

Looking deeper into the science of Immuno-Oncology

Using the body's natural immune response to fight cancer

Bristol-Myers Squibb – At the Forefront of Immuno-Oncology



Bristol-Myers Squibb



Immuno-Oncology



About

These slides help explain key concepts about the rapidly evolving field of Immuno-Oncology (I-O). The information is separated into **five** topics that are color-coded for clarity.

Topic 1. **ESSENTIAL PRINCIPLES OF IMMUNOLOGY**

Topic 2. **REVEALING THE POTENTIAL OF THE IMMUNE SYSTEM IN CANCER**

Topic 3. **EXPLORING PREDICTORS OF RESPONSE: IMMUNE-BIOMARKERS**

Topic 4. **EVOLVING CLINICAL EXPECTATIONS IN I-O**

Topic 5. **REALIZING THE POTENTIAL OF I-O RESEARCH**



Topics covered

Topic 1:

ESSENTIAL PRINCIPLES OF IMMUNOLOGY

- Differentiating *self* from *nonself* is a hallmark of the immune response
- Innate and adaptive immunity are complementary responses
- Innate immunity is rapid and antigen-independent
- Adaptive immunity is durable and antigen-dependent
- T cells migrate throughout the body in search of antigens
- Select cells of the immune system

Topic 2:

REVEALING THE POTENTIAL OF THE IMMUNE SYSTEM IN CANCER

- Introduction to the tumor microenvironment and the immune response
- Antitumor activity of the innate and adaptive immune responses
- Key stages of the antitumor immune response
- Tumor cells can evade and suppress immune activity
- Empowering the immune system to reestablish the antitumor response
- Select pathways that modulate NK cell activity
- Select pathways that modulate effector T cell activity
- Select pathways that modulate non-effector cell activity
- Immune pathways combine to refine response

Topic 3:

EXPLORING PREDICTORS OF RESPONSE: IMMUNE-BIOMARKERS

- Immune-biomarkers are indicators of immune activity
- Exploratory immune-biomarkers

Topic 4:

EVOLVING CLINICAL EXPECTATIONS IN I-O

- Immune responses have the potential to deepen and sustain over time
- Pseudo-progression may reflect development of antitumor immunity
- Pseudo-progression may be considered until disease progression can be confirmed
- Endpoint considerations for I-O research
- Immune-mediated adverse reactions

Topic 5:

REALIZING THE POTENTIAL OF I-O RESEARCH

- Depth of evidence for the immune response to cancer
- Broad potential of I-O research

Topic 1:

ESSENTIAL PRINCIPLES OF IMMUNOLOGY

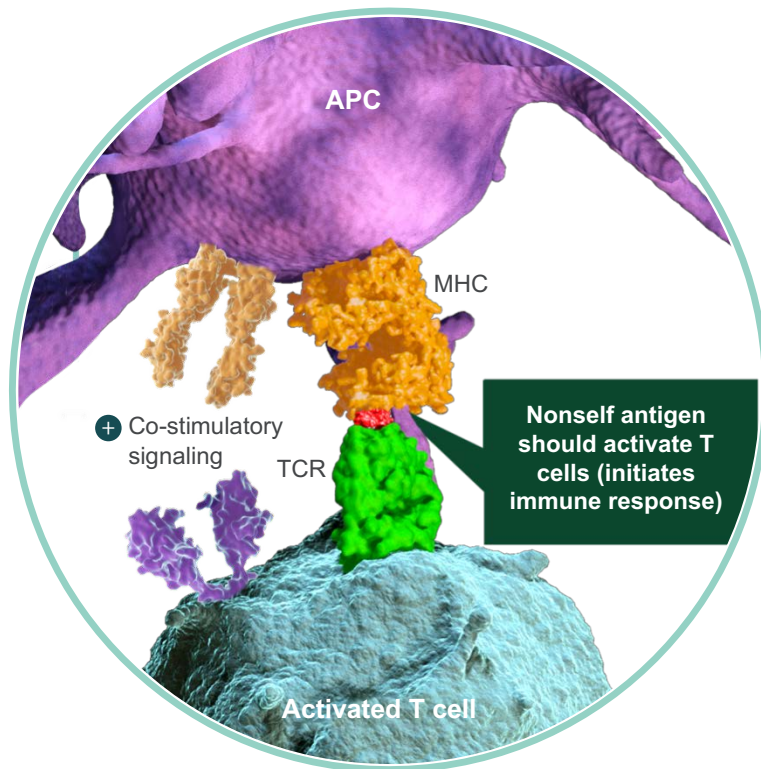
The immune system identifies nonself invaders through both innate and adaptive immunity.



Differentiating *self* from *nonself* is a hallmark of the immune response

The immune system is a network of tissues, cells, and signaling molecules that work to protect the body by recognizing and attacking **foreign cells (nonself)**, while seeking to minimize the damage to **healthy cells (self)**.^{1,2}

Antigens, small molecules or peptides capable of eliciting an immune response, are a key element in the process of distinguishing self from nonself.¹

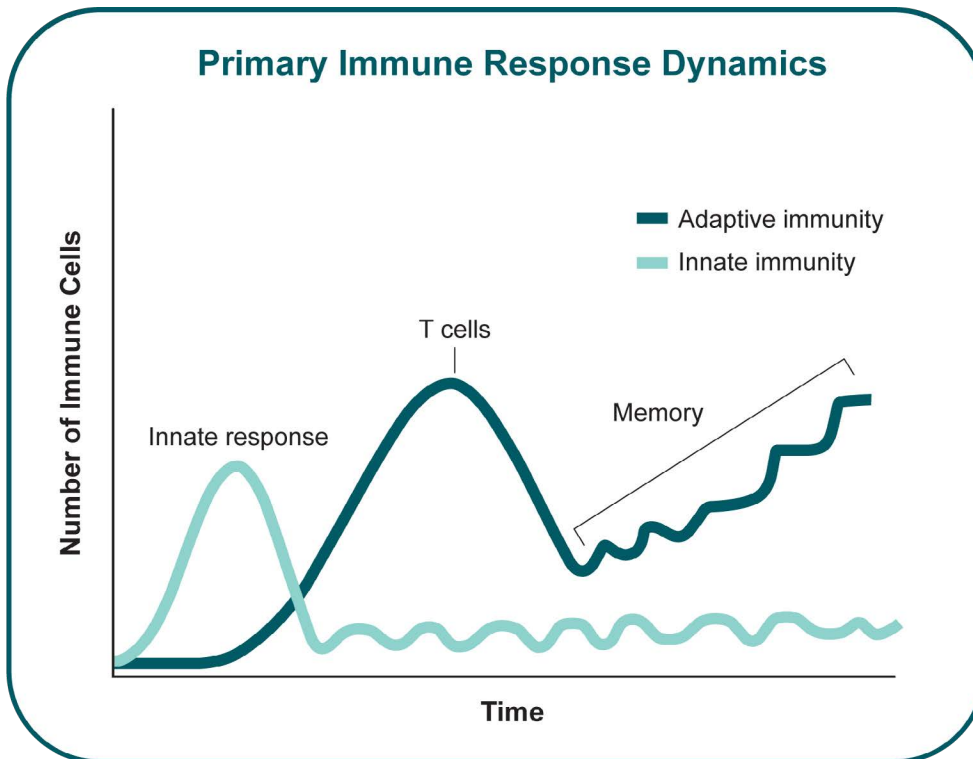


- **Inactive T cells search for nonself antigens** by transiently binding to antigens presented by antigen-presenting cells (APCs)³
- **Immune cells learn to overlook self antigens** from normal cells to prevent autoimmunity²
- Although originating from normal cells, **tumor antigens can be recognized as nonself** and activate cytotoxic T cells^{1,4,5}
- **Neoantigens are a type of tumor antigen** that arise from self proteins that have been mutated or modified, making them unique to the tumor^{4,5}



Innate and adaptive immunity are complementary responses

The immune system identifies nonself invaders through both **innate** and **adaptive immunity**. Activated through **distinct and often complementary mechanisms**, innate and adaptive immunity deploy different effector cells to attack and destroy abnormal / foreign cells such as cancer.¹

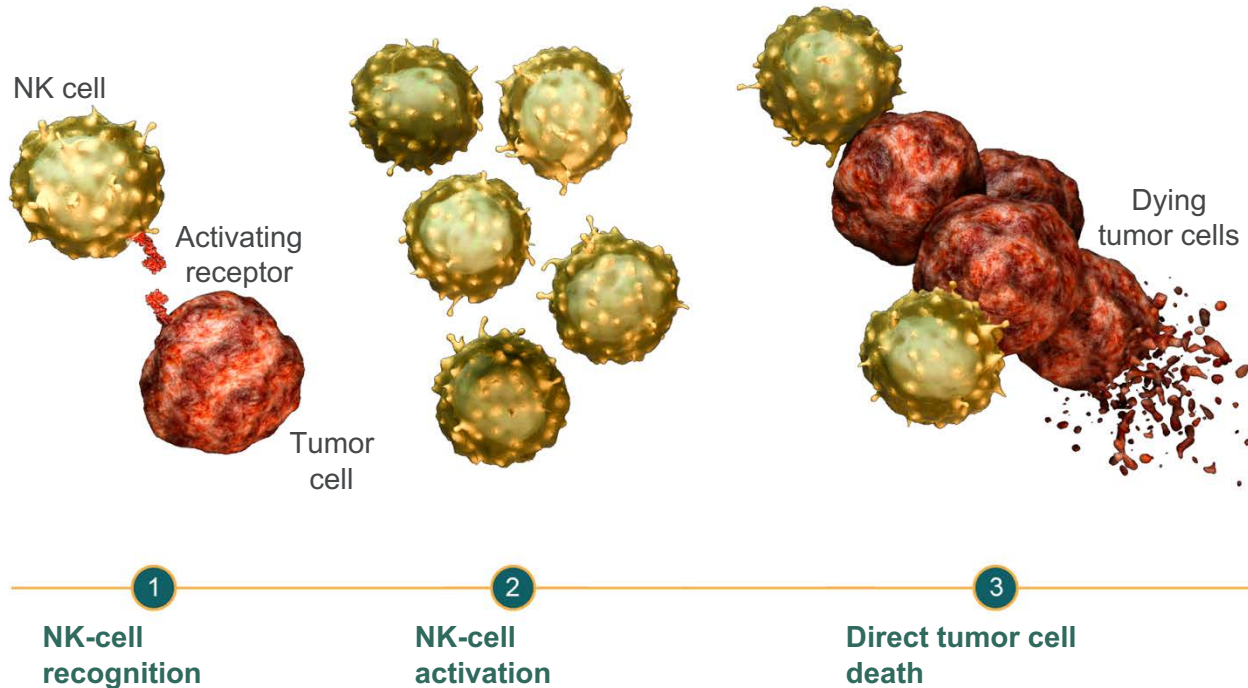


- The innate immune response is **rapid**, while the adaptive immune response is not as immediate but can produce a **durable response** through the development of memory cells, including memory T cells^{1,6}
- As the immune response continues to expand, some cytotoxic T cells mature into **memory T cells** that may provide long-term immune protection, even if the original stimulus is no longer present^{7,8}



Innate immunity is rapid and antigen-independent

Innate immunity, the body's first line of defense, is **non-specific** and independent of antigens, allowing for the **rapid** identification and elimination of foreign threats.¹ The primary effector cells of the innate immune response, natural killer (NK) cells, continually scan the body for abnormal cells to attack.^{1,9,10 *}



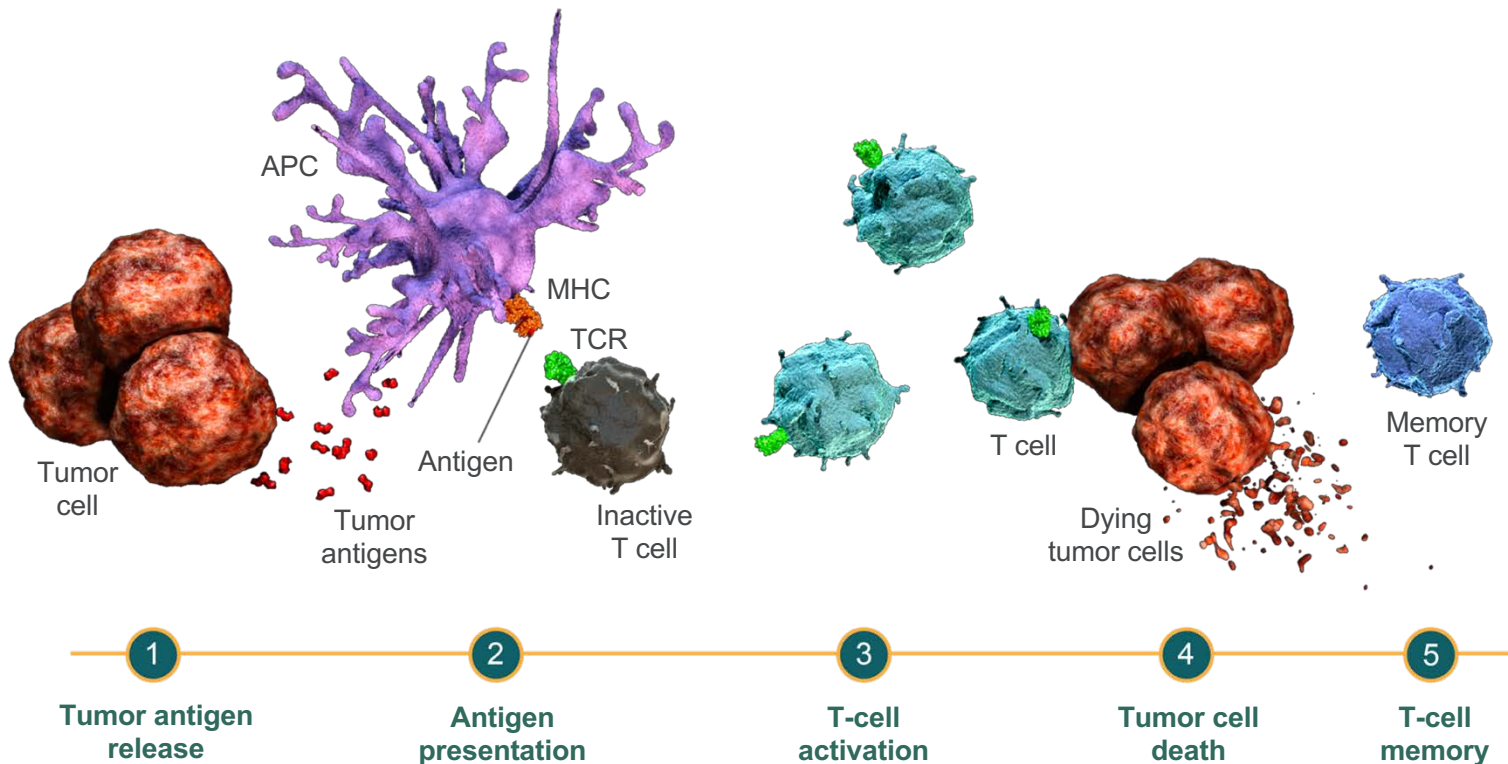
NK cells express receptors that interact with activating and inhibitory signals from normal and abnormal cells. The balance of these signals determines NK cell behavior.¹¹

*Numerous cell types are involved with the innate immune response, including macrophages, neutrophils, dendritic cells, mast cells, basophils, eosinophils, natural killer (NK) cells, and lymphocytes (T cells).¹



Adaptive immunity is durable and antigen-dependent

Adaptive immunity is **antigen-dependent** and able to produce a **durable response**.¹ Cytotoxic T cells, the primary effector cells of the adaptive immune response, can be activated by the detection of tumor antigens.^{1,12} Once activated, cytotoxic T cells proliferate, migrate to the location of the antigen, infiltrate it, and directly initiate cell death.¹³

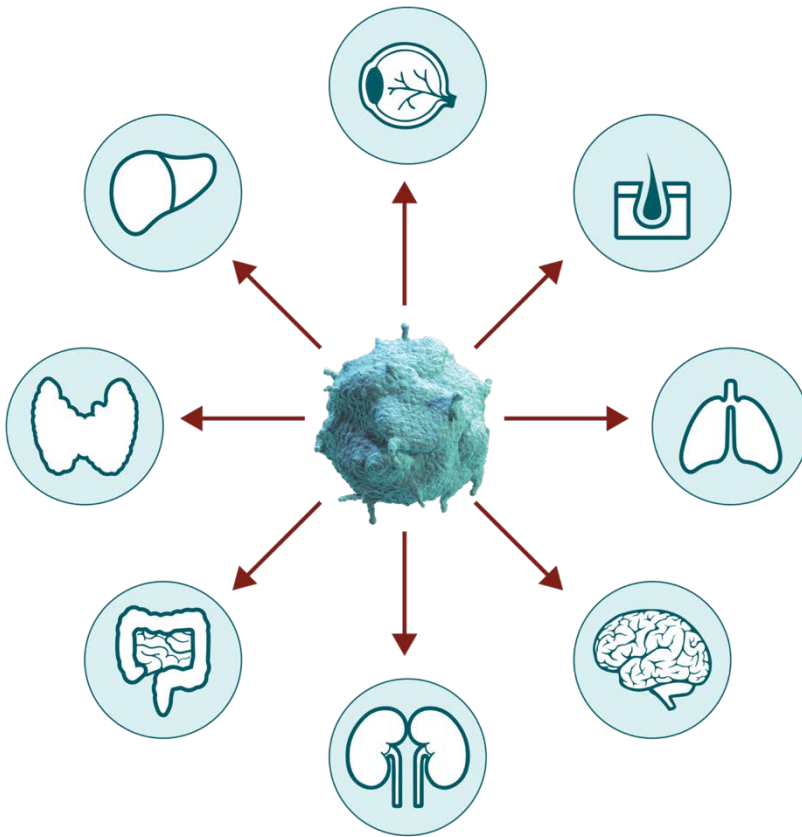


Unlike the innate immune response, adaptive immunity is not immediate, but can be sustained through a memory cell response, which includes memory T cells.^{1,8}



T cells migrate throughout the body in search of antigens

To identify and eliminate tumor cells, **cytotoxic and memory T cells** must be able to **scan peripheral tissues** in search of a unique activating antigen.^{13,14}



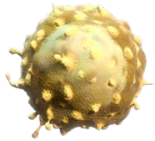
- To make this possible, activated T cells upregulate factors that enable them to recognize threats and **migrate through blood vessel walls**, into affected tissues^{15,16}
- T-cell migration occurs across non-lymphoid tissues, with documented trafficking to even particularly **selective tissues such as the eye and brain**¹⁷⁻²³
- After the activated cytotoxic T cell population diminishes, **memory T cells remain capable of trafficking to surrounding tissues** in the event of antigen reoccurrence¹⁸



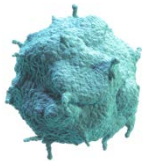
Select cells of the immune system

Effector Cells

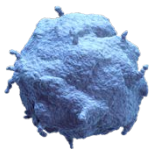
Effector cells such as cytotoxic T cells and NK cells are actively involved in the destruction of foreign pathogens and cancer.



Natural Killer (NK) cells are the primary effector cells of the innate immune response. NK cells express activating and inhibitory receptors that interact directly with signals from other cells. NK cells do not require antigen-bound MHC* to identify and attack abnormal cells.^{1,14}



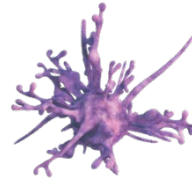
Cytotoxic T cells are the primary effector cells of the adaptive immune response. Following activation by recognition of antigens presented by MHC* class I molecules, T cells directly kill pathogens and abnormal cells that express the respective antigen.^{14,24}



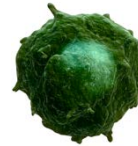
Memory T cells are derived from activated cytotoxic T cells and represent a long-lived population of antigen-experienced cells that can rapidly respond upon antigen recurrence.^{1,25}

Non-effector Cells

Non-effector cells such as APCs, Tregs, TAMs, and MDSCs directly or indirectly modulate the cytotoxic effector T-cell response. These cells cannot induce tumor cell death on their own.



Antigen-Presenting Cells (APCs) (such as dendritic cells) recognize, process, and present antigens to T cells through MHC* molecules.^{14,26}



Regulatory T cells (Tregs) are a unique subset of T cells that modulate the activation of other effector T cells to inhibit the immune response.^{14,26}



Tumor-Associated Macrophages (TAMs) are cells derived from the macrophage lineage that are recruited to the tumor microenvironment to promote tumor cell survival by driving immunosuppression.^{27,28}



Myeloid-Derived Suppressor Cells (MDSCs) are cells derived from the myeloid lineage that function to suppress T cell responses.²⁷

*Major histocompatibility complex (MHC)

Topic 2:

REVEALING THE POTENTIAL OF THE IMMUNE SYSTEM IN CANCER

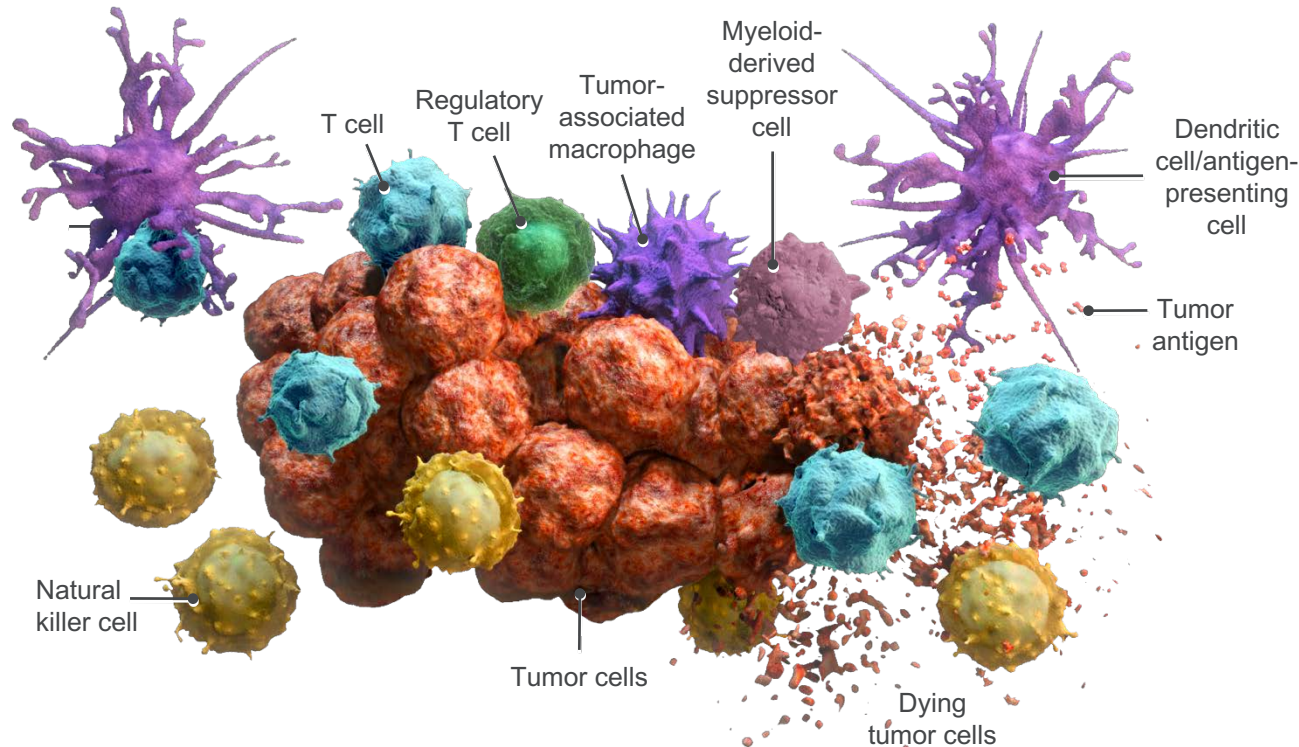
The ability of the immune system to detect and destroy cancer is the foundation of Immuno-Oncology research.



Introduction to the tumor microenvironment and the immune response

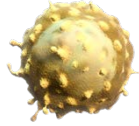
The immune system is capable of **recognizing and eliminating tumor cells** in the tumor microenvironment. Innate and adaptive immunity act as a complementary network of self-defense against foreign threats.¹

This ability to recognize **foreign threats (nonself)** as distinct from **normal cells (self)**, is an essential feature of the immune system.^{2,4,29} Despite originating from normal cells, tumor cells can be recognized as nonself through production of tumor antigens.⁵





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^{1,24,30,31}
- It recognizes activating and inhibitory signals from target cells to distinguish self from nonself^{11,32,33}
- **Natural killer (NK) cells** are the main effector cells of innate immunity¹



Adaptive immune response

- An antigen-specific response that can be activated by recognition of tumor antigens (nonself)^{1,24}
- Once activated, it can be sustained through a durable memory response¹⁸
- **Cytotoxic T cells** are the main effector cells of adaptive immunity¹

The antitumor activity of NK cells and cytotoxic T cells is regulated through a network of **activating** and **inhibitory** signaling pathways:^{14,29,34}

+ ACTIVATING

Stimulating pathways trigger immune responses

- INHIBITORY

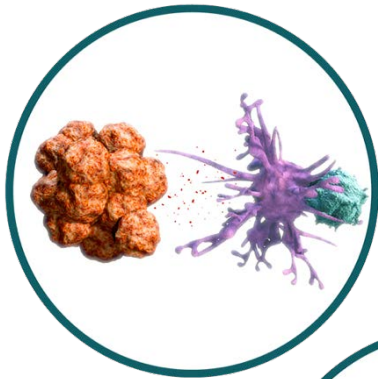
Pathways that counterbalance immune activation

The **balance between activating and inhibitory pathways** normally enables the immune system to attack tumor cells, while sparing healthy cells.¹⁴



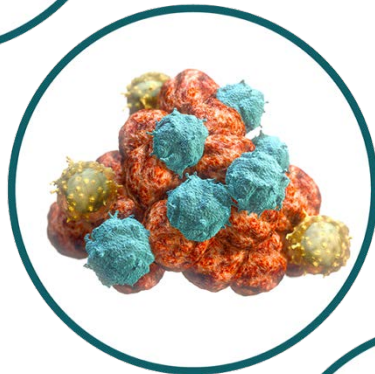
Key stages of the antitumor immune response

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



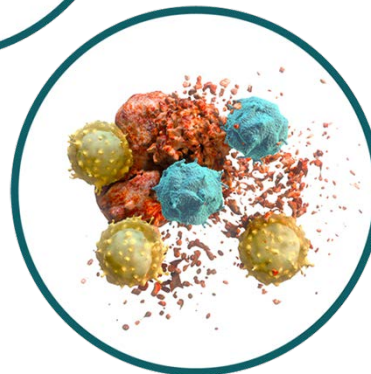
Presentation

- 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^{30,35}



Infiltration

- Tumor antigens and other factors attract immune cells to the tumor site, where they invade and attack³⁵



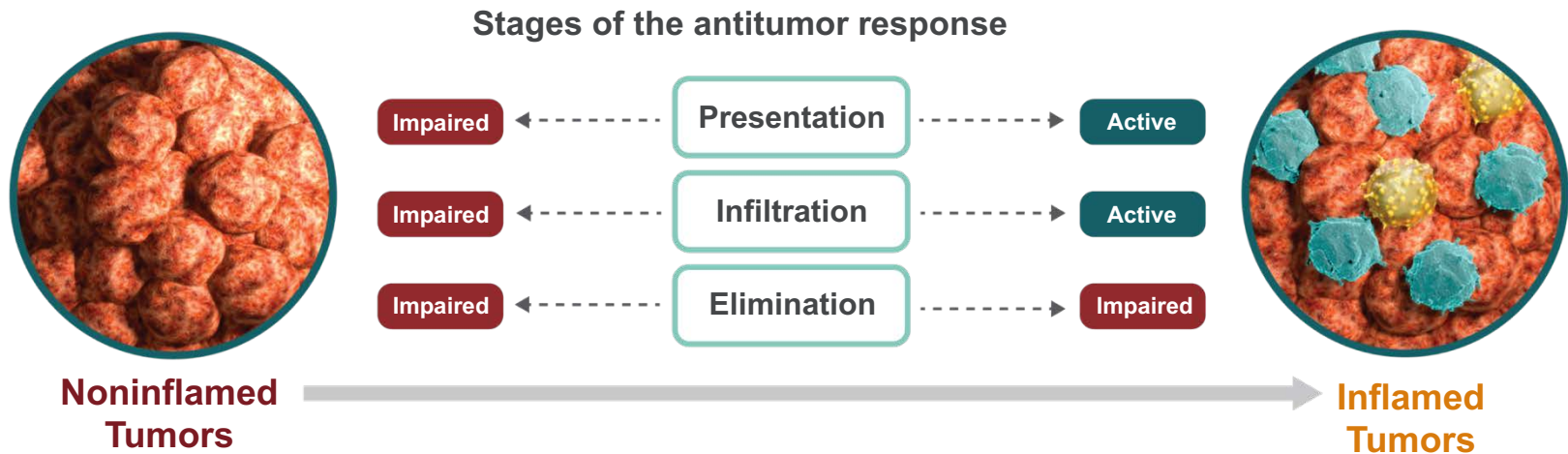
Elimination

- Activated cytotoxic T cells recognize tumor cells as the source of the antigen and target them for elimination³⁵



Tumor cells can evade and suppress immune activity

In order to survive and grow, tumor cells employ **different strategies** to outsmart the stages of the antitumor immune response. The success of these strategies determines the ability of immune cells to react to the tumor.³⁶ Depending upon their degree of immune cell infiltration, tumors are defined on a range from **inflamed** to **noninflamed**.³⁶



Characterized by poor presence of immune cells^{36,37}

- Impaired ability to **present** tumor antigens to T cells or secrete key factors (chemokines)^{37,38}
- Less able to direct tumor-specific T cells to the tumor and promote T cell **infiltration**, ultimately preventing tumor cell **elimination**^{37,38}

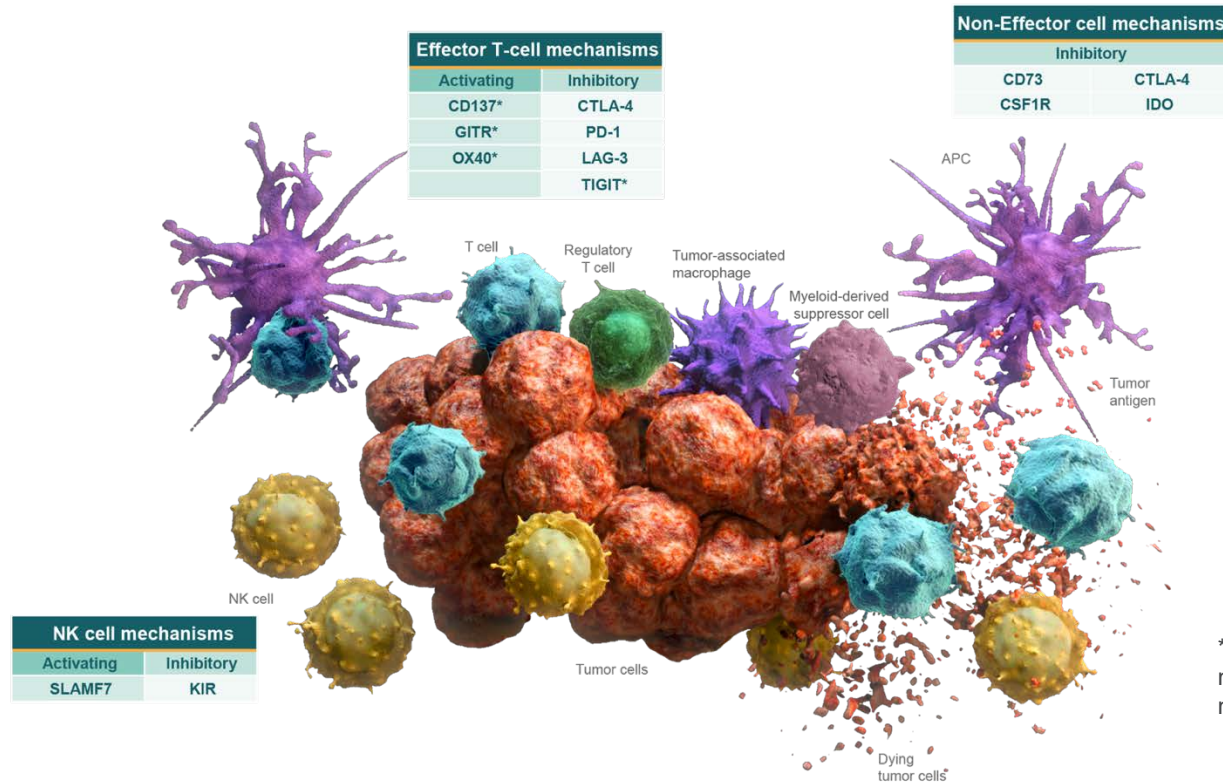
Characterized by presence of immune cells^{36,37}

- Antigen **presentation** and expression of chemokines allow for **infiltration** of activated cytotoxic T cells^{37,39-41}
- However, tumor cells may increase their expression of **inhibitory proteins** to prevent **elimination** by cytotoxic T cells^{40,42,43}



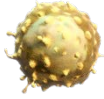
Empowering the immune system to reestablish the antitumor response

The immune system uses a **network of signaling pathways** to detect and eliminate tumor cells.^{29,34} Ongoing immuno-oncology research focuses on the following select pathways, either alone or in combination, to understand how they can be modulated to restore the body's natural ability to fight cancer.



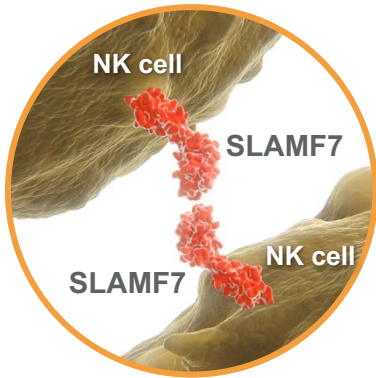
*Targets are listed by primary mechanism. Secondary mechanisms may exist.

Reestablishing the fundamental stages that are impaired within tumors—presentation, infiltration, and elimination—is a key strategy in improving the broad potential of Immuno-Oncology.



Select pathways that modulate NK cell activity

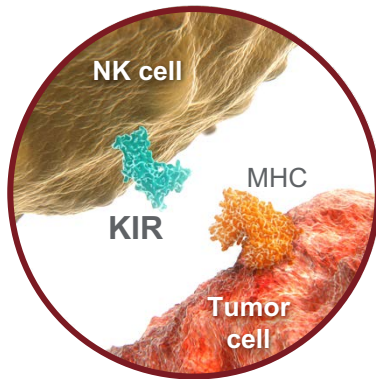
Current research is investigating the following **NK cell mechanisms** to understand how they can be modulated to restore the body's natural ability to fight cancer:



+ activating

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.^{31,45}

Continuous activation of NK cells through pathways like SLAMF7 may initiate the development of long-term immunity.^{30,46}



- inhibitory

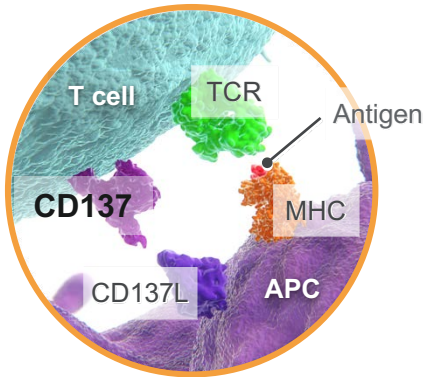
KIR is an immune checkpoint receptor on the surface of NK cells that acts to stop NK cells from killing normal cells.³² Tumor cells can use the KIR pathway to disguise themselves as normal cells and escape detection by NK cells.⁴⁷

Preclinical data suggests that blockade of inhibitory KIRs can help restore NK cell-mediated immune activity.^{48,49}



Select pathways that modulate effector T cell activity (1/4)

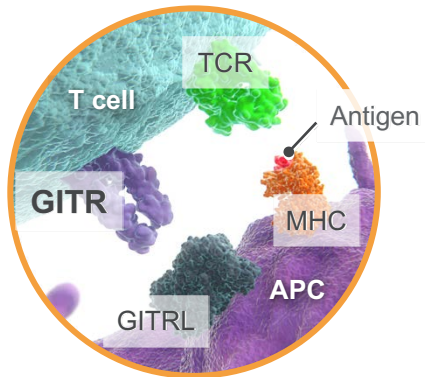
Current research is investigating the following **activating** effector T-cell mechanisms to understand how they can be modulated to restore the body's natural ability to fight cancer:



+ activating

CD137 is an activating receptor on the surface of **NK cells and T cells** that can stimulate them to reproduce and generate antitumor activity.^{50,51} CD137 also plays a critical role on T cells in the development of immune memory and the creation of a durable immune response, in animal models.⁵²

Preclinical data suggests that activation of CD137 **can stimulate both NK-cell and cytotoxic T-cell activity** and generate a lasting memory response.^{53,54}



+ activating

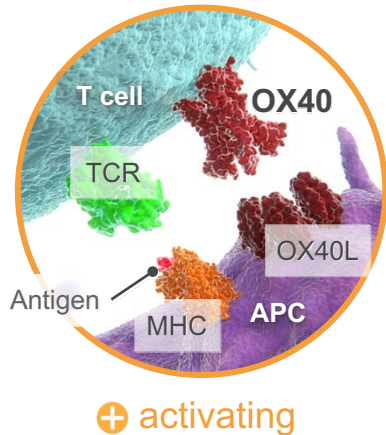
GITR is an activating receptor on the surface of T cells and other immune cells that helps to enhance cell reproduction and generate antitumor activity.⁵⁵⁻⁵⁷ GITR signaling can also block the suppressive abilities of regulatory T cells (Tregs), further enhancing cytotoxic T-cell function.⁵⁸

Preclinical data suggests that activation of GITR signaling can help enhance immunity through the activation of cytotoxic T cells and inhibition of Treg activity.⁵⁹



Select pathways that modulate effector T cell activity (2/4)

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



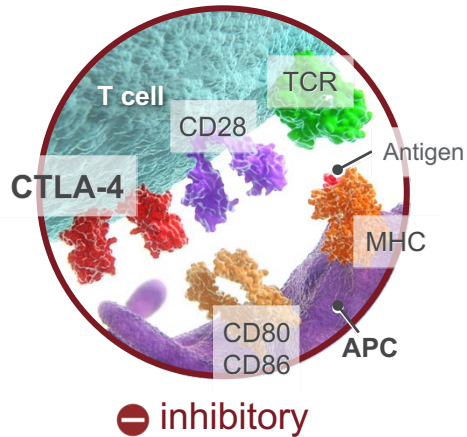
OX40 is an activating receptor on the surface of activated cytotoxic T cells and Tregs.⁶⁰⁻⁶² OX40 plays a dual role in the immune response, both activating and amplifying T-cell responses. This dual effect helps create a tumor microenvironment that is more favorable to antitumor response.⁶³⁻⁶⁶

Preclinical data suggests that OX40 increases the number and activity of cytotoxic T cells and curtails the immunosuppressive impact of Tregs.⁶⁷⁻⁶⁹



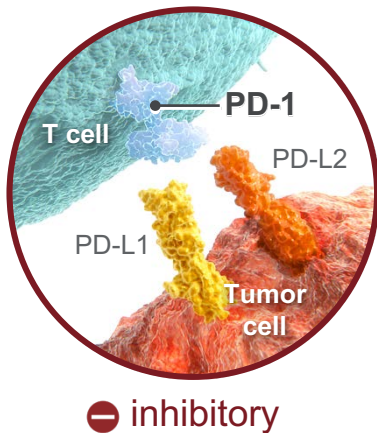
Select pathways that modulate effector T cell activity (3/4)

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



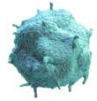
CTLA-4 is an immune checkpoint receptor on T cells that plays a key role in preventing T-cell overactivation.⁷⁰⁻⁷³ Tumor cells use the CTLA-4 pathway to suppress initiation of an immune response, resulting in decreased T-cell activation and ability to proliferate into memory T cells.^{74,75} CTLA-4 signaling diminishes the ability of memory T cells to sustain a response, damaging a key element of durable immunity.⁷⁶

Preclinical data suggests that treatment with antibodies specific for CTLA-4 can restore an immune response through increased survival of memory T cells and depletion of regulatory T cells.⁷⁷⁻⁸⁰



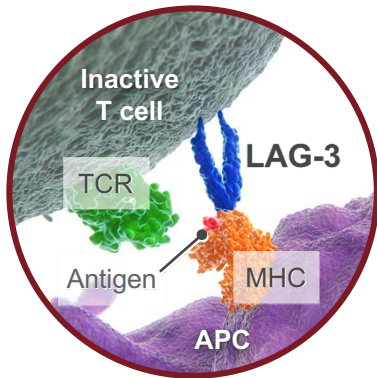
PD-1 is an immune checkpoint receptor on cytotoxic T cells that plays a key role in T-cell exhaustion and prevention of autoimmunity.⁸¹⁻⁸³ Tumor-infiltrating T cells across solid tumors and hematologic malignancies display evidence of exhaustion, including upregulation of PD-1.⁴³

Preclinical data suggests that PD-1 blockade reinvigorates exhausted T cells and restores their cytotoxic immune function.⁸² Inhibiting both PD-1 ligands (PD-L1 and PD-L2) may be more effective at reversing T-cell exhaustion than inhibiting PD-L1 alone.⁸⁴



Select pathways that modulate effector T cell activity (4/4)

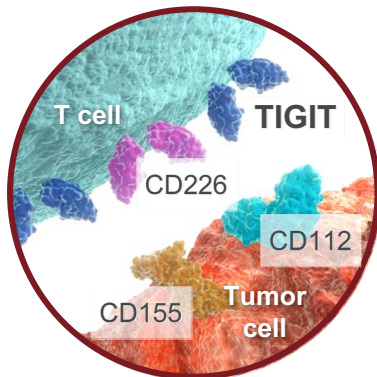
Current research is investigating the following **inhibitory effector T-cell mechanisms** to understand how they can be modulated to restore the body's natural ability to fight cancer:



⊖ inhibitory

LAG-3 is an immune checkpoint receptor on the surface of both activated cytotoxic and regulatory T cells (Tregs).^{85,86} When bound to the antigen-MHC complex, LAG-3 can negatively regulate T-cell proliferation and the development of lasting memory T cells.⁸⁷ Repeated exposure to tumor antigen causes an increase in the presence and activity of LAG-3, leading to T-cell exhaustion.^{88,89}

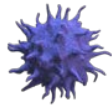
Preclinical data suggests that inactivation of LAG-3 allows T cells to regain cytotoxic function.⁹⁰



⊖ inhibitory

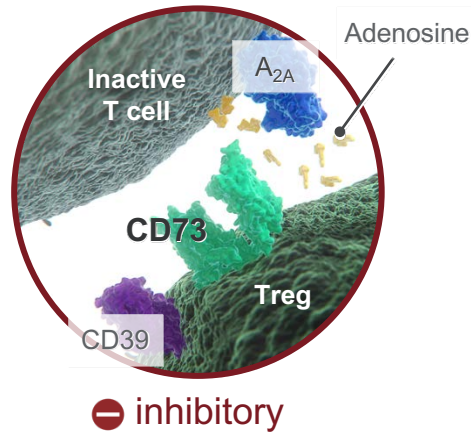
TIGIT is an immune checkpoint receptor expressed on the surface of cytotoxic, memory, and regulatory T cells (Tregs), as well as natural killer (NK) cells.^{91,92} On cytotoxic T cells and NK cells, interaction of TIGIT with either of its ligands suppresses immune activation.^{91,92} When TIGIT is expressed on Tregs, however, this interaction enhances their ability to suppress the immune response.⁹³

Preclinical data suggests that inhibition of TIGIT signaling increases the proliferation and function of cytotoxic T cells.^{94,95}



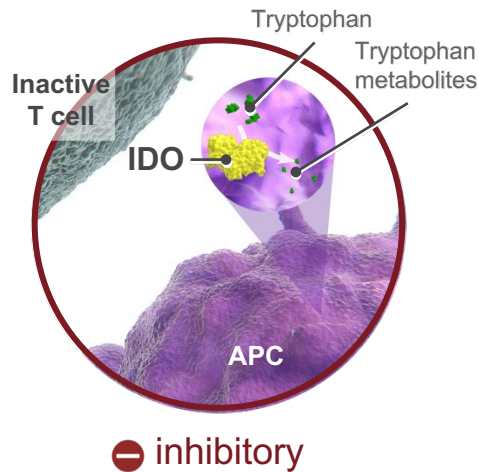
Select pathways that modulate non-effector cell activity (1/2)

Current research is investigating the following **inhibitory non-effector cell mechanisms** to understand how they can be modulated to restore the body's natural ability to fight cancer:



CD73 is a cell-surface enzyme on Tregs. CD73 is a critical checkpoint in the production of adenosine, which has been demonstrated to be a powerfully immunosuppressive molecule in cellular studies.⁹⁶ Tumor cells exploit this pathway by expressing CD73 and releasing adenosine into the tumor microenvironment.⁹⁷⁻⁹⁹

Preclinical data suggests that inhibition of CD73 activity can stimulate T-cell activity.¹⁰⁰



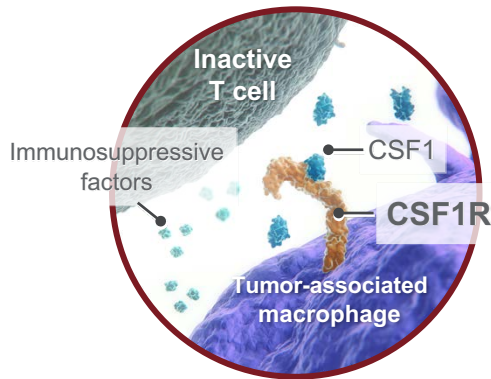
IDO is an intracellular enzyme that initiates the breakdown of tryptophan, an amino acid that is essential for T-cell survival.¹⁰¹⁻¹⁰³ Tumor cells can upregulate IDO activity in order to suppress T-cell antitumor function.^{104,105}

Preclinical data suggests that blockade of IDO can restore cytotoxic T-cell function.^{106,107}



Select pathways that modulate non-effector cell activity (2/2)

Current research is investigating the following **inhibitory non-effector cell mechanisms** to understand how they can be modulated to restore the body's natural ability to fight cancer:



— inhibitory

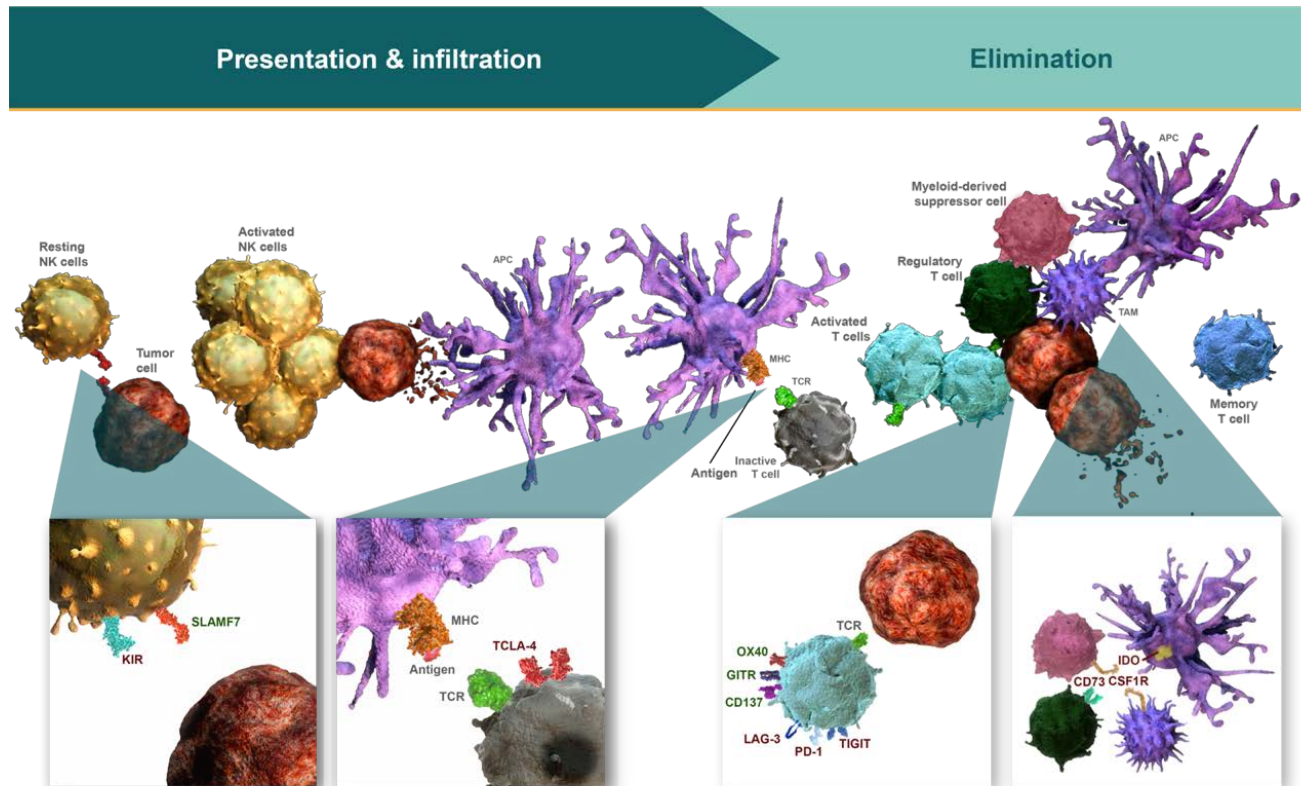
CSF1R is a receptor on the surface of macrophages and other cells of the myeloid lineage.¹⁰⁸ In the tumor microenvironment, some macrophages evolve from antitumor to protumor in their activity.²⁸ Protumor, or tumor-associated macrophages (TAMs) can drive immunosuppression and support tumor growth.²⁸ Mouse models have shown that tumor cells use CSF1 to target CSF1R on macrophages, stimulating the development and survival of TAMs.¹⁰⁹

Preclinical data suggests that blockade of CSF1R can result in depletion of TAMs and improved T-cell responses.^{110,111}



Immune pathways combine to refine response

Activating and inhibitory signaling pathways **combine to maintain immune balance** by regulating the three key stages of the immune response: presentation, infiltration, and elimination.^{29,34} Once an immune response is initiated, each stage can potentiate or limit the activity of subsequent stages.¹¹²



Modulating immune pathways in combination may enhance the immune response, as suggested by preclinical data.¹¹³⁻¹¹⁶

Topic 3:

EXPLORING PREDICTORS OF RESPONSE: IMMUNE-BIOMARKERS

Research in the field of immune-biomarkers seeks to characterize immune activity in the tumor microenvironment.



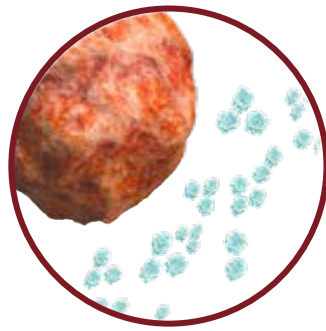
Immune-biomarkers are indicators of immune activity

Immune-biomarkers are **measures of activity** within the tumor microenvironment, differing from established gene mutation biomarkers, such as BRAF and EGFR.¹¹⁷⁻¹²⁰

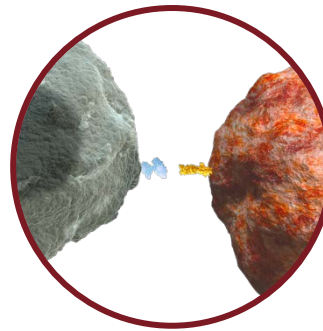
As **components and regulators of the immune response**, immune-biomarkers include¹¹⁷:



Tumor-infiltrating
immune cells



Secreted
peptides



Cell surface
proteins



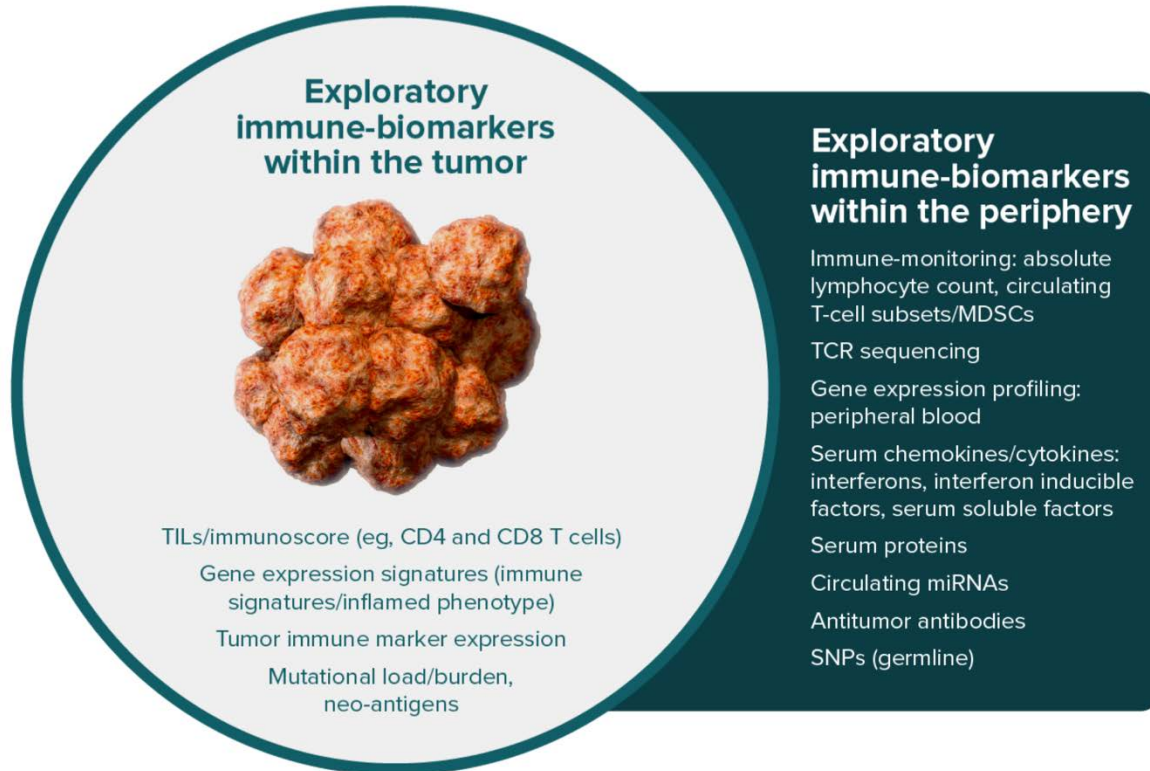
Immunosuppressive
cells

Evaluating multiple immune-biomarkers may provide a more realistic representation of the tumor microenvironment, as well as a more accurate and comprehensive assessment of clinical relevance.^{120,121}



Exploratory immune-biomarkers

New immune-biomarkers are now being investigated across tumor types:¹²²⁻¹³³



The field of immune-biomarkers aims to characterize the ongoing interactions between the immune system and cancer.

Topic 4:

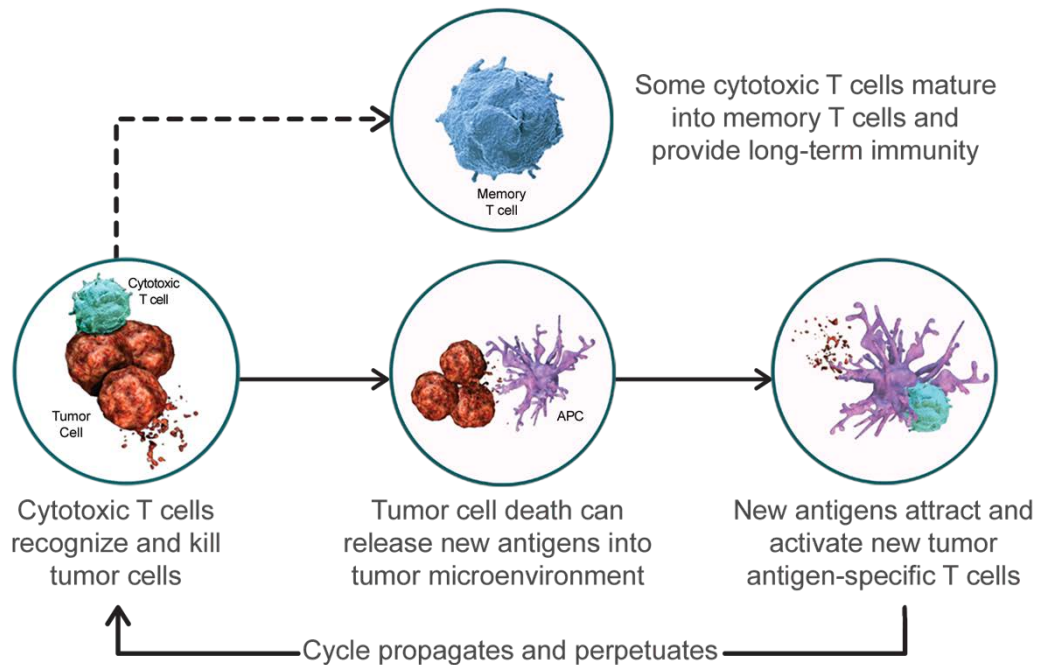
EVOLVING CLINICAL EXPECTATIONS IN I-O

Immuno-Oncology (I-O) is a fundamentally different approach to cancer treatment. With this new approach comes unique considerations and distinctive characteristics that continue to be researched.



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 intelligent nature of the immune response.³⁵ Immune responses are dynamic and have the potential to improve and deepen over time.¹³⁴



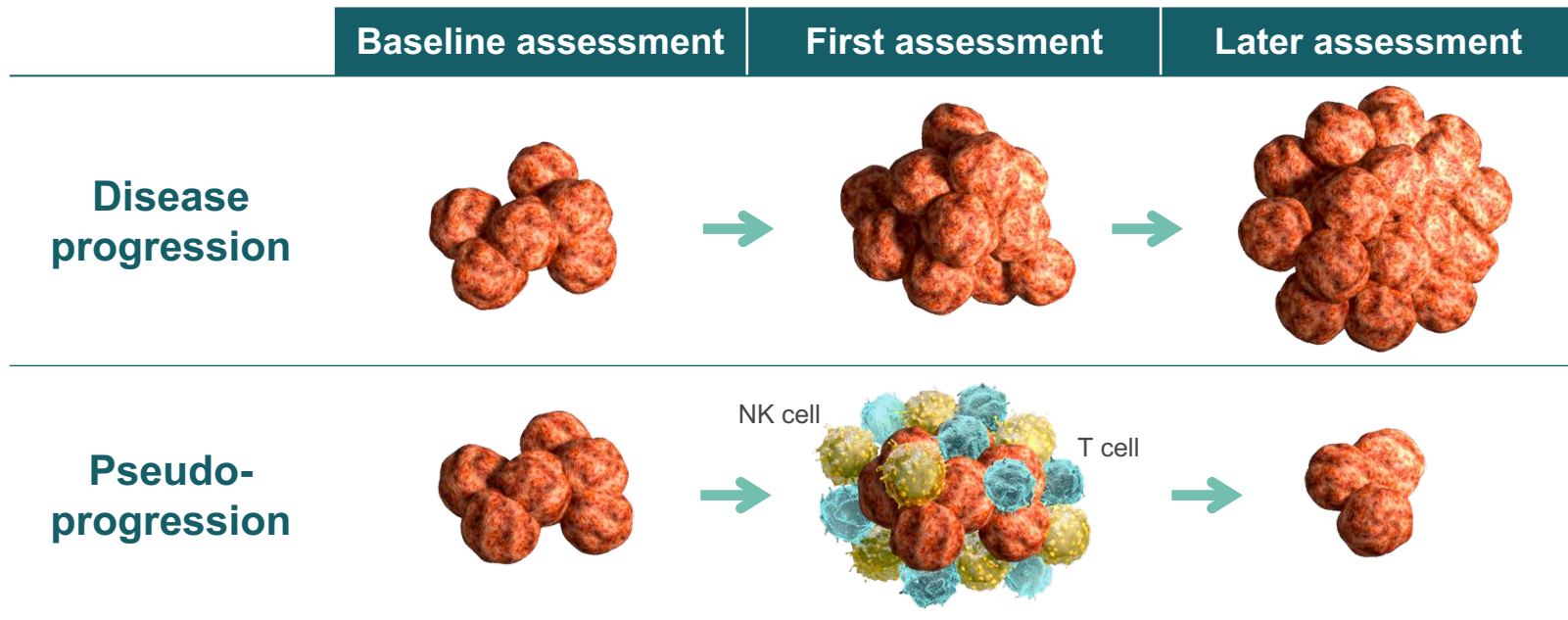
As the immune response continues to expand, some cytotoxic T cells mature into memory T cells that may provide long-term immune protection, even if the original stimulus is no longer present.^{7,8}



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.¹³⁵ This is known as **pseudo-progression**. Pseudo-progression does not reflect tumor cell growth, but may be misclassified as disease progression.^{135,136}

Tumors may **appear to grow or new lesions may appear when immune cells infiltrate the tumor site.**¹³⁵ Due to the time required to mount an adaptive immune response, pseudo-progression may also reflect continued tumor growth until a sufficient response develops.^{135,137}





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

While uncommon, **pseudo-progression is an important consideration** when evaluating response to Immuno-Oncology therapies.¹³⁷ Histologic confirmation is not always possible, but close monitoring of the following factors may help identify pseudo-progression:^{135,138}

| | 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 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 |

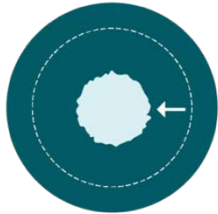


Endpoint considerations for I-O research (1/2)

The criteria currently used to assess potential benefit of cancer therapies are based on surgery, radiation therapy, and chemotherapy.¹³⁹ However, for **Immuno-Oncology**, a different way to fight cancer, a more comprehensive approach to endpoint assessment may be needed to recognize potential benefit.¹⁴⁰⁻¹⁴⁴

Magnitude and duration are both key measures of response

Response can be assessed by both **magnitude (size)** and **duration (time)**.¹⁴⁵



Objective response rate (ORR) is the proportion of patients with a predefined decrease in tumor burden.¹⁴⁵ ORR reflects solely the magnitude of response, and is generally defined as a sum of partial and complete responses.¹⁴⁵



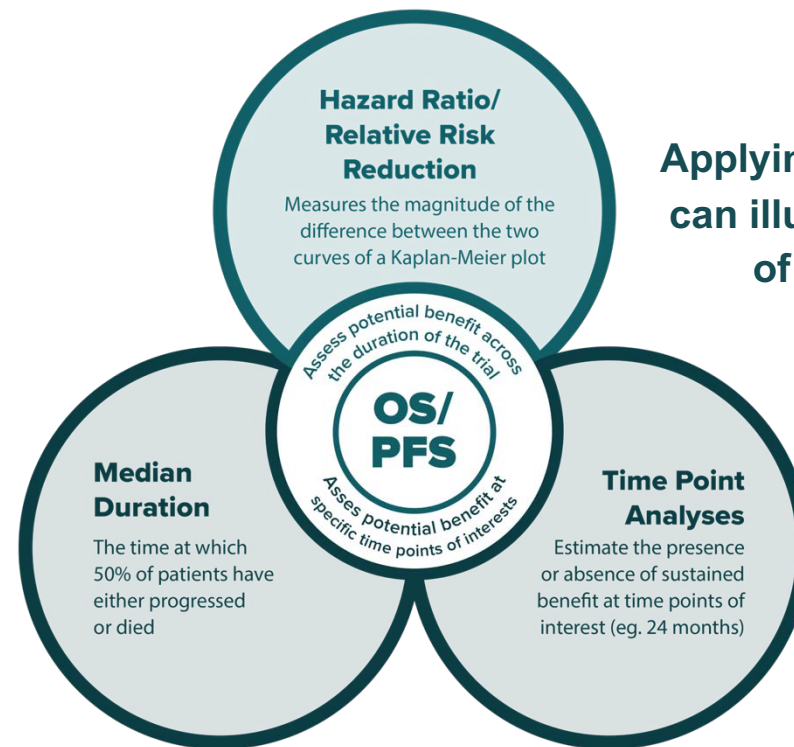
Duration of response (DoR) measures the time from initial tumor response to disease progression.¹⁴⁵ As our understanding of research continues to evolve, the DoR may prove even more relevant to potential benefit than the magnitude of tumor reduction.¹⁴⁶

Because responses range in both size and duration, these measures should be evaluated together to more accurately assess advances in Immuno-Oncology research.¹⁴⁵



Endpoint considerations for I-O research (2/2)

Overall survival (OS), progression-free survival (PFS), and response rate are among endpoints used to measure outcomes in oncology research.^{145,146} OS is the **gold standard** to assess therapeutic benefit when possible.¹⁴⁶



Applying multiple measures can illustrate the full scope of clinical benefit.

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.^{141-143,147}



Immune-mediated adverse reactions

Immuno-Oncology (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.¹⁴⁸

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

- Patients, caregivers, and physicians should be educated to remain vigilant throughout and after Immuno-Oncology treatment to minimize complications, some of which may be life threatening¹⁴⁸
- In addition, treatment algorithms are available for use by healthcare providers to assist them in managing immune-mediated adverse reactions¹⁴⁹

As research in immune system activation advances and more data are made available, understanding and appropriate management of immune-mediated adverse reactions will evolve.¹⁵⁰

Topic 5:

REALIZING THE 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 Immuno-Oncology (I-O) research across tumor types.

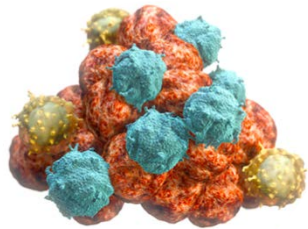


Depth of evidence for the immune response to cancer

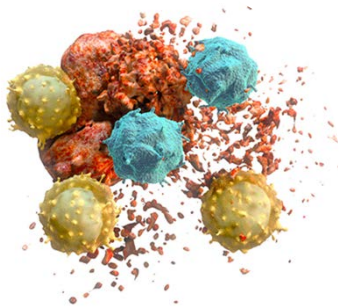
Both solid tumors and hematologic malignancies are able to induce an immune response that can regulate their growth. This ability is known as **tumor immunogenicity**.^{151,152} The body is able to recognize and attack cancer through the following mechanisms:



PRESENTATION: Traditionally, immunogenic tumors are defined by a high rate of mutations.¹⁵³ These mutations create **tumor antigens that can be recognized** by the immune system, activating an antitumor immune response.¹⁵⁴



INFILTRATION: Tumor-infiltrating immune cells are present in the tumor microenvironment.¹⁵⁵⁻¹⁶⁷ Their presence demonstrates their capacity to **identify and migrate to tumor cells**.¹⁶⁸



ELIMINATION: Early in their development, some tumors display evidence of spontaneous regression.¹⁶⁹ 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.^{169,170}



Broad potential of I-O research

There is evidence of immunogenicity across a wide range of malignancies:¹⁷¹

| Tumor Type | Evidence for tumor immunogenicity | | |
|---|-----------------------------------|--------------------------------------|------------------------------------|
| | PRESENTATION | INFILTRATION | ELIMINATION |
| | Presence of somatic mutations | Evidence of immune-cell infiltration | Evidence of spontaneous regression |
| Bladder ^{153,165} | ● 153 | ● 165 | |
| Breast ^{167,172} | ● 172 | ● 167 | |
| Colorectal ¹⁶⁶ | ● 166 | ● 166 | |
| Gastric/Esophageal ^{158,173} | ● 173 | ● 158 | |
| Glioblastoma ^{154,156} | ● 154 | ● 156 | |
| Head & Neck ^{159,174} | ● 174 | ● 159 | |
| Hepatocellular ¹⁶³ | ● 163 | ● 163 | |
| Lung ^{153,158} | ● 153 | ● 158 | |
| Melanoma ^{153,158,169} | ● 153 | ● 158 | ● 169 |
| Ovarian ^{162,175} | ● 175 | ● 162 | |
| Pancreatic ¹⁶⁶ | ● 166 | ● 166 | |
| Prostate ^{160,176} | ● 176 | ● 160 | |
| Renal ^{153,161} | ● 153 | ● 161 | ● 161 |
| Non-Hodgkin Lymphoma ^{155,177} | ● 177 | ● 155 | |
| Hodgkin Lymphoma ^{164,178} | ● 178 | ● 164 | |
| Leukemia ¹⁷⁹ | ● 179 | | |
| Multiple Myeloma ^{157,180} | ● 180 | ● 157 | |



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 signalling pathways, either alone or in combination, and how they can be modulated to restore the body's natural ability to fight cancer
- Understanding predictors of response, such as immune-biomarkers, to help identify patients who are more likely to benefit from Immuno-Oncology therapies
- Developing a more comprehensive approach to endpoint assessment, to better recognize the potential benefit of Immuno-Oncology 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.



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