Bristol Myers Squibb™

Immuno-Oncology

Understanding the science behind Immuno-Oncology

Using the body's natural immune response to fight cancer

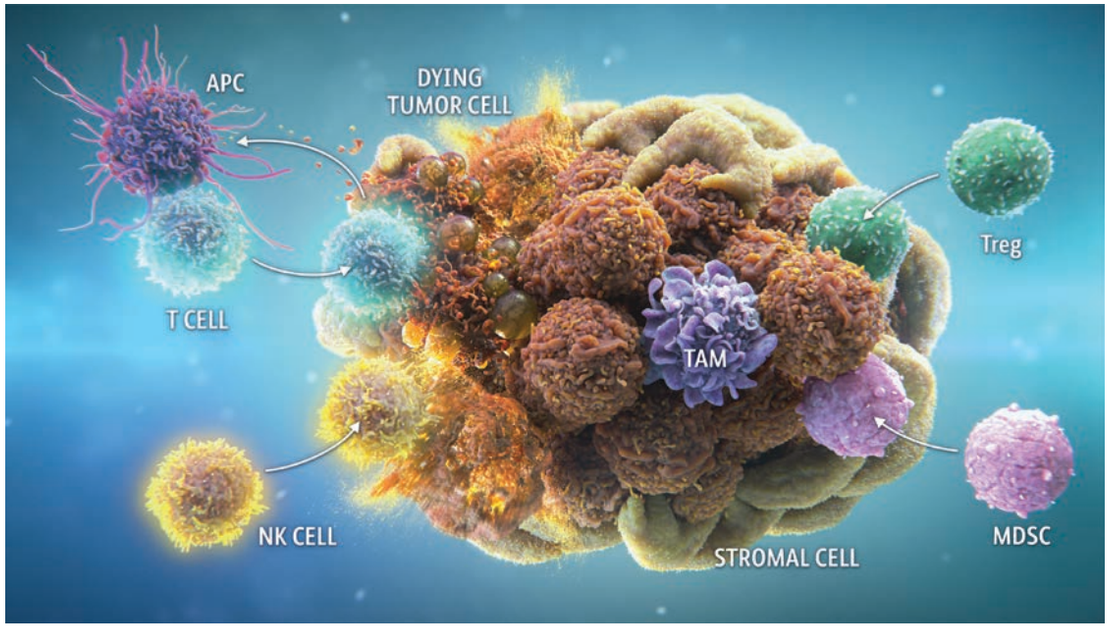
Bristol Myers Squibb: At the forefront of **Immuno-Oncology** research

Contents

Revealing the potential of the immune system in cancer

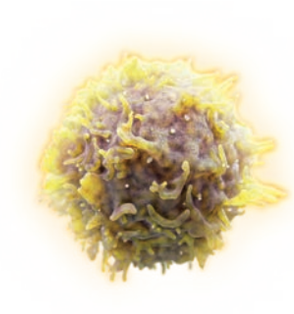
Introduction to the tumor microenvironment and the immune response

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]



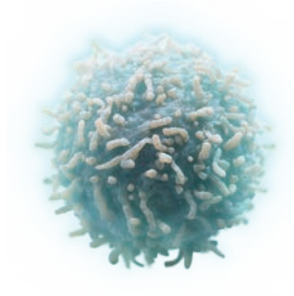
In cancer, normal cells have mutated into tumor cells and are recognized as nonself by both the innate and adaptive immune systems.[5,6]

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] 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]

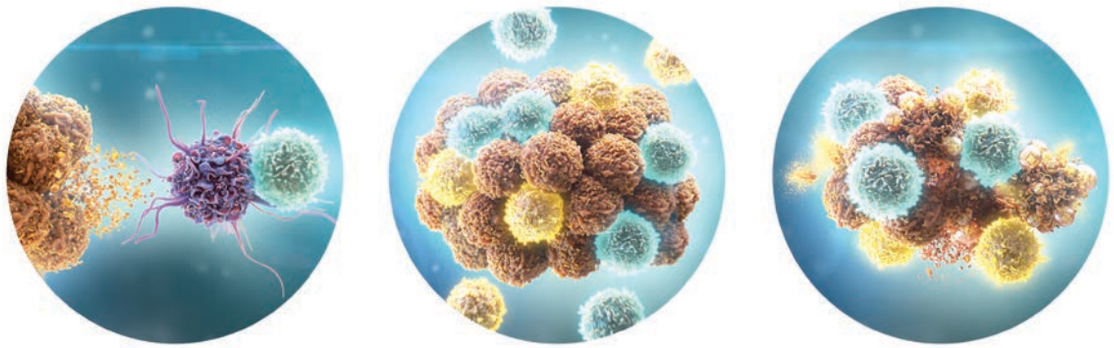


Adaptive immune response

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]

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 → **Infiltration** → **Elimination**

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.[14,15]

Infiltration

Tumor antigens and other factors attract immune cells to the tumor site, where they invade and attack.[14]

Elimination

Activated cytotoxic T cells recognize tumor cells as the source of the antigen and target them for elimination.[14]

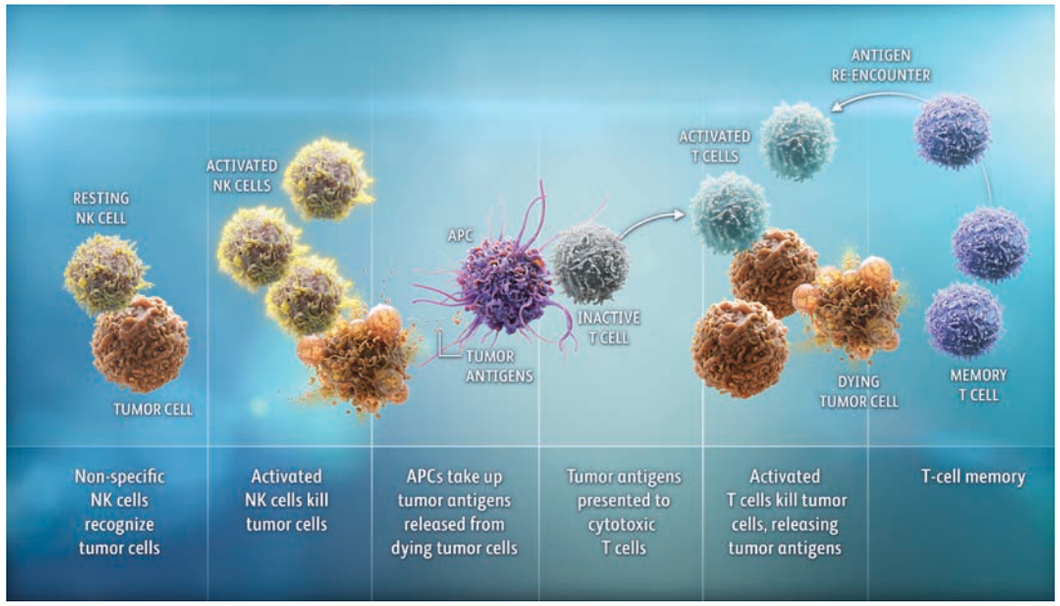
Tumor cells can evade and suppress immune activity

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.[16] 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.[16,17]

The tumor microenvironment consists of different cell types that help tumor cells evade antitumor immune activity.[18,19] As tumors evolve, they can influence the activation and composition of cells within the tumor microenvironment.[17]

Immune pathways combine to refine response

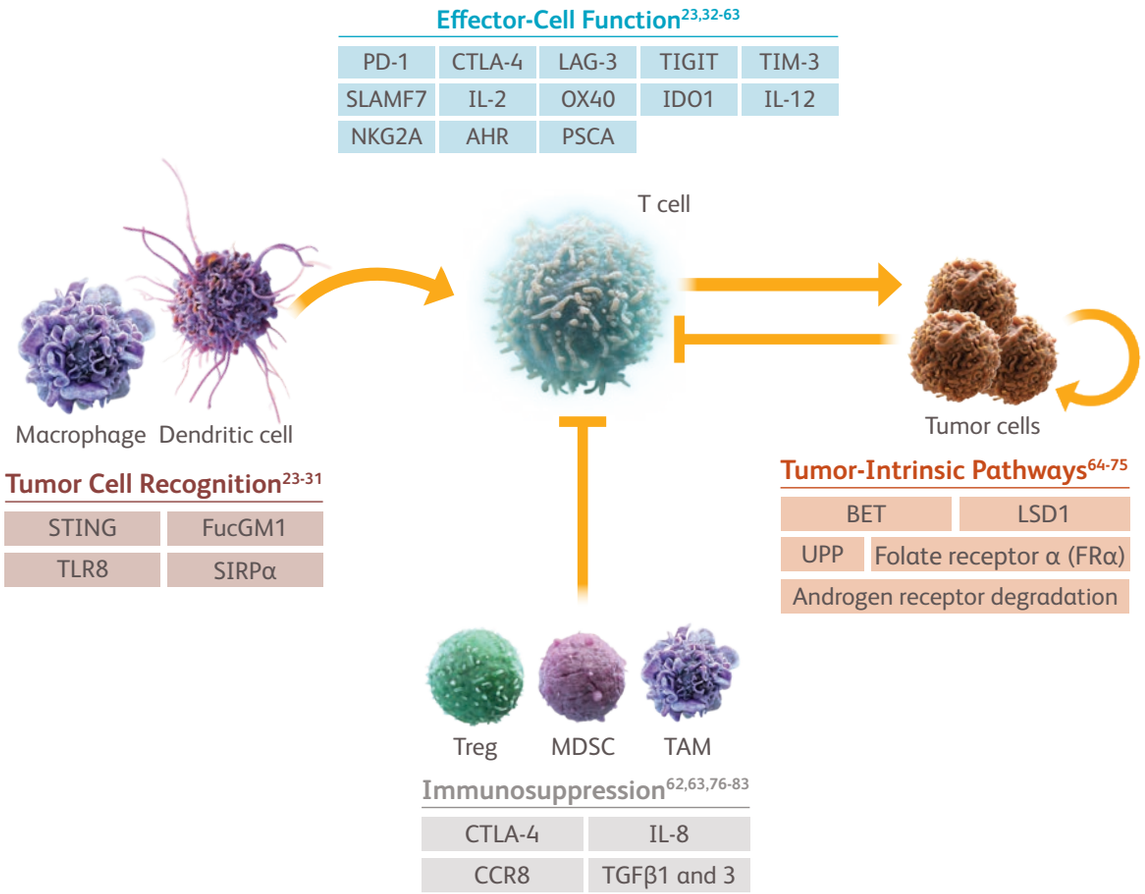
The 3 stages of the immune response—presentation, infiltration, and elimination—are regulated through a network of **activating** and **inhibitory** signaling pathways that **combine to maintain immune balance**.[3,14,20] Establishing fundamental stages of immune response that are impaired within noninflamed tumors is a strategy to improve the broad potential of I-O.



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.[3,20-22] 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.

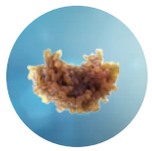
There are multiple emerging pathways under investigation for tumor detection and elimination*



*Not a comprehensive list of immune pathways.

Select pathways that modulate tumor cell recognition

Tumors use several mechanisms to avoid detection by the immune system. Current research is investigating modulation of pathways, including those involved in antigen presentation and phagocytosis, to promote better tumor cell recognition.[23,24]

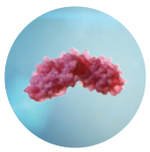


STING is an intracellular protein expressed in APCs, such as DCs, which serves as an innate immune activator that stimulates APCs to drive cytotoxic T-cell activity.[25,26]

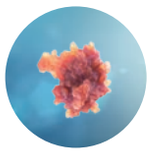
FucGM1 is a ganglioside that is highly expressed on the surface of certain cancer cells and enables cell communication.[31,84,85]

Select pathways that modulate immunosuppression

Some tumors can avoid destruction by thriving in an immunosuppressive environment and dampening the immune response. Current research is investigating modulation of pathways that regulate immunosuppressive activity in order to increase antitumor response.[76,77]



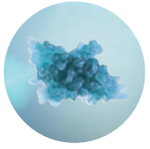
CTLA-4 is an immune checkpoint receptor on activated T cells and Tregs that inhibits T-cell activation.[62,63,86] Binding of CTLA-4 on cytotoxic T cells to CD80/86 on APCs inhibits T-cell activation.[87,88]



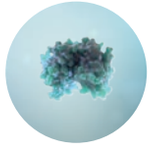
IL-8 is a cytokine produced by macrophages, monocytes, and stromal cells that promotes the recruitment of immunosuppressive MDSCs and, during the normal healing process, activates the angiogenic response to generate new blood vessels.[79,80,89,90]

Select pathways that modulate effector cell function

Various components of the immune system and tumor microenvironment regulate effector cell ability to eliminate tumors. Current research is investigating the following pathways involved in the regulation of effector cells in order to enhance their activity.[23,32]



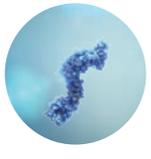
PD-1 is an immune checkpoint receptor on cytotoxic T cells that plays a key role in T-cell exhaustion and prevention of autoimmunity.[33-36,91]



TIGIT is an immune checkpoint receptor expressed on the surface of cytotoxic and memory T cells, Tregs, and NK cells.[47,98] On all of these cells, TIGIT can play a role in immune suppression.[47,98,99]

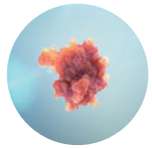
CTLA-4 is an immune checkpoint receptor that, in addition to being expressed on activated T cells, is also found on Tregs, where it is a key driver of their ability to suppress the immune response. Tumor cells utilize the CTLA-4 pathway to suppress the immune response, decreasing T-cell activation and ability to proliferate into memory T cells.[21,38,62,63,92,93]

TIM-3 is an immune checkpoint receptor involved in the suppression of both innate and adaptive immune cells.[45,46,100] 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.[45,46]

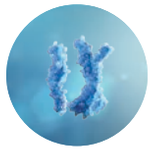


LAG-3 is an immune checkpoint receptor on the surface of both activated cytotoxic and regulatory T cells.[39,40,94] LAG-3 can negatively regulate T-cell proliferation and promote T-cell exhaustion.[95-97]

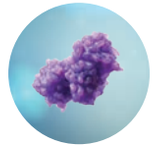
SLAMF7 is an activating receptor on the surface of NK cells and other immune cells.[44] When engaged, SLAMF7 activates NK cells, the rapid responders of the immune system and the body's first line of defense against cancer.[5,101]



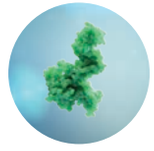
IL-2 is an activating receptor expressed on the surface of immune cells including cytotoxic T cells, NK cells, and Tregs.[41-43,102] The interaction of IL-2 with its receptor, IL-2R, promotes the activation and proliferation of various immune cells.[42,102]



OX40 is an activating, transmembrane receptor protein that is expressed on the surface of activated cytotoxic T cells and Tregs.[103-105] OX40 helps to create a tumor microenvironment more favorable to the antitumor immune response.[106-108]



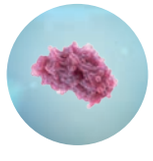
IDO1 is an enzyme expressed in tumor cells and APCs.[59,60] It metabolizes tryptophan, an amino acid that is essential for T-cell survival, into immunosuppressive kynurenine, which normally acts as a counterbalance to suppress T cells and prevent overactivation of the immune response.[59,109-111]



IL-12 is a pro-inflammatory cytokine released by APCs and B cells.[112,113] It increases effector T cell and NK activity of the innate and adaptive antitumor immune response. Antitumor immunity can also be promoted through IFN-γ production and the development of Th1 and Th17 cells.[112,114,115]

Select tumor-intrinsic pathways

Various signaling and metabolic pathways intrinsic to tumor cells can drive oncogenesis and tumor growth. Current research is investigating blocking these pathways in order to promote tumor cell death.[64,65]



BET is a family of proteins that are widely expressed and are responsible for regulating a variety of cellular processes.[69,116-118] In cancer, they upregulate the transcription of *c-Myc,* which is a major factor in the regulation of tumor proliferation.[119]

LSD1 is a demethylating enzyme that potentially plays a role in nucleosome remodeling, which may regulate genes critical to stem cell differentiation and cancer development.[120-122]

Preclinical studies suggest modulating multiple immune pathways may augment antitumor activity[23,32,92]*

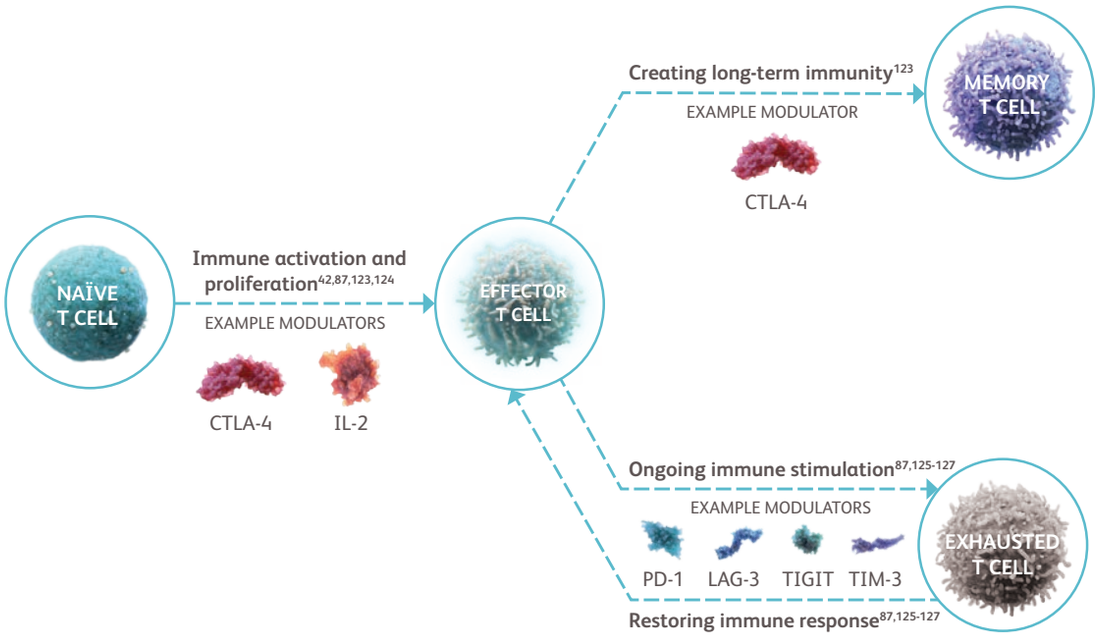


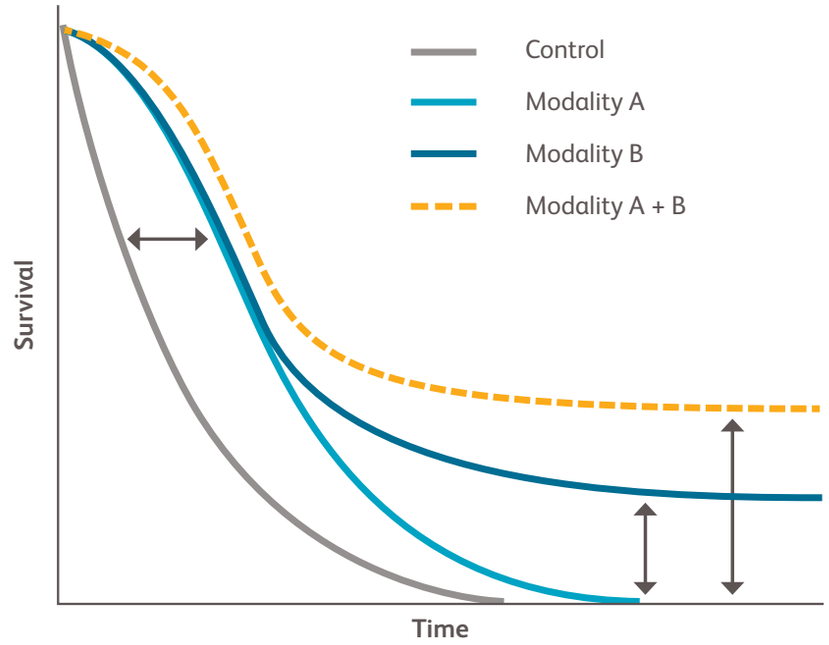
*Image intended to provide examples of pathways that may promote/inhibit T cells and long-term immunity.

Research is also ongoing to explore potential synergistic effects of immunotherapy in combination with chemotherapy and/or radiation or targeted therapies

Preclinical studies suggest that chemoradiation combined with immunotherapy may augment the antitumor response by generating cytotoxic T cells against tumor cells.[128-131]

Combining immunotherapy with the blockade of pathways essential for tumor survival and growth may increase antitumor response.[132,133]

Ongoing research aims to understand how combining immunotherapies with other treatment modalities may enhance an antitumor response[77,134]



- Modality A may have improved survival compared to control but lacks duration of response
- Modality B can have improved survival and longer duration of response in a fraction of patients
- Research is ongoing to assess the possibility for improved survival with longer duration of response for more patients with combination A + B

Hypothetical graph illustrating a scientific concept. This does not represent data or intend to directly predict clinical outcomes.

Modulating a combination of signaling pathways can more efficiently promote antitumor activity than either pathway alone, as suggested by preclinical data.[135-139]

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.[140,141]

I-O biomarkers are a class of biomarker that can help evaluate an active antitumor immune response within the body.[142] I-O biomarkers can be prognostic, predictive, or pharmacodynamic, or a combination.[143-146]

Prognostic biomarkers may identify the likelihood of a clinical event, such as disease progression, disease recurrence, or death, independent of the therapy received.[143,144]

Predictive biomarkers may identify whether individuals are more likely to experience a favorable or unfavorable response to treatment.[143,144]

Pharmacodynamic biomarkers may show that a biologic response has occurred in an individual who has received treatment.[144,145]

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.[147,148]

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.[147,149] I-O biomarker research aims to further characterize the unique interplay between the immune system and tumor cells in the following categories*:

Circulating biomarkers[150-153]

- IL-8
- ctDNA
- MRD

Immune modulators[154,155]

- TILs
- Tregs
- MDSCs
- PD-L1
- LAG-3

Digital technologies[156,157]

- Digital pathology
- AI-based signatures

Genomic features[154,155]

- TMB
- MSI-H/dMMR
- Immune gene signatures

*Not a comprehensive list of biomarkers.

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.[149,158,159]

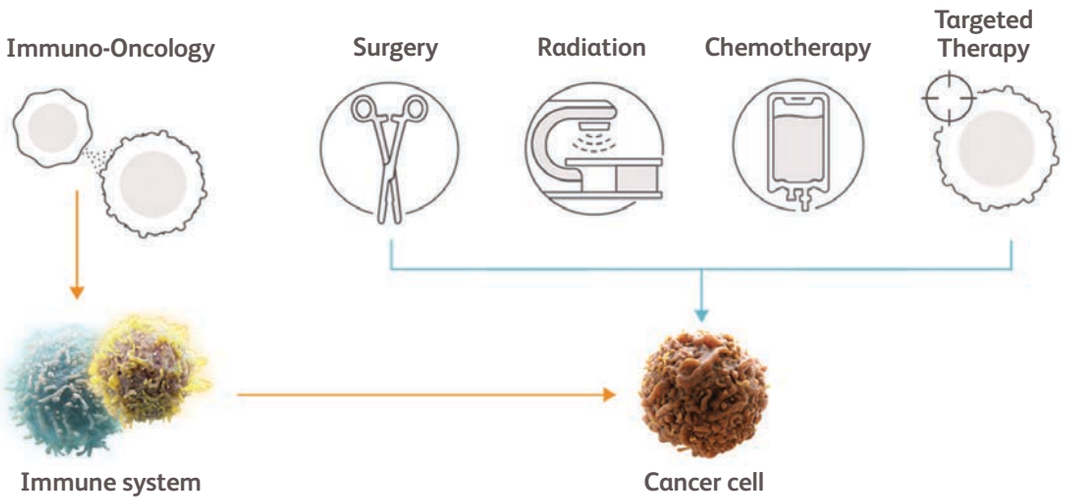
A composite I-O biomarker evaluation may provide a more comprehensive assessment of immune status.[149]

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.[160-163]

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.[164]



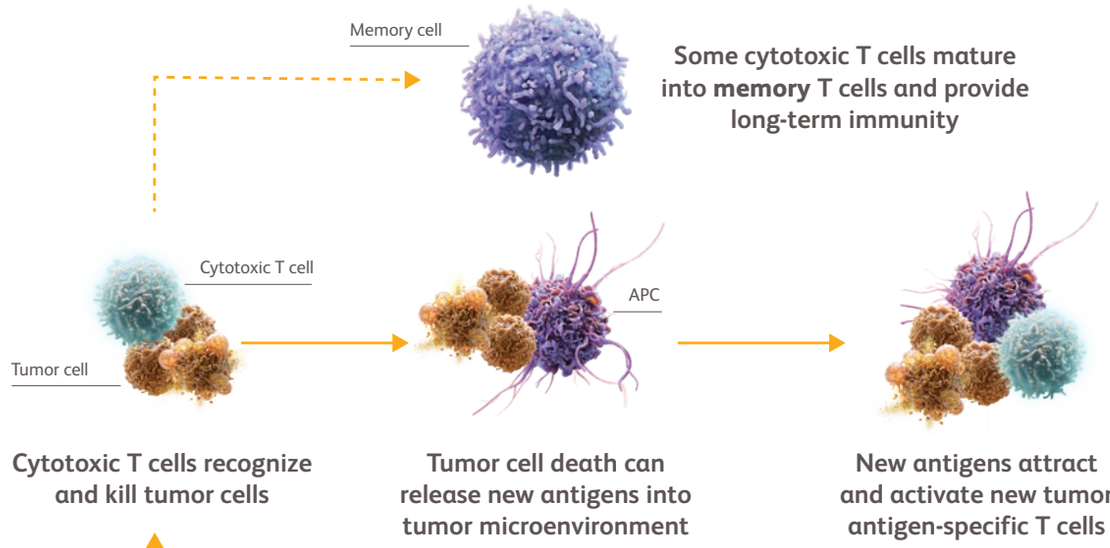
With this approach come unique considerations and distinctive characteristics that continue to be researched, such as:

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

Immune responses have the potential to deepen and be sustained 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.[14]

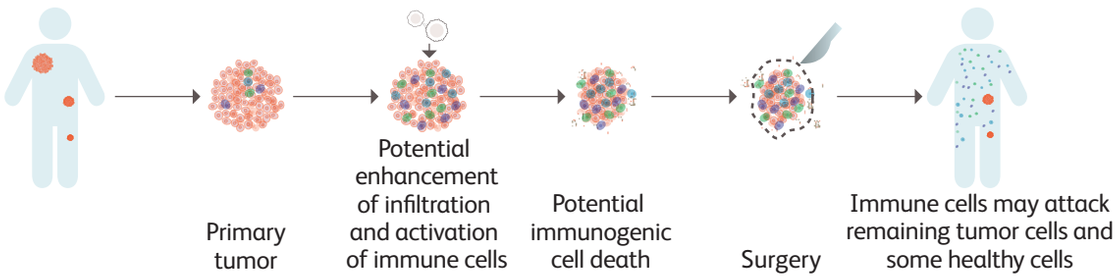
Immune responses are dynamic and have the potential to improve and deepen over time.[165,166]



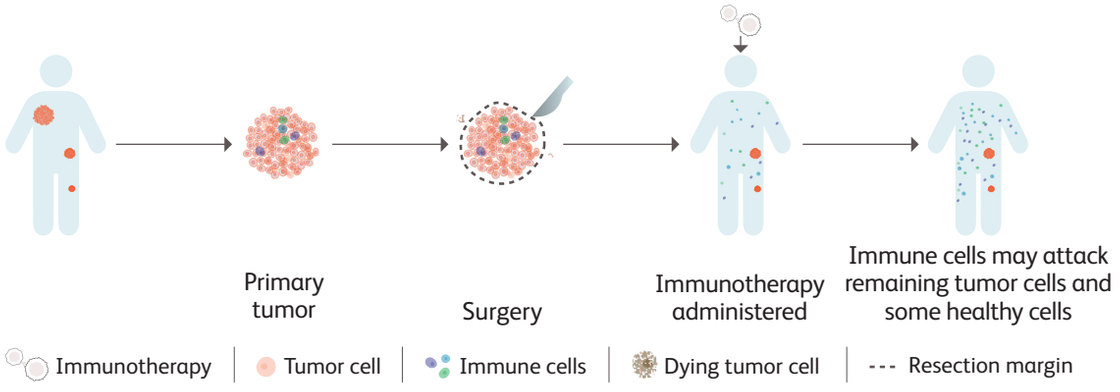
As the immune response continues to expand, some cytotoxic T cells mature into memory T cells that may provide long-term immune protection, even if the original stimulus is no longer present.[13,166,167]

In earlier stages of cancer, the immune system may be more intact and responsive[168]

In the **neoadjuvant setting,** the presence of tumor cells may allow for T cell priming while tumor antigens are abundant, potentially leading to an effective and prolonged antitumor immune response.[169-171]



In the **adjuvant setting,** primed T cells, specific to tumor antigens, may develop into protective memory T cells after surgical excision of the primary tumor.[172]

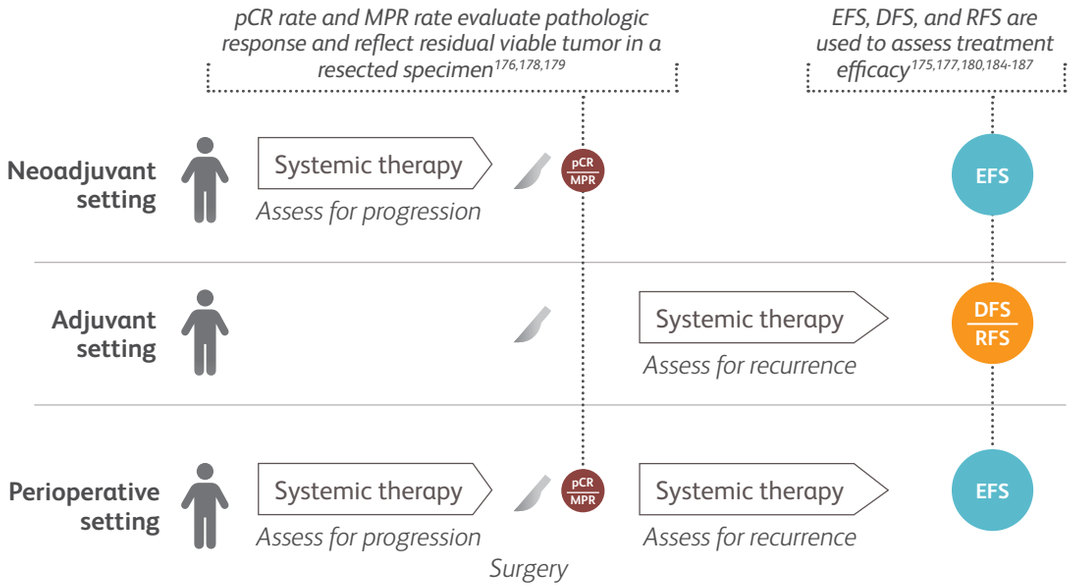


Preclinical studies aim to explore the potential of immunotherapy in earlier stages of cancer.[169-171,173,174]

Surrogate endpoints for survival may help to assess the efficacy of treatment in the neoadjuvant, adjuvant, and perioperative settings[175-179]

While **OS** is a common endpoint in oncology, it requires a longer follow-up period.[175] Surrogate endpoints may potentially correlate with **OS**.[180-183]

Some common surrogate endpoints used in earlier stages of cancer may include **EFS** and **DFS/RFS**.[175,177,180,184-187]



pCR and **MPR**: No residual tumor cells (pCR) or ≤10% tumor cells (MPR) at the primary tumor site after neoadjuvant treatment.[176,182]

EFS: Time from patient randomization until any event, including progression of disease, recurrence, or death irrespective of cause.[175,178]

DFS/RFS: Length of time patient survives after primary treatment without any signs or symptoms of the cancer for which they were treated.[181,182,188]

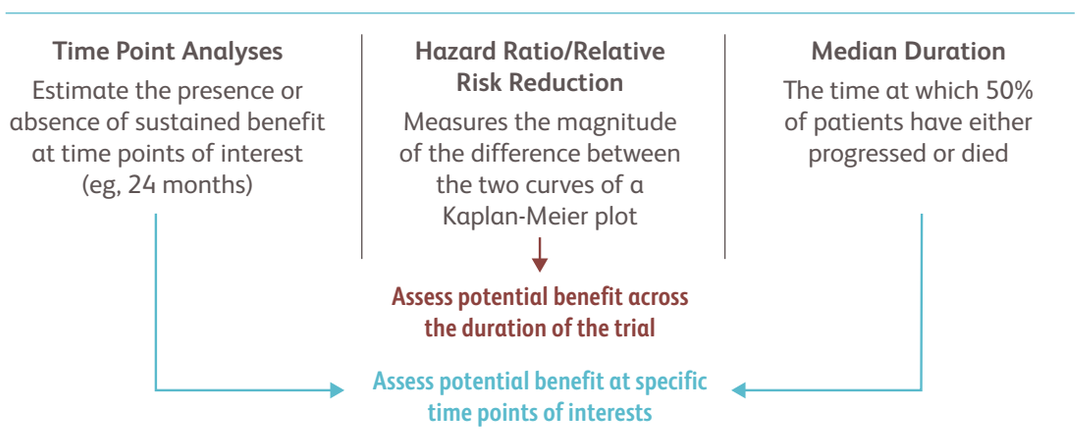
According to research in the neoadjuvant setting, **pCR rate** and **MPR rate** may be emerging surrogate endpoints that evaluate residual tumor in a specimen.[176,178,179]

BMS is investigating OS and surrogate endpoints to assess treatment efficacy in earlier stages of cancer.[189-196]

Other 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.[14] However, for **I-O**—a different way to fight cancer—a more comprehensive approach to endpoint assessment may be needed to recognize potential benefit.[197-201]

- **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[202,203]
- 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)**[202]
- 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.[204,205] PROs evaluate the impact of treatment on QOL based on the patient's own account[206,207]

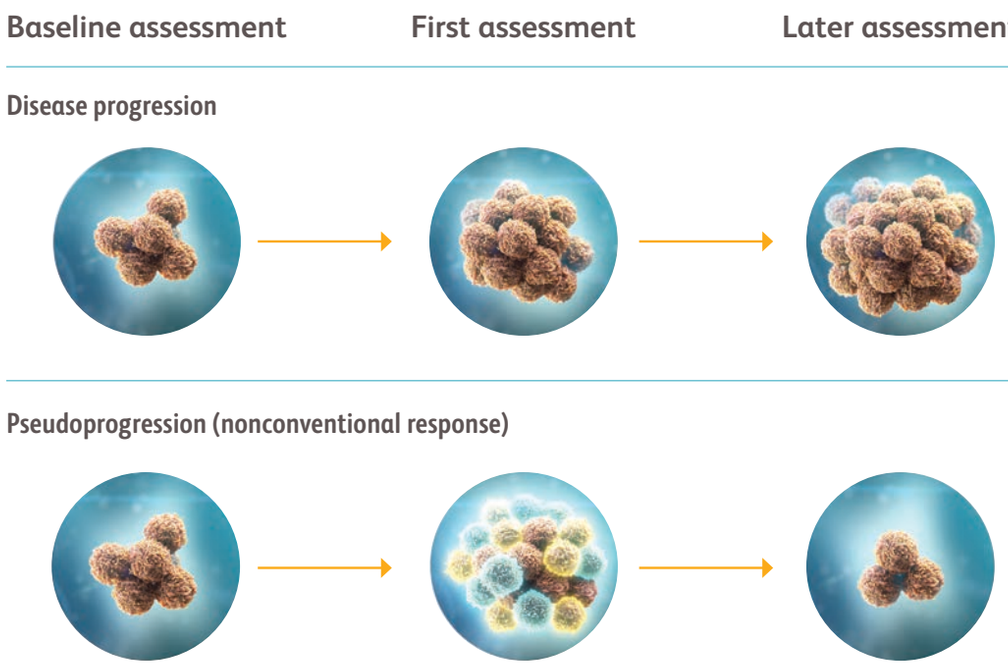


Assessment of these measures in combination can provide a broad and comprehensive picture of the differences between the investigational arm and the control arm with respect to PFS and OS.[198-200,208]

Assessing multiple measures can illustrate the full scope of clinical benefit.[198-200,208,209]

Pseudoprogression 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.[210,211] This is known as pseudoprogression: this does not reflect tumor cell growth but may be misclassified as disease progression.[210,212,213]



Tumors may **appear to grow or new lesions may appear when immune cells infiltrate the tumor site**.[210] Due to the time required to mount an adaptive immune response, pseudoprogression may also reflect continued tumor growth until a sufficient response develops.[210,214]

Pseudoprogression should be considered until disease progression can be confirmed

While uncommon, **pseudoprogression is an important consideration** when evaluating response to I-O therapies.[214] Histologic confirmation is not always possible, but close monitoring of the following factors may help identify pseudoprogression[210,213,215]:

	Disease progression	Pseudoprogression (nonconventional response)
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

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.[14,216-219]

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[219,220]
- Treatment algorithms are available for use by healthcare providers to assist them in managing immune-mediated adverse reactions[221,222]
- Recent guidelines have been published that provide consensus recommendations for the management of immune-mediated adverse reactions.[222-224] Specific guidance for managing immune-mediated adverse reactions for an individual product can be found in the accompanying FDA-approved Prescribing Information[225]

As research in immunotherapy advances and more data are made available, understanding and effective management of immune-mediated adverse reactions will evolve.[225]

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.[17,226]

As tumors evolve over time, they can influence the activation and composition of cells within the tumor microenvironment.[17,226] 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.[227]

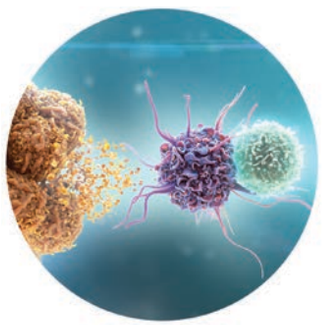
Identification of mechanisms of immunotherapy resistance is an area of research that will inform appropriate treatment options for patients.

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

Realizing the potential of Immuno-Oncology research

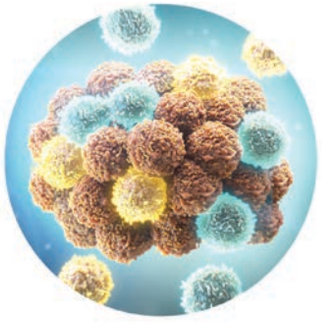
Depth of evidence for the immune response to cancer

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**.[228,229] The body is able to recognize and attack cancer through the following stages of immune response:



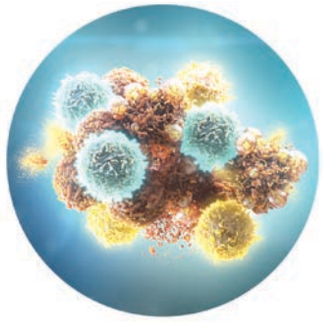
Presentation

There is a broad range of tumors that are traditionally defined by high rates of mutations.[230] These mutations create neoantigens that can be recognized by the immune system, activating an antitumor immune response.[231]



Infiltration

Tumor-infiltrating immune cells are present in the tumor microenvironment. Their presence demonstrates their capacity to identify and migrate to tumor cells.[232-245]



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.[246]

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 types[173]:

	Evidence for tumor immunogenicity		
Tumor type*	**Presentation** Presence of somatic mutations	**Infiltration** Evidence of immune-cell infiltration	**Elimination** Evidence of spontaneous regression
Bladder[230,242]	●	●	
Breast[244,247]	●	●	
Colorectal[243]	●	●	
Gastric/esophageal[235,248,249]	●	●	
Glioblastoma[231,233,250]	●	●	
Head and neck[236,251]	●	●	
Hepatocellular[240,252]	●	●	
Lung[230,235]	●	●	
Melanoma[230,235,246]	●	●	●
Ovarian[239,253]	●	●	
Pancreatic[243]	●	●	
Prostate[237,254]	●	●	
Renal[230,238]	●	●	●
Non-Hodgkin lymphoma[232,255,256]	●	●	●
Hodgkin lymphoma[241,257]	●	●	
Leukemia[258]	●		
Multiple myeloma[234,259]	●	●	

*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

AHR=aryl hydrocarbon receptor

AI=artificial intelligence

APC=antigen-presenting cell

BET=bromodomain and extraterminal domain

CCR8=chemokine (C-C motif) receptor 8

ctDNA= circulating tumor DNA

CTLA-4=cytotoxic T-lymphocyte antigen 4

DC=dendritic cell

DFS=disease-free survival

dMMR=mismatch repair deficient

DOR=duration of response

EFS=event-free survival

FucGM1=fucosyl GM1

IDO1=indoleamine 2,3-dioxygenase-1

IFN-γ=interferon-gamma

IL-2=interleukin-2

IL-2R=interleukin-2 receptor

IL-8=interleukin-8

IL-12=interleukin-12

I-O=Immuno-Oncology

LAG-3=lymphocyte-activation gene 3

LSD1=lysine-specific demethylase 1

MDSC=myeloid-derived suppressor cell

MPR=major pathologic response

MRD=minimal residual disease

MSI-H=microsatellite instability-high

NK=natural killer

NKG2A=natural killer cell protein group 2-A

ORR=overall response rate

OS=overall survival

pCR=pathologic complete response

PD-1=programmed death receptor-1

PD-L1=programmed death ligand 1

PFS=progression-free survival

PRO=patient-reported outcome

PSCA=prostate stem cell antigen

QOL=quality of life

RFS=recurrence-free survival

SIRPα=signal-regulatory protein alpha

SLAMF7=signaling lymphocytic activation molecule family member 7

STING=stimulator of interferon genes

TAM=tumor-associated macrophage

TFS=treatment-free survival

TGFβ1=transforming growth factor beta 1

TIGIT=T-cell immunoreceptor with Ig and ITIM domains

TIL=tumor-infiltrating lymphocyte

TIM-3=T-cell immunoglobulin mucin-3

TLR8=toll-like receptor 8

TMB=tumor mutational burden

Treg=regulatory T cell

UPP=uridine phosphorylase

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