapies and vaccinations.

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