**PROJECT NOTES**

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[www.SimpleAI.ch](http://www.SimpleAI.ch)

**dictionary:**

* **Neoantigens** :
  + Tumor-specific mutations form novel immunogenic peptides called neoantigens. Neoantigens can be used as a biomarker predicting patient response to cancer immunotherapy. Although a predicted binding affinity (IC50) between peptide and major histocompatibility complex class I is currently used for neoantigen prediction, large number of false-positives exist. <https://www.annalsofoncology.org/article/S0923-7534(19)45468-9/fulltext>
* **ICPIs** 
  + **T**reatment with immune checkpoint inhibitors (ICPIs)
* **Tumor immunotherapy**
  + aims to control tumor development by activating the immune system to attack tumor cells.
  + By selecting appropriate antigens, notably neoantigens produced by tumor-specific mutations, an effective tumor-specific immune response can be mounted, and immune tolerance can be minimized. Non-synonymous somatic mutations will produce altered peptides, among which, some are processed and presented by the major histocompatibility complex (MHC) in order to generate neoantigens. These molecules are the key factors required for successful immunotherapy, including immune checkpoint inhibitors (ICIs), personalized tumor vaccines and adoptive T cell transfer immunotherapy ([2](https://www.frontiersin.org/articles/10.3389/fonc.2021.672677/full" \l "B2)–[4](https://www.frontiersin.org/articles/10.3389/fonc.2021.672677/full" \l "B4)). These strategies have shown promise in the treatment of solid tumors
  + A higher number of DNA mutations are associated with higher number of candidate peptides, and results in an increased probability of successfully presented neoantigens ([8](https://www.frontiersin.org/articles/10.3389/fonc.2021.672677/full" \l "B8)). The response to immunotherapy correlates with tumor mutation burden (TMB) and mainly with the number of mutations in the coding region of the genome (exome) of the tumor cells.
* **PFS - progression-free survival**
  + The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the PFS is one way to see how well a new treatment works.

* **PD1, PD-L1 - immune regulatory genes**
  + [**https://en.wikipedia.org/wiki/PD-L1**](https://en.wikipedia.org/wiki/PD-L1)
  + Programmed death-ligand 1 (PD-L1) is a 40kDa type 1 transmembrane protein that has been speculated to play a major role in suppressing the adaptive arm of immune systems during particular events such as pregnancy, tissue allografts, autoimmune disease and other disease states such as hepatitis.
  + PD-L1 and immunotherapy :
    - <https://www.abcam.com/cancer/cancer-immunotherapy-and-the-pd1pdl1-pathway>

SEE MY NOTES BELOW – more info there,

**ECOG Performance Status Scale**

* describes a patient’s level of functioning in terms of their ability to care for them self, daily activity, and physical ability (walking, working, etc.).
* scale 0-5,
* alternatives: **KARNOFSKY PERFORMANCE STATUS**
* https://ecog-acrin.org/resources/ecog-performance-status/

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**FMO ne mutation burden per MB**

* **'FMOne mutation burden per MB'** - Tumor Mutational Burden (TMB) measured with Foundation Medicine panel; <https://www.foundationmedicine.com/test/foundationone-cdx>
* **Tumor mutational burden (TMB)—**the number of somatic mutations per DNA megabase (Mb), used as neoantigen burden that is an independent biomarker associated with ICPI outcomes
  + TMB can be reliably estimated using validated algorithms from next‐generation sequencing assays that interrogate a sufficiently large subset of the exome as an alternative to whole‐exome sequencing.
  + elevated TMB can result from :
    - exposure to cigarette smoke
    - ultraviolet radiation
    - deleterious mutations in mismatch repair leading to microsatellite instability,
    - or from mutations in the DNA repair machinery.
  + patients with higher TMB experience longer survival and greater response rates following treatment with ICPIs compared with those who have lower TMB levels
    - example : TMB threshold of ≥10 mutations per Mb to be predictive of longer progression‐free survival in patients with non‐small cell lung cancer
  + CAUTION: Methods for the calculation of TMB are not standardized between laboratories, with significant variables being the gene content of the panels sequenced and the inclusion or exclusion of synonymous variants in the calculations.

**Articles and online materials**

* **Comparison of commonly used solid tumor targeted gene sequencing panels for estimating tumor mutation burden shows analytical and prognostic concordance within the cancer genome atlas cohort** <https://jitc.bmj.com/content/8/1/e000613>
  + Caution; they used somatic sniper, from David E. Larson, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3268238/>
  + Its early version had problems with fixed number of case-control samples, and min-max used for estimating most probable combination of variants at a given position, then tested with multinomial distrib.
  + It could lead to several artifacts, by lowering the number of observed/accepted variants, even if supported by empirical data
* **Tumor Mutational Burden as a Predictive Biomarker for Response to Immune Checkpoint Inhibitors:** A Review of Current Evidence Published online 2019 Oct 2. doi: [10.1634/theoncologist.2019-0244](https://doi.org/10.1634%2Ftheoncologist.2019-0244)
* **Comparison of commonly used solid tumor targeted gene sequencing panels for estimating tumor mutation burden shows analytical and prognostic concordance within the cancer genome atlas cohort https://jitc.bmj.com/content/jitc/8/1/e000613.full.pdf**

**Neoantigen burden per MB**

* **tumor neoantigen burden (TNB)** is defined by the number of neoantigens per megabase in the genome region ([13](https://www.frontiersin.org/articles/10.3389/fonc.2021.672677/full#B13), [14](https://www.frontiersin.org/articles/10.3389/fonc.2021.672677/full#B14)). Notably, TMB has become a biomarker for immunotherapy, assuming that higher TMB will increase the probability of tumor neoantigens and specific T-cell responses ([15](https://www.frontiersin.org/articles/10.3389/fonc.2021.672677/full#B15)).
  + CHALLENGES:
    - not all mutations produce neoantigens. Only a limited number of mutations can be properly processed, presented on the surface of the MHC complex and recognized by T cells ([19](https://www.frontiersin.org/articles/10.3389/fonc.2021.672677/full#B19))
    - The TMB noted in **pediatric tumors is considerably low** ([20](https://www.frontiersin.org/articles/10.3389/fonc.2021.672677/full#B20)). However, in certain tumors, such as pediatric medulloblastoma or acute lymphoblastic leukemia, which exhibit minimal mutational burden, a strong anti-tumor immune response can be induced by **high-quality neoantigens** ([21](https://www.frontiersin.org/articles/10.3389/fonc.2021.672677/full#B21), [22](https://www.frontiersin.org/articles/10.3389/fonc.2021.672677/full#B22)).
  + TNB vs TMB
    - A positive correlation has been noted between TMB and TNB.
    - However, TNB is directly used for neoantigen evaluation and may be considered an improved biomarker for immunotherapy compared with TMB ([23](https://www.frontiersin.org/articles/10.3389/fonc.2021.672677/full#B23)–[25](https://www.frontiersin.org/articles/10.3389/fonc.2021.672677/full#B25)).
    - High TNB was associated with durable progression-free survival (PFS) in patients with non-small cell lung cancer (NSCLC) treated with programmed death 1 (PD-1) inhibitors ([26](https://www.frontiersin.org/articles/10.3389/fonc.2021.672677/full#B26)). In addition, TNB correlated with clinical benefit in patients with metastatic melanoma treated with cytotoxic T-lymphocyte-associated protein 4 (CTLA4) inhibitors ([27](https://www.frontiersin.org/articles/10.3389/fonc.2021.672677/full#B27)). Similarly, a phase I/II trial performed in patients with stage IV melanoma demonstrated that their clinical benefit was associated with a proposed immune activation signatures score. Among the score items, high TMB and predicted TNB were significantly associated with improved PFS and overall survival ([28](https://www.frontiersin.org/articles/10.3389/fonc.2021.672677/full#B28)). The present review investigated the application of TNB as a biomarker in immunotherapy and other therapies and provided an in-depth discussion of the mechanisms, clinical application and challenges of this biomarker.

**Articles and online materials**

* **Beyond Tumor Mutation Burden: Tumor Neoantigen Burden as a Biomarker for Immunotherapy and Other Types of Therapy Front. Oncol., 29 April 2021 |**[**https://doi.org/10.3389/fonc.2021.672677**](https://doi.org/10.3389/fonc.2021.672677)
  + **the potential application of TNB as a biomarker was evaluated.**
  + **The methods of neoantigen prediction were summarized and the mechanisms involved in TNB were investigated.**
  + **The impact of high TNB and increased number of infiltrating immune cells on the efficacy of immunotherapy was also addressed.**

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