Understanding the Science Behind Immuno-Oncology
Using the body’s natural immune response to fight cancer

Bristol-Myers Squibb: At the forefront of Immuno-Oncology research
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References

Abbreviations
Revealing the potential of the immune system in cancer

Introduction to the tumor microenvironment and the immune response

The immune system is able to recognize foreign threats (nonself) as distinct from normal cells (self). Innate and adaptive immunity act as complementary networks of self-defense against foreign threats, such as pathogens and cancer.

In cancer, normal cells have mutated into tumor cells and are recognized as nonself by both the innate and adaptive immune systems.

Antitumor activity of the innate and adaptive immune responses

- **Innate immune response**: The first line of defense. It rapidly identifies and attacks tumor cells without antigen specificity. It recognizes activating and inhibitory signals from target cells to distinguish self from nonself.
  - **NK cells** are the main effector cells of the innate immune system.

- **Adaptive immune response**: An antigen-specific and durable response. Once activated, it can be sustained through immune memory.
  - **Cytotoxic T cells** are effector cells of the adaptive immune system.

The antitumor activity of NK and cytotoxic T cells is regulated through a network of activating and inhibitory signaling pathways:

- **Activating pathways**: Pathways that trigger immune responses
- **Inhibitory pathways**: Pathways that counterbalance immune activation

The balance between activating and inhibitory pathways normally enables the immune system to attack tumor cells, while sparing healthy cells.
Key stages of the antitumor immune response

In both the innate and adaptive immune responses, immune cells have the potential to recognize and eliminate tumor cells. There are 3 principal stages in this process:

**Presentation**
The innate immune system rapidly identifies and attacks tumor cells. Tumor cell death releases tumor antigens, which can activate the cytotoxic T cells of the adaptive immune system.16,17

**Infiltration**
Tumor antigens and other factors attract immune cells to the tumor site, where they invade and attack.17

**Elimination**
Activated cytotoxic T cells recognize tumor cells as the source of the antigen and target them for elimination.17

Tumor cells can evade and suppress immune activity

The complex network of activating and inhibitory pathways enables the antitumor immune response to detect and eliminate tumor cells at any point in tumor development.18 However, tumors seek to evade or suppress the body’s natural ability to fight cancer, and they can evolve at any phase of growth to “outsmart” the antitumor immune response.18,19

The tumor microenvironment consists of different cell types that help tumor cells evade antitumor immune activity.20,21 As tumors evolve, they can influence the activation and composition of cells within the tumor microenvironment.19

Immune pathways combine to refine response

The 3 stages of the immune response—presentation, infiltration, and elimination—are regulated through a network of activating and inhibitory signaling pathways that combine to maintain immune balance.3,14,17 Reestablishing fundamental stages of immune response that are impaired within noninflamed tumors is a strategy to improve the broad potential of I-O.

*Targets are listed by primary mechanisms. Secondary mechanisms may exist.

Various components of the immune system and the tumor microenvironment, including APCs, immune regulatory cells, stromal cells, and the tumor itself, regulate the ability of effector cells to eliminate tumors.3,14,22,23 Ongoing I-O research at Bristol-Myers Squibb is exploring how targeting these components, either alone or in combination, may restore the body’s natural ability to fight cancer.

Deep insight into tumor-intrinsic signaling and immune biology continues to inform and inspire discoveries—enabling the development of novel combination therapies.
Select pathways that modulate NK-cell activity

Current research is investigating the following NK-cell mechanisms to understand how they can be modulated to restore the body’s natural ability to fight cancer.

- **SLAMF7** is an activating receptor on the surface of NK cells and other immune cells. When engaged, SLAMF7 activates NK cells, the rapid responders of the immune system and the body’s first line of defense against cancer.
  - Activating pathway

- **KIR** is an inhibitory immune checkpoint receptor on NK and cytotoxic T cells that acts to stop NK cells from killing normal cells.
  - Inhibitory pathway

- **ICOS** is an activating receptor expressed on activated cytotoxic T cells, regulatory T cells, NK cells, and other types of T cells that can lead to the activation, proliferation, and survival of cytotoxic T cells, as well as the survival of memory T cells.
  - Activating pathway

- **Oncolytic viruses** are naturally occurring or genetically engineered viruses that preferentially target and replicate within tumor cells, leading to tumor cell destruction and activation of the antitumor immune response.
  - Activating pathway

Select pathways that modulate effector T-cell activity

Current research is investigating the following effector T-cell mechanisms to understand how they can be modulated to restore the body’s natural ability to fight cancer.

- **CTLA-4** is an immune checkpoint receptor on activated T cells that inhibits T-cell activation. CTLA-4 signaling diminishes the ability of memory T cells to sustain an immune response.
  - Inhibitory pathway

- **PD-1** is an immune checkpoint receptor on cytotoxic T cells that plays a key role in T-cell exhaustion and prevention of autoimmunity.
  - Inhibitory pathway

- **ICOS** is an activating receptor expressed on activated cytotoxic T cells, regulatory T cells, NK cells, and other types of T cells that can lead to the activation, proliferation, and survival of cytotoxic T cells, as well as the survival of memory T cells.
  - Activating pathway

- **Oncolytic viruses** are naturally occurring or genetically engineered viruses that preferentially target and replicate within tumor cells, leading to tumor cell destruction and activation of the antitumor immune response.
  - Activating pathway

- **TIM-3** is an immune checkpoint receptor involved in the suppression of both innate and adaptive immune cells. It is expressed on the surface of a wide variety of immune cells, including cytotoxic T cells, Tregs, NK cells, and some APCs, such as DCs.
  - Inhibitory pathway
Select pathways that modulate non–effector-cell activity

Current research is investigating the following non–effector-cell mechanisms to understand how they can be modulated to restore the body’s natural ability to fight cancer.

**NLRP3**

NLRP3 is a protein expressed in APCs, such as DCs, monocytes, and macrophages.75-76 NLRP3 is involved in the assembly of the NLRP3 inflammasome, a protein complex that is a key mediator of innate immunity and the priming of T cells.71-72

**Activating pathway**

**CSF1R**

CSF1R is a receptor on the surface of macrophages and other cells of the myeloid lineage.86 The CSF1/CSF1R pathway is a dominant regulator of macrophage differentiation and function.87

**Inhibitory pathway**

**CTLA-4**

CTLA-4 is an immune checkpoint receptor that, in addition to being expressed on activated T cells, is also found on Tregs, where it is a key driver of their ability to suppress the immune response and counterbalance excessive immune activation.15,22,48,49,88,89

**Inhibitory pathway**

**Select tumor cell pathways**

Current research is investigating the following tumor cell mechanisms to understand how they can be modulated to inhibit tumor growth and induce the body’s natural ability to fight cancer.

**CXCR4**

CXCR4 is a G-protein–coupled receptor on immune cells and tumor cells that directs the migration and recruitment of immune cells.100-101 CXCR4 is implicated in biological processes, such as immune response and cardiovascular development.110

**Tumor pathway**

**BET**

BET is a family of proteins that are widely expressed and are responsible for regulating a variety of cellular processes.112-115 In cancer, they upregulate the transcription of c-Myc, which is a major factor in the regulation of tumor proliferation.116

**Tumor pathway**

**BCR-ABL**

BCR-ABL is a protein expressed in tumor cells, promoting their proliferation and their resistance to apoptosis.117-121

**Tumor pathway**
Biomarkers in I-O research

With a focus on precision medicine, our research and development program aims to rapidly translate research into novel regimens to accelerate delivery of the right treatment, for the right patient, at the right time. Biomarkers are biologic molecules, cells, or processes found in tissues or body fluids (such as blood) that are a sign of a normal or abnormal process or disease.\textsuperscript{122,123}

I-O biomarkers are a class of biomarker that can help evaluate an active antitumor immune response within the body.\textsuperscript{124} I-O biomarkers can be prognostic, predictive, or pharmacodynamic, or a combination\textsuperscript{125-128}:

- **Prognostic biomarkers** may identify the likelihood of a clinical event, such as disease progression, disease recurrence, or death, independent of the therapy received.\textsuperscript{125,126}

- **Predictive biomarkers** may identify whether individuals are more likely to experience a favorable or unfavorable response to treatment.\textsuperscript{125,126}

- **Pharmacodynamic biomarkers** may show that a biologic response has occurred in an individual who has received treatment.\textsuperscript{126,127}

As we continue to learn more about cancer biology—and with advancements in high-throughput technologies—the goal of I-O biomarker testing will be to provide actionable information toward developing personalized I-O therapy, including combinations with other treatment modalities.\textsuperscript{129,130}

Bristol-Myers Squibb aims to identify clinical characteristics and I-O biomarkers to determine the patient populations most likely to benefit from I-O therapy. I-O biomarker research aims to further characterize the unique interplay between the immune system and tumor cells in the following categories:

- **TUMOR ANTIGENS**
  - Tumor antigens are recognized as nonself or foreign by the host immune system and can initiate the adaptive immune response.
  - Neoantigens | TMB | MSI-H/dMMR

- **INFLAMED TUMORS**
  - Inflamed tumors show evidence of immune-cell infiltration and activation in the tumor microenvironment.
  - PD-L1 | PD-L2 | TILs | Inflammation gene signatures

- **IMMUNE SUPPRESSION**
  - Cells and proteins within the tumor and its microenvironment are associated with inhibition of the antitumor immune response.
  - LAG-3 | Tregs | MDSCs | IDO1

- **HOST ENVIRONMENT**
  - Many factors within the host environment may play a role in modulating an immune response.
  - Microbiome

*Effector T cell or NK cell.

As I-O biomarkers are dynamic and complex, the presence or absence of any single I-O biomarker may not provide a complete understanding of the diverse interactions occurring within the tumor microenvironment.\textsuperscript{131-133}

A composite I-O biomarker evaluation may provide a more comprehensive assessment of immune status.\textsuperscript{132}
I-O is a different approach that fights cancer by targeting the immune system

Treatment approaches currently approved to fight cancer include chemotherapy, radiation, targeted therapy, and immunotherapy. Radiation, chemotherapy, and targeted therapy are all directed toward killing tumor cells.\textsuperscript{134-137}

In contrast, I-O seeks to activate the body’s natural immune response to fight cancer. This is a fundamentally different approach to cancer treatment.\textsuperscript{138}

With this approach comes unique considerations and distinctive characteristics that continue to be researched, such as:

- Immune responses having the potential to deepen and sustain over time
- Resistance to immunotherapy, which can be present at the start of treatment or form over time
- Unique patterns of response, such as pseudo-progression
- Comprehensive endpoint considerations
- Immune-mediated adverse reactions

Immune responses have the potential to deepen and sustain over time

The immune response evolves and expands over time by constantly recognizing and remembering tumor antigens. This ability—to propagate and perpetuate—suggests the adaptive nature of the immune response.\textsuperscript{17}

Immune responses are dynamic and have the potential to improve and deepen over time.\textsuperscript{139,140}

As the immune response continues to expand, some cytotoxic T cells mature into memory T cells that may provide long-term immune protection, even if the original stimulus is no longer present.\textsuperscript{13,140,141}
Resistance to immunotherapy can be present at the start of treatment or form over time

Advances in immunotherapy have resulted in enhanced antitumor responses. A significant challenge is the development of resistant disease and disease progression during or after therapy.\(^{19,142}\)

As tumors evolve over time, they can influence the activation and composition of cells within the tumor microenvironment.\(^{19,142}\) Some tumors do not respond from the beginning of treatment with immunotherapies, and this is termed “primary resistance.” In contrast, “acquired resistance” describes tumors that initially respond to immunotherapies, but then fail to respond after a period of time.\(^{143}\)

Identification of mechanisms of immunotherapy resistance is an area of research that will inform appropriate treatment options for patients.

Bristol-Myers Squibb is committed to understanding the tumor immune response and exploring mechanisms underlying primary and secondary acquired resistance.

Pseudo-progression may reflect development of antitumor immunity

The nature of the antitumor immune response can create the appearance of disease progression, either as tumor growth or appearance of new lesions.\(^{144,145}\) This is known as pseudo-progression. Pseudo-progression does not reflect tumor cell growth, but may be misclassified as disease progression.\(^{144,146,147}\)

Tumors may appear to grow or new lesions may appear when immune cells infiltrate the tumor site.\(^{144}\) Due to the time required to mount an adaptive immune response, pseudo-progression may also reflect continued tumor growth until a sufficient response develops.\(^{144,148}\)
Evolving clinical expectations in Immuno-Oncology

Pseudo-progression should be considered until disease progression can be confirmed

While uncommon, pseudo-progression is an important consideration when evaluating response to I-O therapies.\(^{148}\) Histologic confirmation is not always possible, but close monitoring of the following factors may help identify pseudo-progression\(^{144,147,149}\):

<table>
<thead>
<tr>
<th>DISEASE PROGRESSION</th>
<th>PSEUDO-PROGRESSION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Performance status</strong></td>
<td>Deterioration of performance</td>
</tr>
<tr>
<td><strong>Systemic symptoms</strong></td>
<td>Worsen</td>
</tr>
<tr>
<td><strong>Symptoms of tumor enlargement</strong></td>
<td>Present</td>
</tr>
<tr>
<td><strong>Tumor burden</strong></td>
<td>Increase</td>
</tr>
<tr>
<td></td>
<td>New lesions</td>
</tr>
<tr>
<td></td>
<td>Biopsy may reveal</td>
</tr>
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</table>

### Endpoint considerations for I-O research

The criteria currently used to assess potential benefit of cancer therapies are based on surgery, radiation therapy, and chemotherapy.\(^{150}\) However, for I-O—a different way to fight cancer—a more comprehensive approach to endpoint assessment may be needed to recognize potential benefit.\(^{151-155}\)

- **Overall survival (OS), progression-free survival (PFS), and overall response rate (ORR)** are among endpoints used to measure outcomes in oncology research. OS is the gold standard to assess therapeutic benefit when possible.\(^{156,157}\)

- In addition, key measures of response are magnitude (size)—measured as the proportion of patients with a predefined decrease in tumor burden, called the ORR—and duration (time)—assessed as the time from initial tumor response to disease progression, called the duration of response (DOR).\(^{156}\)

- Finally, other measures such as treatment-free survival (TFS) and patient-reported outcomes (PROs) may also integrate a patient’s QOL. TFS measures the time a patient spends off treatment, while incorporating QOL and toxicities experienced.\(^{158,159}\) PROs evaluate the impact of treatment on QOL based on the patient’s own account.\(^{160-162}\)

Assessing multiple measures can illustrate the full scope of clinical benefit.\(^{152-154,163}\)

Assessment of these measures in combination can provide a broad and comprehensive picture of the difference between the investigational arm and the control arm with respect to PFS and OS.\(^{152-154,163,164}\)
Each treatment approach can damage tumor and healthy cells related to their respective mechanism of action

Both traditional cancer therapies and immunotherapy can lead to adverse reactions related to their respective mechanisms of action.

**Radiation**

Radiation induces DNA damage by directing high-energy particles to cells.\(^{165,166}\) Adverse reactions observed with radiation exposure arise due to damage of normal cells in the irradiated sites.\(^{165,167}\)

**Chemotherapy**

Chemotherapy can cause damage to rapidly dividing cells, including tumor cells and healthy cells, such as hematopoietic stem cells and gastrointestinal mucosal epithelium cells, leading to adverse reactions.\(^{168-170}\)

**Targeted therapy**

Targeted therapies interfere with signaling pathways that promote cell proliferation.\(^{171}\) While targeted therapies have a high affinity for the molecule of interest, they can often bind to other molecules, resulting in both on- and off-target effects.\(^{172,174}\)

**Immunotherapy**

Immunotherapy promotes the antitumor response of activated cytotoxic T cells by targeting the immune system, enabling T cells to attack the tumor. However, this can sometimes cause T cells to target healthy tissue, leading to adverse events known as immune-mediated adverse reactions.\(^{175}\)

**Immune-mediated adverse reactions**

I-O therapies that modulate immune pathways may enable the immune system to attack healthy cells along with tumor cells. The effects are known as immune-mediated adverse reactions.\(^{176-179}\)

When managing complications of immune-mediated adverse reactions, please consider:

- Patients, caregivers, and physicians should be educated to remain vigilant throughout and after I-O treatment to potentially minimize complications, some of which may be life-threatening.\(^{179,180}\)
- Treatment algorithms are available for use by healthcare providers to assist them in managing immune-mediated adverse reactions.\(^{181,182}\)
- Recent guidelines have been published that provide consensus recommendations for the management of immune-mediated adverse reactions.\(^{182-184}\) Specific guidance for managing immune-mediated adverse reactions for an individual product can be found in the accompanying FDA-approved Prescribing Information.\(^{185}\)

As research in immunotherapy advances and more data are made available, understanding and effective management of immune-mediated adverse reactions will evolve.\(^{185}\)
Realizing the potential of Immuno-Oncology research

Depth of evidence for the immune response to cancer

Both solid tumors and hematologic malignancies are able to induce an immune response that can regulate their initial growth. This ability is known as **tumor immunogenicity**.186,187 The body is able to recognize and attack cancer through the following stages of immune response:

**PRESENTATION**

There is a broad range of tumors that are traditionally defined by high rates of mutations.188 These mutations create neoantigens that can be recognized by the immune system, activating an antitumor immune response.189

**INfiltrATION**

Tumor-infiltrating immune cells are present in the tumor microenvironment. Their presence demonstrates their capacity to identify and migrate to tumor cells.190-203

**ELIMINATION**

Early in their development, some tumors display evidence of spontaneous regression. This suggests that the immune system is able to recognize and eliminate some tumor cells and supports the concept that the body’s own immune system has the ability to induce an antitumor response against cancer.204

Broad potential of I-O research

Evidence for tumor immunogenicity across a wide range of solid tumors and hematologic malignancies provides the rationale for the breadth of I-O research across tumor types205:

<table>
<thead>
<tr>
<th>TUMOR TYPE*</th>
<th>PRESENTATION</th>
<th>INFILTRATION</th>
<th>ELIMINATION</th>
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<td>Bladder188,200</td>
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<td>Breast202,206</td>
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<tr>
<td>Gastric/esophageal193,207,208</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Glioblastoma189,191,209</td>
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<td>●</td>
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<td>Head and neck194,210</td>
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<td>Lung188,193</td>
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<tr>
<td>Melanoma188,193,204</td>
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<tr>
<td>Ovarian197,212</td>
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<tr>
<td>Pancreatic201</td>
<td>●</td>
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<tr>
<td>Prostate195,213</td>
<td>●</td>
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<td>●</td>
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<tr>
<td>Renal188,196</td>
<td>●</td>
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<tr>
<td>Non-Hodgkin lymphoma190,214,215</td>
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<tr>
<td>Hodgkin lymphoma199,216</td>
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<tr>
<td>Leukemia217</td>
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<tr>
<td>Multiple myeloma192,218</td>
<td>●</td>
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<td>●</td>
</tr>
</tbody>
</table>

*List of tumors represents common types of cancer but is not exhaustive.
I-O research is constantly evolving

Some of the ongoing research at Bristol-Myers Squibb focuses on:

› Building an understanding of the dynamic mechanisms that govern the immune system’s response to cancer
› Understanding the role of immune signaling pathways, either alone or in combination, and how they can be modulated to restore the body’s natural ability to fight cancer
› Identifying I-O biomarkers that clarify the unique interplay between the immune system and the tumor that may help to optimize personalized medicine and improve patient outcomes
› Developing a more comprehensive approach to endpoint assessment, to better recognize the potential benefit of I-O research

The potential of I-O research continues to expand, driven by the many patients with advanced cancer who await the offer of renewed hope and the potential of a longer life.

For more detailed information on the science behind I-O, please visit IOHCP.com.

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## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>APC</td>
<td>antigen-presenting cell</td>
</tr>
<tr>
<td>BET</td>
<td>bromodomain and extraterminal domain</td>
</tr>
<tr>
<td>BCR-ABL</td>
<td>breakpoint cluster region-Abelson</td>
</tr>
<tr>
<td>CCR2</td>
<td>chemokine (C-C motif) receptor 2</td>
</tr>
<tr>
<td>CCR5</td>
<td>chemokine (C-C motif) receptor 5</td>
</tr>
<tr>
<td>CSF1</td>
<td>colony-stimulating factor 1</td>
</tr>
<tr>
<td>CSF1R</td>
<td>colony-stimulating factor 1 receptor</td>
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<td>CCR1</td>
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<td>CT1A</td>
<td>cytotoxic T-lymphocyte antigen 1</td>
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<td>CT1A</td>
<td>cytotoxic T-lymphocyte antigen 4</td>
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<tr>
<td>DC</td>
<td>dendritic cell</td>
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<tr>
<td>dMMR</td>
<td>mismatch repair deficient</td>
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<td>EP4</td>
<td>prostaglandin E receptor 4</td>
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<tr>
<td>ICOS</td>
<td>inducible T-cell co-stimulator</td>
</tr>
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<td>IDO1</td>
<td>indoleamine 2,3-dioxygenase-1</td>
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<td>immunoglobulin</td>
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<td>immunoreceptor tyrosine-based inhibitory motif</td>
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<td>killer cell immunoglobulin-like receptor</td>
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<td>lymphocyte-activation gene 3</td>
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<td>myeloid-derived suppressor cell</td>
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<td>microsatellite instability-high</td>
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<td>NK</td>
<td>natural killer</td>
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<td>NLRP3</td>
<td>nucleotide-binding oligomerization domain-like receptor family, pyrin domain containing 3</td>
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<td>programmed death receptor-1</td>
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<td>QOL</td>
<td>quality of life</td>
</tr>
<tr>
<td>SLAMF7</td>
<td>signaling lymphocytic activation molecule family member 7</td>
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<tr>
<td>STING</td>
<td>stimulator of interferon genes</td>
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<tr>
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<tr>
<td>TIGIT</td>
<td>T-cell immunoreceptor with Ig and ITIM domains</td>
</tr>
<tr>
<td>TIL</td>
<td>tumor-infiltrating lymphocyte</td>
</tr>
<tr>
<td>TIM-3</td>
<td>T-cell immunoglobulin mucin-3</td>
</tr>
<tr>
<td>TMB</td>
<td>tumor mutational burden</td>
</tr>
<tr>
<td>Treg</td>
<td>regulatory T cell</td>
</tr>
</tbody>
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## Notes