TUMOR MUTATIONAL BURDEN:
AN EMERGING BIOMARKER IN IMMUNO-ONCOLOGY

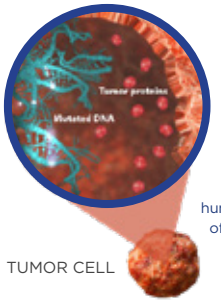
The immune system is complex and dynamic, with a number of different mechanisms through which the body can fight cancer. However, these mechanisms also can be manipulated by cancer to grow and spread.

Every patient's cancer is unique, and that's why Bristol-Myers Squibb researchers are investigating the potential of predictive biomarkers—biological signs that can be measured—to help select the right treatment for each individual patient at each stage of therapy.

Tumor mutational burden (TMB), a measurement of the mutations carried by tumor cells, is one type of biomarker that is being studied to evaluate its association with response to Immuno-Oncology (I-O) therapy.

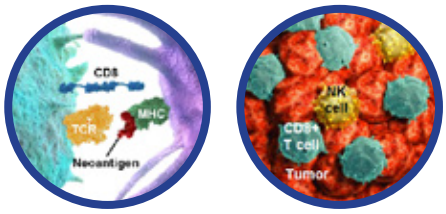
TUMOR MUTATIONS AND THE IMMUNE RESPONSE

- Tumors may accumulate mutations in their genetic material as they grow.
- These acquired (or "somatic") mutations can be passed along to new cancer cells during cell division.
- Acquired mutations in tumor cells may alter the expression of proteins, resulting in the formation of neoantigens—bits of protein presented on the surface of the tumor cell. Not all tumor mutations result in altered proteins.
- These neoantigens can be recognized by T cells, inciting an anti-tumor immune response.



TUMOR CELL

Individual tumor cells can contain hundreds to thousands of mutations, some of which may alter key cellular functions.



Memory T cells learn to recognize specific antigens and can respond quickly when exposed again. Effector T cells respond to memory cell activation and then assist in the immune response.

HOW IS TMB MEASURED?

- DNA sequencing is typically used to determine the number of acquired mutations in the tumor.
- TMB is reported as the number of mutations in a specific area of genetic material, such as:
  - Mutations in a single cell
  - Mutations in an entire tumor
  - Mutations per megabase, or an area of the genome equal to the length of 1 million bases (the four chemicals that serve as the building blocks of DNA)

TUMOR MUTATIONAL BURDEN AS A POTENTIAL IMMUNE BIOMARKER

Measuring the quantity of mutations carried by a tumor—the tumor mutational burden (TMB)—is under investigation to evaluate whether TMB may help predict the likelihood that a patient will benefit from certain I-O therapies.

- Tumor cells with high TMB may have more neoantigens, with an associated increase in cancer-fighting T cells in the tumor microenvironment and periphery.
- Therefore, high TMB may indicate a higher likelihood of responding to I-O treatment.
- TMB levels vary by tumor type, with some tumors more likely to express high TMB and others expressing low TMB levels.

Bristol-Myers Squibb is committed to ongoing research exploring TMB as a potential biomarker in clinical trials.

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