

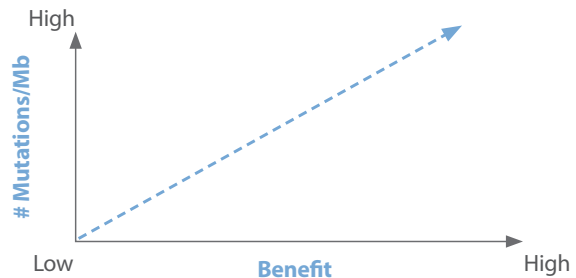
# Tumor Mutational Burden (TMB) Threshold Aligned Across all Solid Tumors *Powered by Whole Exome Sequencing*

## TMB Is a Pan-Tumor Biomarker for IO Response

TMB by Whole Exome Sequencing measures the total number of non-synonymous, somatic mutations identified per megabase (Mb) of the genome coding area of DNA (a megabase is 1,000,000 DNA basepairs).

- Non-synonymous mutations are changes in DNA that result in amino acid changes in the protein.<sup>1,2</sup>
- The new protein changes result in new shapes (neo-antigens) that are considered to be foreign to the immune system.<sup>1,3</sup>
- Immune checkpoint inhibitors are able to stimulate and allow the immune system to detect these neo-antigens and destroy the tumor.<sup>1</sup>
- Germline (inherited) mutations are not included in TMB because the immune system has a higher likelihood of recognizing these alterations as normal.<sup>4</sup>

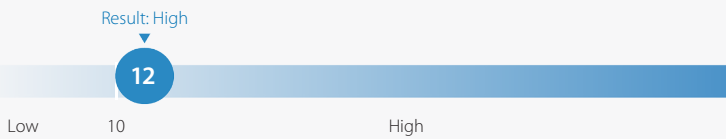
### TMB: Immune Checkpoint Indication for Response



**Tumors with significant numbers of mutations resulting in altered proteins (neo-antigens) may respond more effectively to immunotherapies.**

TMB has emerged as an important biomarker when considering immunotherapy in solid tumors. This is highlighted by the recent U.S. FDA accelerated approval of pembrolizumab (KEYTRUDA®) for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [ $\geq 10$  mutations/megabase (mut/Mb)] solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. This approval is based on the results of the KEYNOTE-158 trial, which achieved an overall response rate of 29% (95% CI: 21, 39), with a 4% complete response rate and 25% partial response rate.<sup>5</sup>

## Genomic Signatures

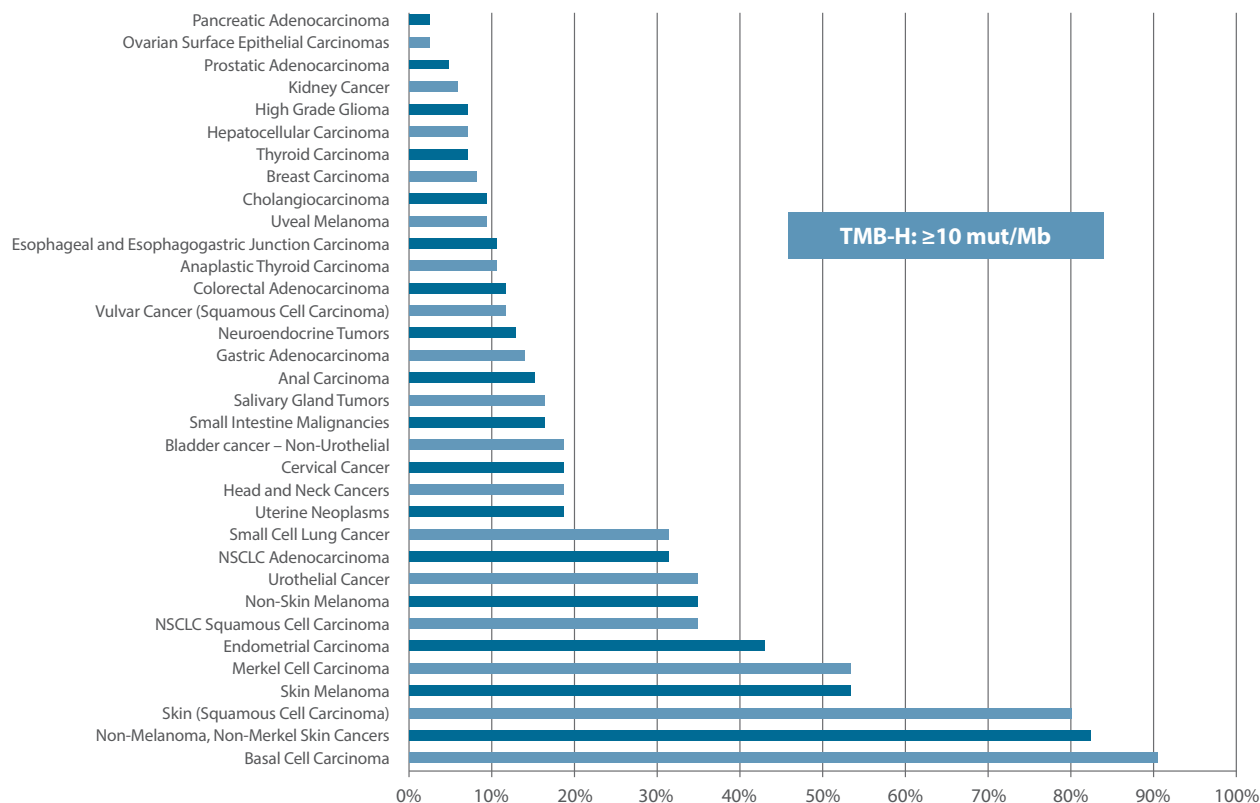
Biomarker	Method	Analyte	Result
Microsatellite Instability (MSI)	Seq	DNA-Tumor	Stable
Tumor Mutational Burden (TMB)	Seq	DNA-Tumor	<div style="text-align: center;">                     Result: High   </div>
Genomic Loss of Heterozygosity (LOH)	Seq	DNA-Tumor	Low - 12% of tested genomic segments exhibited LOH (assay threshold is $\geq 16\%$ )

**TMB is included with all Caris Molecular Intelligence orders (MI Profile™ and MI Tumor Seek™) and is performed using Whole Exome Sequencing**



# Caris Molecular Intelligence TMB-H Cutoff Aligned Across All Solid Tumors

## High TMB Across 60,000 Caris Molecular Intelligence Cases



**Genomic profiling with Caris Molecular Intelligence can help you make more informed therapy decisions when considering immune checkpoint inhibitors.**

In addition, Caris has been working in collaboration with the Friends of Cancer Research *TMB Harmonization Project* to systematically characterize and standardize TMB testing and reporting to a common industry standard.<sup>6</sup> Based on this collective work and exciting KEYNOTE-158 result and drug approval, Caris has updated the TMB high/low threshold to reflect greater than or equal to 10 mutations per megabase across all solid tumors, aligning the testing results to pembrolizumab for TMB-H cases.<sup>5</sup>

### References

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4. Stewart TJ. *Oncogene.* 2008;27:5894-5903. doi:10.1038/onc.2008.268
5. U.S. Food and Drug Administration. (2020, June 16). FDA approves pembrolizumab for adults and children with TMB-H solid tumors [Press release].
6. Stenzinger, A, Allen, JD, Maas, J, et al. Tumor mutational burden standardization initiatives: Recommendations for consistent tumor mutational burden assessment in clinical samples to guide immunotherapy treatment decisions. *Genes Chromosomes Cancer.* 2019; 58: 578– 588. <https://doi.org/10.1002/gcc.22733>

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