CARIS MI®
MOLECULAR INTELLIGENCE

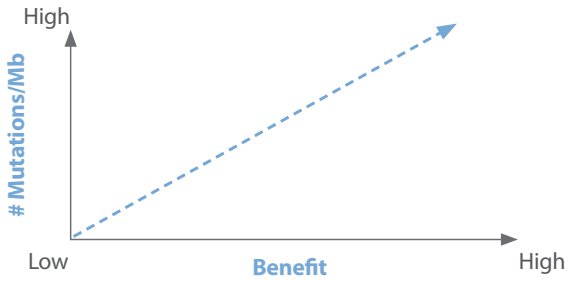
Tumor Mutational Burden (TMB) Threshold Aligned Across all Solid Tumors
Powered by Whole Exome Sequencing

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.[1,2]
- The new protein changes result in new shapes (neo-antigens) that are considered to be foreign to the immune system.[1,3]

TMB: Immune Checkpoint Indication for Response



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

- Immune checkpoint inhibitors are able to stimulate and allow the immune system to detect these neo-antigens and destroy the tumor.[1]
- Germline (inherited) mutations are not included in TMB because the immune system has a higher likelihood of recognizing these alterations as normal.[4]

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) [≥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.[5]

Genomic Signatures

Biomarker	Method	Analyte	Result
Microsatellite Instability (MSI)	Seq	DNA-Tumor	Stable
Tumor Mutational Burden (TMB)	Seq	DNA-Tumor	Result: High 12 — Low 10 High
Genomic Loss of Heterozygosity (LOH)	Seq	DNA-Tumor	Low - 12% of tested genomic segments exhibited LOH (assay threshold is ≥ 16%)

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

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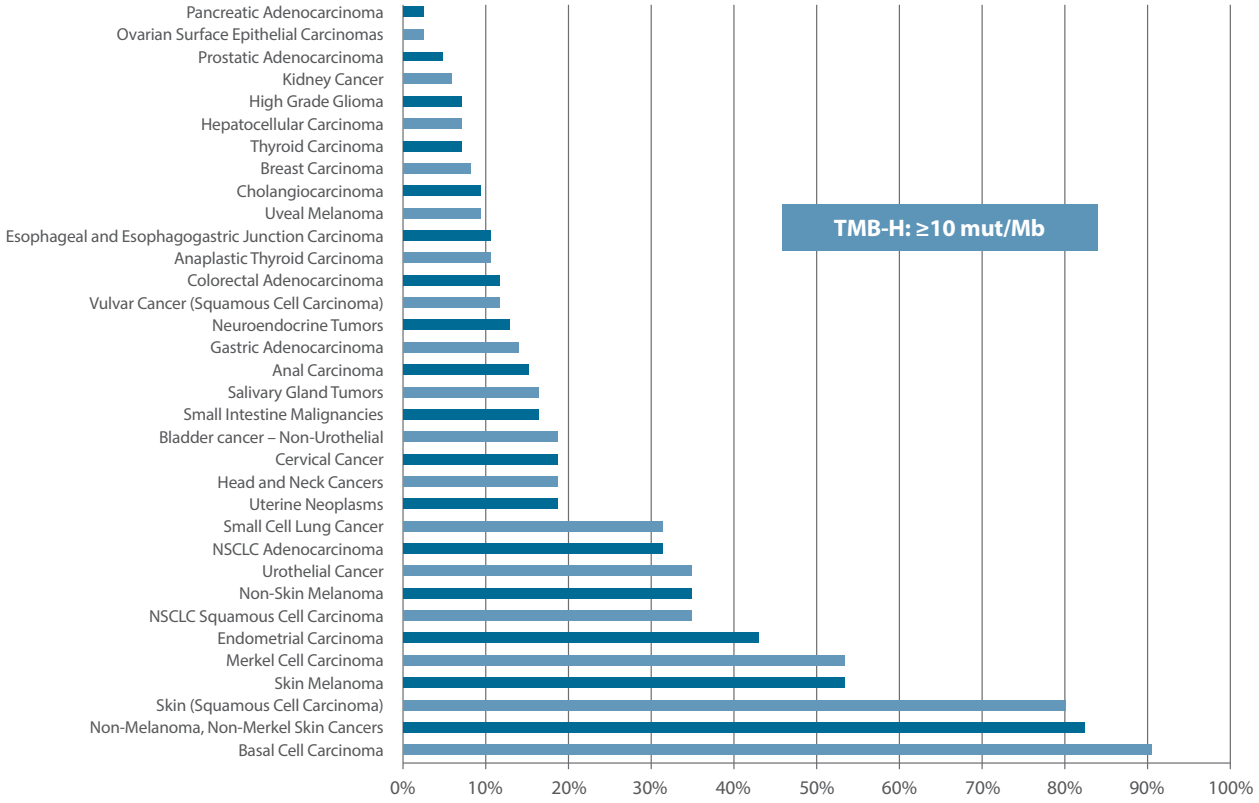
Caris Molecular Intelligence TMB-H Cutoff Aligned Across All Solid Tumors

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.[6] 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.[5]

References

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2. Le DT. N Engl J Med. 2015;372:2509-2520. doi:10.1056/NEJMoa1500596
3. Rosenberg JE. The Lancet. 2016; 387(10031):1909-1920. doi:10.1016/S0140-6736(16)00561-4.
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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