

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*



Bristol-Myers Squibb



Immuno-Oncology



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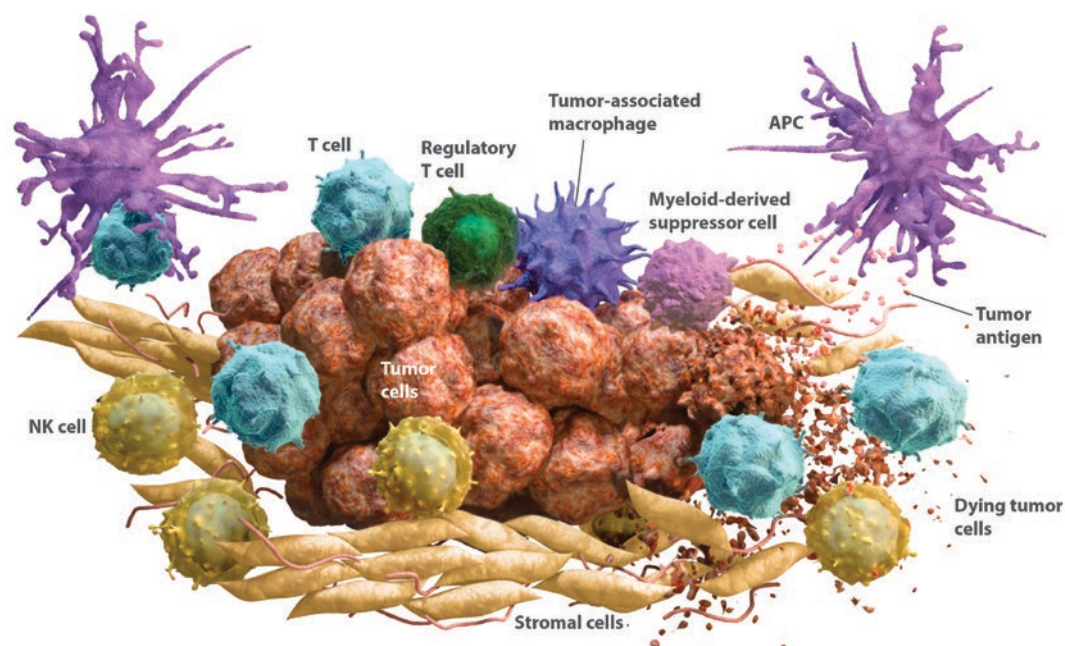
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Revealing the potential of the immune system in cancer

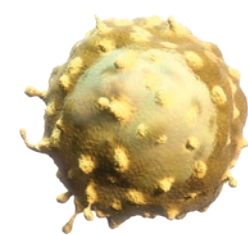
Introduction to the tumor microenvironment and the immune response

The immune system is able to recognize **foreign threats (nonself)** as distinct from **normal cells (self)**.¹⁻³ Innate and adaptive immunity act as complementary networks of self-defense against foreign threats, such as pathogens and cancer.⁴

In cancer, normal cells have mutated into tumor cells and are recognized as nonself by both the innate and adaptive immune systems.^{5,6}

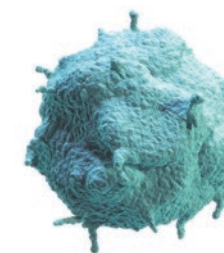


Antitumor activity of the innate and adaptive immune responses



Innate immune response

The first line of defense. It rapidly identifies and attacks tumor cells without antigen specificity.^{4,5,7-10} It recognizes activating and inhibitory signals from target cells to distinguish self from nonself.⁸⁻¹⁰ **NK cells** are the main effector cells of the innate immune system.^{11,12}



Adaptive immune response

An antigen-specific and durable response.^{4,7} Once activated, it can be sustained through immune memory.¹³ **Cytotoxic T cells** are effector cells of the adaptive immune system.⁴

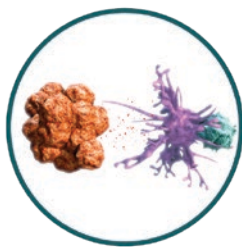
The antitumor activity of NK and cytotoxic T cells is regulated through a network of **activating** and **inhibitory** signaling pathways^{3,14,15}:



The **balance between activating and inhibitory pathways** normally enables the immune system to attack tumor cells, while sparing healthy cells.¹⁵

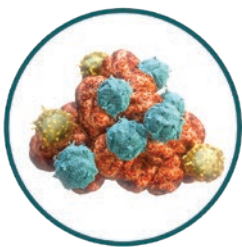
Key stages of the antitumor immune response

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

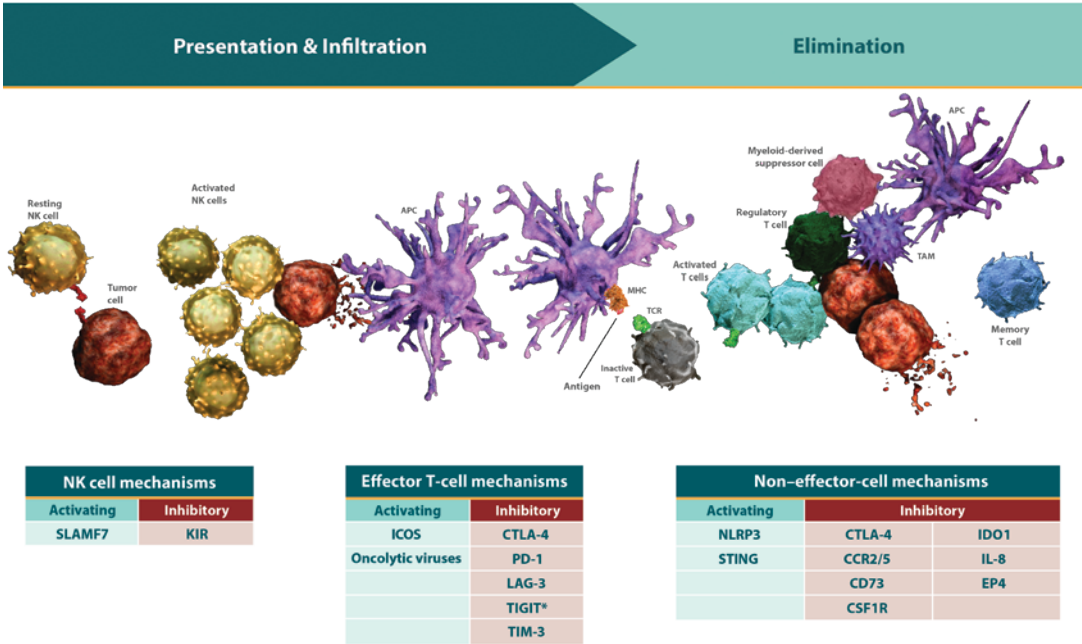
Tumor cells can evade and suppress immune activity

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.

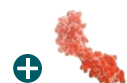
Various components of the immune system and the tumor microenvironment, including APCs, immune regulatory cells, stromal cells, and the tumor itself, regulate the ability of effector cells to eliminate tumors.^{3,14,22,23} Ongoing I-O research at Bristol-Myers Squibb is exploring how targeting these 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.

Modulating a combination of signaling pathways can more efficiently promote antitumor activity than either pathway alone, as suggested by preclinical data.^{17,24-28}

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.²⁹ When engaged, SLAMF7 activates NK cells, the rapid responders of the immune system and the body's first line of defense against cancer.^{5,30}

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.^{9,31}

Inhibitory 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.



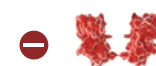
ICOS is an activating receptor expressed on activated cytotoxic T cells, regulatory T cells, NK cells, and other types of T cells that can lead to the activation, proliferation, and survival of cytotoxic T cells, as well as the survival of memory T cells.³²⁻⁴⁰

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.⁴¹⁻⁴⁷

Activating pathway



CTLA-4 is an immune checkpoint receptor on activated T cells that inhibits T-cell activation.⁴⁸⁻⁵⁰ CTLA-4 signaling diminishes the ability of memory T cells to sustain an immune response.^{51,52}

Inhibitory pathway



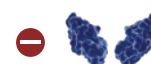
PD-1 is an immune checkpoint receptor on cytotoxic T cells that plays a key role in T-cell exhaustion and prevention of autoimmunity.⁵³⁻⁵⁷

Inhibitory pathway



LAG-3 is an immune checkpoint receptor on the surface of both activated cytotoxic and regulatory T cells.⁵⁸⁻⁶⁰ LAG-3 can negatively regulate T-cell proliferation and promote T-cell exhaustion.⁶¹⁻⁶³

Inhibitory pathway



TIGIT is an immune checkpoint receptor expressed on the surface of cytotoxic and memory T cells, Tregs, and NK cells.^{64,65} On all of these cells, TIGIT can play a role in immune suppression.⁶⁴⁻⁶⁶

Inhibitory pathway



TIM-3 is an immune checkpoint receptor involved in the suppression of both innate and adaptive immune cells.⁶⁷⁻⁶⁹ 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.^{67,68}

Inhibitory pathway

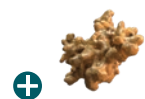
Select pathways that modulate non-effector-cell activity

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 is a protein expressed in APCs, such as DCs, monocytes, and macrophages.⁷⁰ 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



STING is an intracellular protein expressed in APCs, such as DCs, which serves as an innate immune activator that stimulates APCs to drive cytotoxic T-cell activity.^{73,74}

Activating pathway



CCR2 and **CCR5** regulate the recruitment of immunosuppressive cells through the stroma.^{75,76} CCR2 and CCR5 are both expressed on the surface of T cells, Tregs, monocytes, MDSCs, and TAMs.⁷⁷⁻⁸²

Inhibitory pathway



CD73 is a cell-surface enzyme on Tregs.⁸³ CD73 is a critical checkpoint in the production of adenosine, which is a powerful inhibitor of the antitumor immune response, including proliferation and production of cytokines.⁸³⁻⁸⁵

Inhibitory pathway



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 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



IDO1 is an enzyme expressed in APCs.^{90,91} It metabolizes tryptophan, an amino acid that is essential for T-cell survival, into immunosuppressive kynurenine, which normally acts as a counterbalance to suppress T-cell function and prevent overactivation of the immune response.^{90,92-94}

Inhibitory pathway



IL-8 is a cytokine produced by macrophages, monocytes, and stromal cells that promotes the recruitment of immunosuppressive MDSCs and, during the normal healing process, activates the angiogenic response to generate new blood vessels.⁹⁵⁻⁹⁸

Inhibitory pathway



EP4 is a prostanoid receptor that plays a role in the suppression of both innate and adaptive immune functions. It is expressed by MDSCs, TAMs, DCs, T cells, NK cells, and other immune cells.⁹⁹⁻¹⁰⁵

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 is a G-protein-coupled receptor on immune cells and tumor cells that directs the migration and recruitment of immune cells.¹⁰⁶⁻¹¹¹ CXCR4 is implicated in biological processes, such as immune response and cardiovascular development.¹¹⁰

Tumor pathway



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

Tumor pathway

Discovering the possibilities of Immuno-Oncology biomarkers

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.^{122,123}

I-O biomarkers are a class of biomarker that can help evaluate an active antitumor immune response within the body.¹²⁴ I-O biomarkers can be prognostic, predictive, or pharmacodynamic, or a combination¹²⁵⁻¹²⁸:

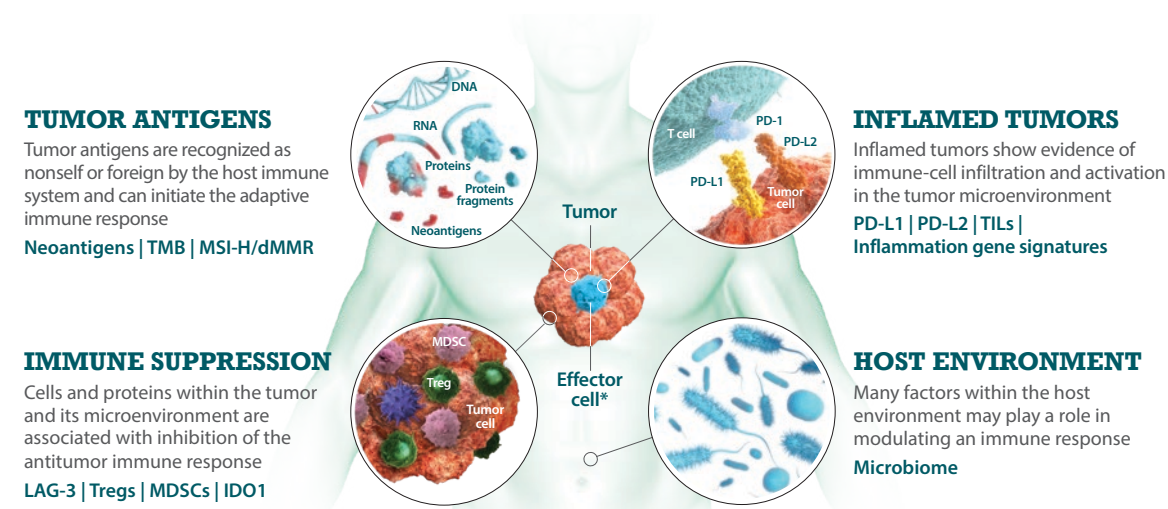
Prognostic biomarkers may identify the likelihood of a clinical event, such as disease progression, disease recurrence, or death, independent of the therapy received.^{125,126}

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

Pharmacodynamic biomarkers may show that a biologic response has occurred in an individual who has received treatment.^{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.^{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:



*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.¹³¹⁻¹³³

A composite I-O biomarker evaluation may provide a more comprehensive assessment of immune status.¹³²

Evolving clinical expectations in Immuno-Oncology

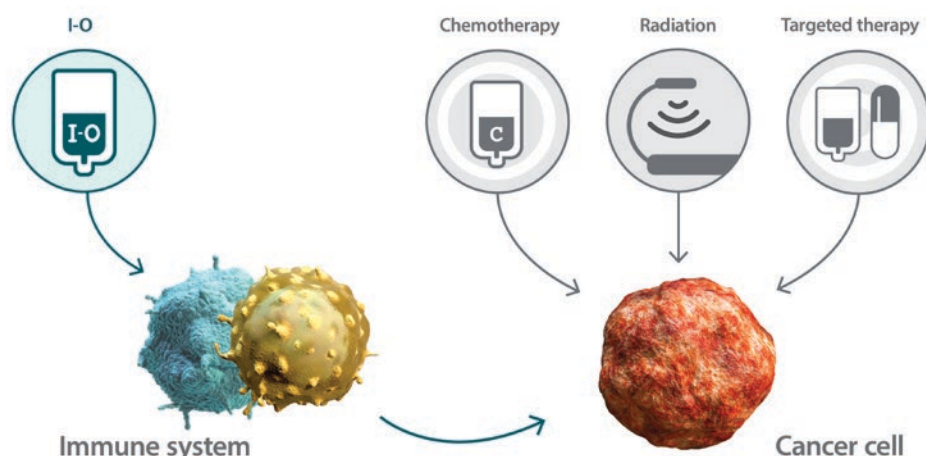
I-O is a different approach that fights cancer by targeting the immune system

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.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.¹³⁸

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

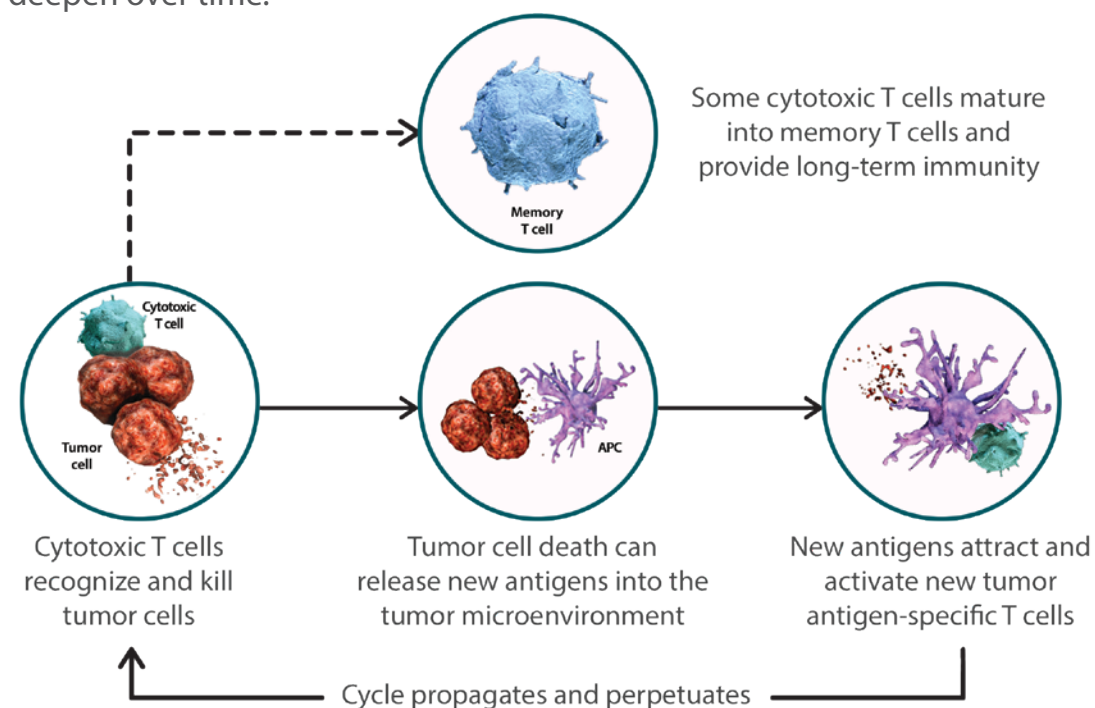
- › Immune responses having the potential to deepen and sustain over time
- › Resistance to immunotherapy, which can be present at the start of treatment or form over time
- › Unique patterns of response, such as pseudo-progression
- › Comprehensive endpoint considerations
- › Immune-mediated adverse 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.¹⁷

Immune responses are dynamic and have the potential to improve and deepen over time.^{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.^{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

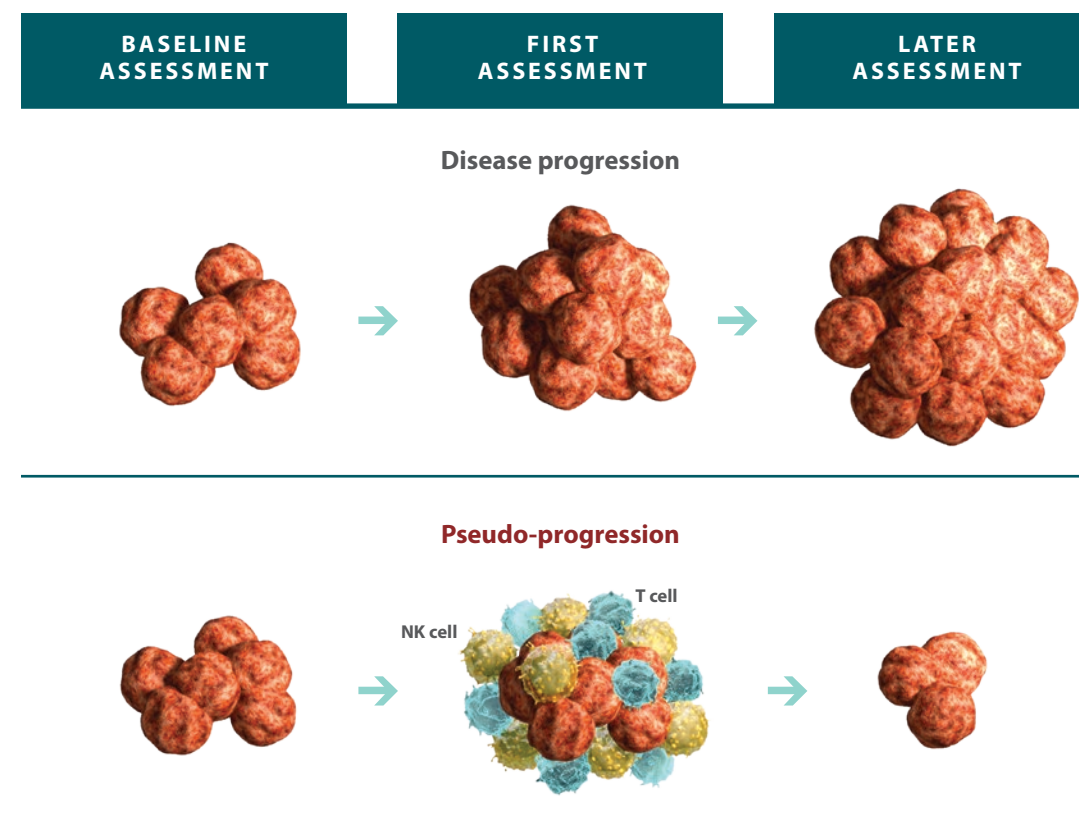
Identification of mechanisms of immunotherapy resistance is an area of research that will inform appropriate treatment options for patients.

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}



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

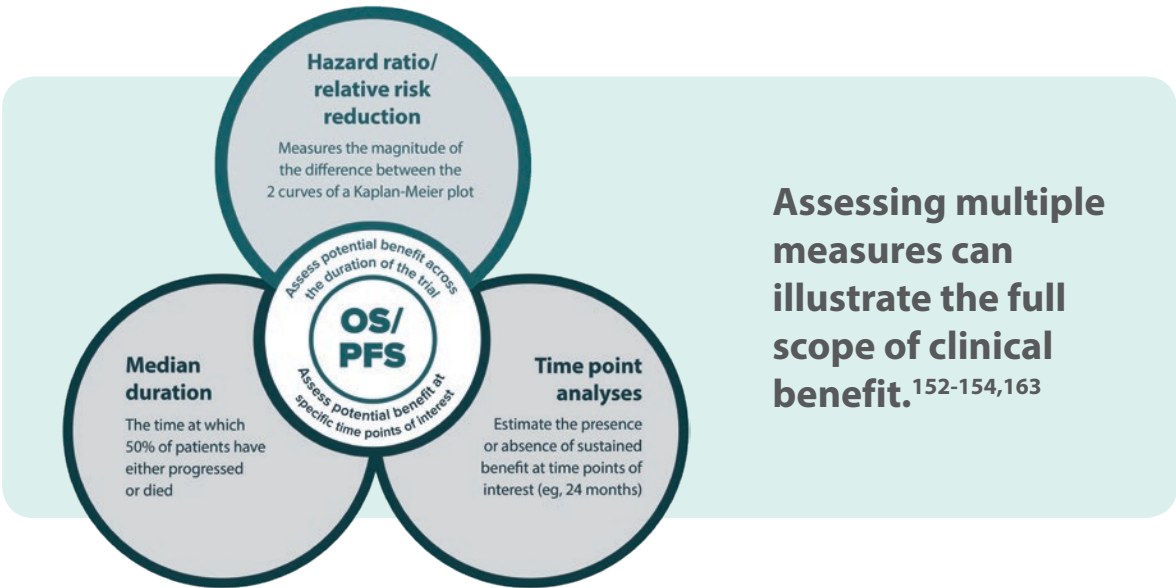
While uncommon, **pseudo-progression is an important consideration** when evaluating response to I-O therapies.¹⁴⁸ Histologic confirmation is not always possible, but close monitoring of the following factors may help identify pseudo-progression^{144,147,149}:

	DISEASE PROGRESSION	PSEUDO-PROGRESSION
Performance status	Deterioration of performance	Remains stable or improves
Systemic symptoms	Worsen	May or may not improve
Symptoms of tumor enlargement	Present	May or may not be present
Tumor burden		
Baseline	Increase	Initial increase followed by a response
New lesions	Appear and increase in size	Appear then remain stable and/or subsequently respond
Biopsy may reveal	Evidence of tumor growth	Evidence of immune-cell infiltration

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 account¹⁶⁰⁻¹⁶²

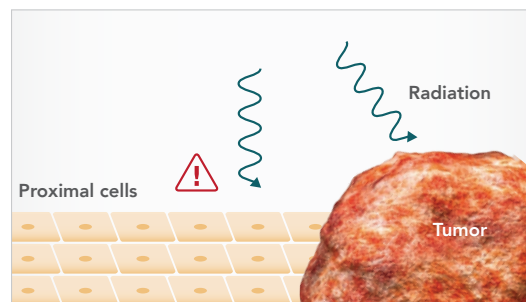


Assessment of these measures in combination can provide a broad and comprehensive picture of the difference between the investigational arm and the control arm with respect to PFS and OS.^{152-154,163,164}

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



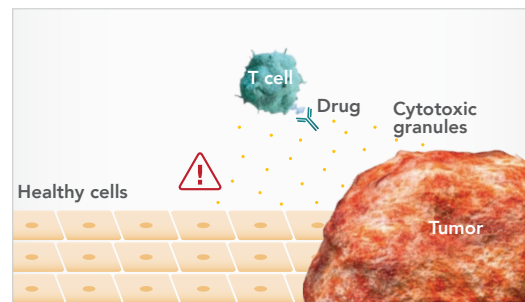
Chemotherapy can cause damage to rapidly dividing cells, including tumor cells and healthy cells, such as hematopoietic stem cells and gastrointestinal mucosal epithelium cells, leading to adverse reactions.¹⁶⁸⁻¹⁷⁰

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 Information¹⁸⁵

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

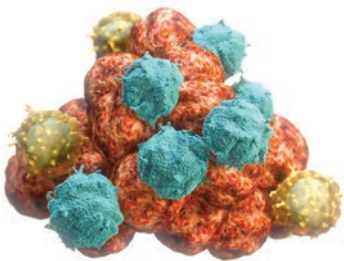
Depth of evidence for the immune response to cancer

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:



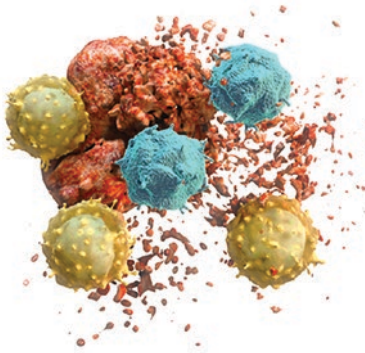
PRESENTATION

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:

TUMOR TYPE*	EVIDENCE FOR TUMOR IMMUNOGENICITY		
	PRESENTATION	INFILTRATION	ELIMINATION
	Presence of somatic mutations	Evidence of immune-cell infiltration	Evidence of spontaneous regression
Bladder ^{188,200}	●	●	
Breast ^{202,206}	●	●	
Colorectal ²⁰¹	●	●	
Gastric/esophageal ^{193,207,208}	●	●	
Glioblastoma ^{189,191,209}	●	●	
Head and neck ^{194,210}	●	●	
Hepatocellular ^{198,211}	●	●	
Lung ^{188,193}	●	●	
Melanoma ^{188,193,204}	●	●	●
Ovarian ^{197,212}	●	●	
Pancreatic ²⁰¹	●	●	
Prostate ^{195,213}	●	●	
Renal ^{188,196}	●	●	●
Non-Hodgkin lymphoma ^{190,214,215}	●	●	●
Hodgkin lymphoma ^{199,216}	●	●	
Leukemia ²¹⁷	●		
Multiple myeloma ^{192,218}	●	●	

*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

APC=antigen-presenting cell	NLRP3=nucleotide-binding oligomerization domain-like receptor family, pyrin domain containing 3
BET=bromodomain and extraterminal domain	
BCR-ABL=breakpoint cluster region-Abelson	PD-1=programmed death receptor-1
CCR2=chemokine (C-C motif) receptor 2	PD-L1=programmed death ligand 1
CCR5=chemokine (C-C motif) receptor 5	PD-L2=programmed death ligand 2
CSF1=colony-stimulating factor 1	QOL=quality of life
CSF1R=colony-stimulating factor 1 receptor	SLAMF7=signaling lymphocytic activation molecule family member 7
CTLA-4=cytotoxic T-lymphocyte antigen 4	
CXCR4=chemokine (C-X-C motif) receptor 4	STING=stimulator of interferon genes
DC=dendritic cell	TAM=tumor-associated macrophage
dMMR=mismatch repair deficient	TCR=T-cell receptor
EP4=prostaglandin E receptor 4	TIGIT=T-cell immunoreceptor with Ig and ITIM domains
ICOS=inducible T-cell co-stimulator	TIL=tumor-infiltrating lymphocyte
IDO1=indoleamine 2,3-dioxygenase-1	TIM-3=T-cell immunoglobulin mucin-3
Ig=immunoglobulin	TMB=tumor mutational burden
IL-2=interleukin-2	Treg=regulatory T cell
IL-8=interleukin-8	
I-O=Immuno-Oncology	
ITIM=immunoreceptor tyrosine-based inhibitory motif	
KIR=killer cell immunoglobulin-like receptor	
LAG-3=lymphocyte-activation gene 3	
MDSC=myeloid-derived suppressor cell	
MGMT=O6-methylguanine-DNA methyltransferase	
MHC=major histocompatibility complex	
MSI-H=microsatellite instability-high	
NK=natural killer	

Notes

Notes

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