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Short Communication

The mutational burden of targeted genes significantly correlated with overall survival after targeted therapy in metastatic renal cell carcinoma

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Abstract

This study aimed to find the correlation between tumor mutation burden and systemic first line therapeutic response in metastatic tissue samples from patients with metastatic renal cell carcinoma (mRCC).

Between 2005 and 2017, 168 triplet-tissue block samples (with at least one tissue block having passed their quality checks) from 56 mRCC patients were selected for targeted gene sequencing (TGS) using the 88 targeted genes from the National Cancer Center, Korea (NCC) kidney cancer panel. The patients' medical records, including therapeutic responsive profiles with overall survival (OS) to first-line targeted therapy, were evaluated with the mutational burden of triplet tissue samples using 88 TGS. The OS was defined as the time interval between the diagnosis of metastasis and death. A few significant target genes associated with therapeutic response towards targeted therapy were identified after comparing the mutational burden of positive for all three blocks and one or two positive blocks (p-value < 0.05).

The median PFS for the first-line targeted therapy and OS were 8.7 and 42 months, respectively. MSKCC and Heng risk criteria showed 28.9/65.8/5.3% and 26,3/57.9/15.8% for favorable, intermediate, and poor risk groups, respectively. Also, 55.3% and 52.6% patients received metastatectomy and nephrectomy, respectively. The clinical T stage comprised of T1 26.8%, T2 16.1%, T3 8.9%, T4 1.8%, and Tx 46.4% and N stage of 26.3% of N1. The histopathology showed 50.0%, 1.8%, and 48.2% of clear, non-clear, and unknown cells, respectively.

Eighteen (32.1%) patients had all triplet blocks passed for quality check, whereas 21 (37.5%) and 17 (30.4%) patients had two or one passed tissue blocks, respectively. Among the 18 patients with triplet-block, TP53, URB4, PTK2, and SGO2 genes had significant discrimination power for OS on comparing their mutational burden in the three blocks positive group (N=7) and two or fewer blocks positive groups (N=11) (p<0.05).

Among the 39 patients with either doublet or triplet blocks passed for quality check, TP53, URB1, PTK2, SGO2, BRAF, NEDD4, PDXDC1, CDH1, FGFR2, RET, RUNX1, and SDHB genes had significant discrimination power for DFS when comparing their mutational burden in the three blocks positive group (N=7) and two or fewer blocks positive groups (N=14) (p<0.01).

Keywords:

kidney cancer, metastasis, tumor burden, target gene

Introduction:

Currently, immune checkpoint blockade (ICB) therapy has incremented the overall survival (OS) rates of patients with advanced melanoma, non-minute-cell lung cancer (NSCLC), urothelial cancer (UC), renal cell carcinoma (RCC), and other cancer types.

Tumors often upregulate immune checkpoints to evade being detected and killed by the host immune system. Activation of checkpoint cascades such as those controlled by programmed cell death protein (PD-1) or CTLA-4 result in inactivation of tumor-concrete T cells and immune evasion Treatment with anti-PD-1, anti-programmed death-ligand 1 (anti-PD-L1), or anti-CTLA-4 reinvigorates T cells and sanctions the adaptive immune system to target tumor cells. Detection of tumor and/or immune cell PD-L1 by immunohistochemical quantification has been extensively studied as a soothsayer of replication to anti-PD(L)-1 treatment and has been convincingly demonstrated to be a valid biomarker in some settings. PD-L1 expression by immunohistochemistry (IHC) is an Pabulum and Drug Administration (FDA)-approved companion diagnostic test for pembrolizumab in NSCLC, gastric/gastroesophageal junction adenocarcinoma, cervical cancer and UC and has shown some predictive faculty across several other cancer types including head and neck and minuscule-cell lung carcinoma PD-L1 quantitation for immunotherapy replication prognostication is imperfect and there is a desideratum for ameliorated biomarkers of replication. The presence of tumor-infiltrating lymphocytes (TILs) might confer a prognostic and a predictive impact The T-cell-inflamed gene expression profile (GEP) immune gene expression signatures as well as description of the microbiome withal represent emerging predictive biomarkers.

Cancer is a genetic disease. Neoplastic transformation results from the accumulation of somatic mutations in the DNA of affected cells. These genetic alterations include driver mutations, mutations that directly affect tumor magnification such as those in TP53, epidermal magnification factor receptor (EGFR) or RAS, and passenger mutations, which are alterations that do not directly impact the magnification of the cancer cell. Genetic transmutations in tumors can include non-synonymous muta-

tions largely comprised of missense mutations (point mutations that transmute the amino acid codon), synonymous mutations (silent mutations that do not alter amino acid coding), insertions or effacements (indels, which can cause frameshifts), and replicate number gains and losses. There is dramatic variation in the frequency of each type of these genetic alterations between individual tumors and between different tumor types. Tumor mutation burden (TMB) can be habituated to soothsay ICB efficacy and has since become a utilizable biomarker across many cancer types for identification of patients that will benefit from immunotherapy.

TMB is not without circumscriptions. It is a relatively incipient type of biomarker, and defining standards for tenaciousness and reporting of TMB are not well established. Proteins engendered from gene fusions and post-translational modifications of non-mutated proteins are not accounted for in current iterations of TMB, but nonetheless may contribute to neoantigenic load. More critically, current iterations of the TMB assign an equal weight to each tumor mutation, but it is increasingly clear that not all mutations are engendered equipollent. Some mutations result in the formation of higher 'quality' antigens, which are more yarely identified as 'non-self' by the immune system and are more liable to induce a robust antitumor immune replication. Antigens resulting from viral open reading frames in a cancer's genome are an example of a high-quality antigen. This may be the reason the subset of Merkel-cell carcinoma that is associated with the Merkel-cell polyomavirus has a moderate TMB but amongst the highest replication rates of any tumor type with anti-PD1 therapy. Another example of a tumor type with intermediate levels of TMB but a high replication rate to ICB is RCC. Recent work by Turajlic et al. shows that in additament to single nucleotide variants, frameshift mutations engendered by insertion and expunctions that result in the generation of an entirely incipient peptide amino acid chain afore a cessation codon being reached, withal contribute to the generation of potent tumor neoantigens and the overall TMB of cancers. Fascinatingly, they demonstrated that RCCs have the highest frequency and number of indel mutations across cancer types. In MSI tumors, genetic instability manifests as short indels resulting from lack of rehabilitation of slippages during replication. This, in MMR deficient tumors, indels may withal need to be considered in defining total TMB.

Another challenge is to understand how to utilize TMB while taking into account concrete mutations that have been shown to influence replication to ICB treatment. For example, mutations in genes have been shown to affect ICB replication. Some mutations such as those in JAK1 and JAK2 are recherche and do not validate in all patient cohorts. Similarly, some immune evasion mechanisms such as transforming magnification factor signaling or indoleamine 2,3-dioxygenase activity may influence ICB replication. The consequentiality of these alterations will have to be tested in prospective tribulations. For the variables that are currently validated as most subsidiary, a model taking into consideration TMB, individual mutations or pathways that affect ICB outcomes, and PD-L1 levels—perhaps in the form of a nonogram—could be developed to further amend predictive models. Homogeneous models are in utilization for presaging the likelihood of disease control in patients with prostate cancer and for quantifying benefit from chemotherapy for breast cancer patients. It should be noted that the utilization of expression signatures have had a checkered past in the cancer biomarker field. Despite thousands of expression signatures nominated for utilize as biomarkers, very few have found reliable use in the clinic, especially when the expression signatures do not correlate with reproducible genetic alterations. Consequently, utilization of expression signatures in the immuno-oncology setting needs to be meticulously vetted. Indeed, the history of cancer biomarker development suggests that genetic alterations and not simply altered expression of a given target or pathway of interest, which can often be reversible, are more robust prognosticators of replication to a therapy targeting that pathway. Despite expression of IDO1 in tumors, genetic evidence that IDO is a cancer driver is destitute. It is perhaps not surprising, then, that a recent sizably voluminous phase III tribulation testing an IDO inhibitor in coalescence with anti-PD-1 did not shown benefit leading to the widespread discontinuation of IDO inhibitor development. However, some expression signatures appear to be promising for detection of prosperous anticancer immunity. Fascinatingly, Cristescu et al. show that TMB and a T-cell inflamed gene expression signature can both provide predictive value for clinical replication in patients treated on four Keynote tribulations.

Furthermore, the utility of TMB and other biomarkers noted above in patients treated with ICB plus chemotherapy is obscure and will require to be studied. If TMB is predictive in these settings, it is likely that incipient thresholds may need to be established.

Regardless, building future algorithms for identifying patients that will benefit from ICB will likely require assessment of tumor and immune cells qualitatively and quantitatively. TMB, concrete mutations in oncogenes, as well as PD-L1 expression will describe the tumor component while immune cell PD-L1 expression, HLA genotype, TCR repertoire, and possibly immune signatures (as resolute, e.g. by gene expression analysis) might be taken into account for the immune component of replication.

Conclusions:

The relationship between TMB and replication to immune checkpoint inhibitors is paving the way towards a precision immuno-genetics approach to cancer treatment. From the initial clinical visual examinations associating tumors with genetic damage from environmental factors, we have commenced a peregrination of revelation that will greatly broaden the scope and practice of precision oncology. TMB and other genetic determinants of replication to immunotherapy have already provided exhilarating incipient avenues to make cancer treatment more precise. Nevertheless, challenges remain. Our erudition of how genetics shapes immune

replication in obscure and this gap in cognizance must be bridged in order to build even better predictive models. How TMB can be utilized in coalescence with PD-L1 quantitation or measures of tumor inflammation needs to be ameliorated. Moreover, the impact of how HLA genotype and other germline variations influence the effect of TMB and replication to ICB needs to be explored further. Lastly, as discussed above, we highlight the desideratum for cross-assay standardization of NGS methods and solidification of interpretation of TMB levels in order to ascertain reliable treatment decisions in the clinic predicated on tumor genetics.