FOUNDATION MEDICINE®

Tumor Mutational Burden

Frequently Asked Questions

What is tumor mutational burden (TMB)?

Tumor mutational burden (TMB) is an emerging biomarker that may provide guidance to oncologists who are deciding whether to treat their patients with immunotherapies. TMB measures the extent of somatic mutations within a tumor to approximate the burden of neo-antigens, thereby providing a measure of the probability that a patient may benefit from immunotherapy based on his or her likelihood of developing an immune response.

Why is TMB important?

Higher levels of TMB correlate with increased expression of neo-antigens, which help our immune system recognize tumors. TMB can help identify patients who may be more likely to benefit from cancer immunotherapies in some tumor types.[1] Identifying these patients in advance of treatment with immunotherapy is critical given its high cost and the potential for severe side effects.

Foundation Medicine has conducted six retrospective clinical studies of TMB in more than 1,300 patients across 21 different cancer types, and results have shown that TMB may be able to effectively stratify patients based on response to and survival on immunotherapy.[2] The first prospective, randomized clinical trial using TMB as a biomarker for first-line, non-small cell lung cancer patients achieved its coprimary endpoint of improved progression-free survival (PFS) for patients with high TMB (≥ 10 mut/Mb) receiving combination immunotherapy versus chemotherapy regardless of PD-L1 IHC expression.[3]

How is TMB different than programmed death ligand-1 (PD-L1)?

PD-L1 is a protein that allows cells to escape attack of specific immune cells. Normally, healthy cells use PD-L1 to keep the immune response from overreacting, or "in check". But in cancer, tumor cells can hijack this 'checkpoint' mechanism to avoid an immune response by specialized immune cells—called T-cells— that would normally attack cancer cells. Immunotherapies, sometimes called checkpoint inhibitors, block the activity of PD-L1, thereby returning T-cells to their "active" state and allowing recognition of the cancer cells in order to kill them. Checkpoint inhibitors have been shown to provide benefit for a subset of cancer patients across cancer types.

PD-L1 testing with immunohistochemistry (IHC) provides an estimate of the level of the protein in tumor cells, determined by looking at a stained biopsy slide of cancer tissue. Patients with high PD-L1 scores may be more likely to benefit from immunotherapy. However, PD-L1 testing has been shown to provide inconsistent results as a consequence of a complex and variable sample preparation process, multiple scoring criteria, and subjective interpretation. TMB is a quantitative biomarker that is measured across many genes—rather than only those associated with DNA mismatch repair (MMR)—through comprehensive genomic profiling, thus eliminating the subjectivity in testing and interpretation.[4]

At the 2017 American Association of Cancer Research Annual Meeting, Foundation Medicine presented results from over 88,000 clinical samples which demonstrated that a relatively high proportion of advanced skin, lung, bladder and other cancers had high levels of TMB. The published TMB validation from Foundation Medicine analyzed over 100,000 human cancer genomes across hundreds of tumor types to more precisely map the distribution of TMB.[2]

These large-scale studies reveal that there are some patients with high-TMB across cancers, including those for which immunotherapies are not typically considered – such as brain, breast, soft tissue angiosarcomas and cancers of unknown primary origin.[1] With further studies, this could mean that TMB has the ability to predict response to immunotherapy for many cancer types and provide an important alternative to PD-L1 expression by IHC in many settings.

How is TMB different than *EGFR* and *ALK*?

EGFR and *ALK* are common oncogenic drivers in lung cancer, and certain alterations in these genes may identify patients who are eligible for associated targeted therapies that target *EGFR* or *ALK*. However, patients without alterations in oncogenes such as *EGFR* and *ALK* may have cancers that can be successfully targeted by other approaches, such as immunotherapy, and TMB is a biomarker that could help inform those decisions. Unlike targeted therapies, which target specific proteins responsible for cancer growth, immunotherapies use the body's immune system to attack cancer cells.

Traditional single-gene tests can detect alterations in *EGFR* or *ALK* but they do not include information on biomarkers such as TMB. Single gene tests also fail to guide treatment when tumors are *EGFR*- or *ALK*-negative. Comprehensive genomic profiling tests performed by Foundation Medicine provide results on genomic alterations in these and many other oncogenes, and on biomarkers like TMB, all from a single biopsy. These results can be used to inform treatment with targeted therapies and help inform immunotherapy decisions.

How is TMB measured at Foundation Medicine?

TMB is a measure of the somatic mutation rate within a tumor genome, and it is reported as the number of mutations per megabase of DNA sequenced. A sufficient area of the tumor genome, typically greater than 800,000 base pairs, must be sequenced in order to accurately report TMB.[5] TMB also requires accurately removing inherited, or germline, mutations from the count, as well as removing particular mutations associated with cancer, such as *EGFR* or *ALK*, in order to reduce the bias associated with a gene panel that focuses on cancer-driving mutations. FoundationOne®—and by extension FoundationOne CDx™—has been validated to accurately assess TMB in this way.[4] This provides a clinically viable way to report TMB, which may help with treatment decisions for patients with certain cancers, such as non-small cell lung cancer.

How is TMB on Foundation Medicine tests different than whole exome sequencing (WES)?

Whole exome sequencing (WES) is one method that can be used to assess TMB but given the time-consuming and costly nature of this process, it may not be practical for clinical decision-making. TMB, as measured by comprehensive genomic profiling tests such as FoundationOne CDx and FoundationOne, can demonstrate accuracy compared with WES and can be performed in clinical practice.[2] Furthermore, there is a growing body of evidence to support the clinical utility of TMB from FoundationOne or FoundationOne CDx compared to TMB derived from WES.

Why does Foundation Medicine classify patients as TMB-high for scores ≥ 20 mut/MB?

Foundation Medicine reports TMB results as both the quantitative measurement in mutations per megabase, as well as a qualitative status of high, intermediate and low. These three categories were initially developed as a reference against the general population distribution of TMB.[1] We expect that over time each cancer subtype will be defined according to a specific TMB cutoff that segments the population according to response and survival based on a specific immunotherapy.

I am interested in getting my patients tested for TMB.

TMB is currently provided on all FoundationOne CDx, FoundationOne and FoundationOneHeme reports. Please visit *www.foundationmedicine.com/genomic-testing/order* to learn more about how to order.

Reference

1. Goodman AM, et al. Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers. Mol Cancer Ther. 2017 Nov;16(11):2598-2608.
2. Chalmers ZR, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Medicine. 2017;9:34.
3. Carbone DP, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small Cell Lung Cancer. N Engl J Med. 2017;376:2415-2426.
4. Kerr KM, Hirsch FR. Programmed death ligand-1 immunohistochemistry friend or foe? Arch Pathol Lab Med. 2016;140:326–31.
5. Campesato LF, et al. Comprehensive cancer-gene panels can be used to estimate mutational load and predict clinical benefit to PD-1 blockade in clinical practice. Oncotarget. 2015 Oct 27;6(33):34221-7.

FOUNDATION MEDICINE®

www.foundationmedicine.com | Tel. 888.988.3639 | Fax 617.418.2290 | MKT-0193-02