# Understanding the Science behind Immuno-Oncology

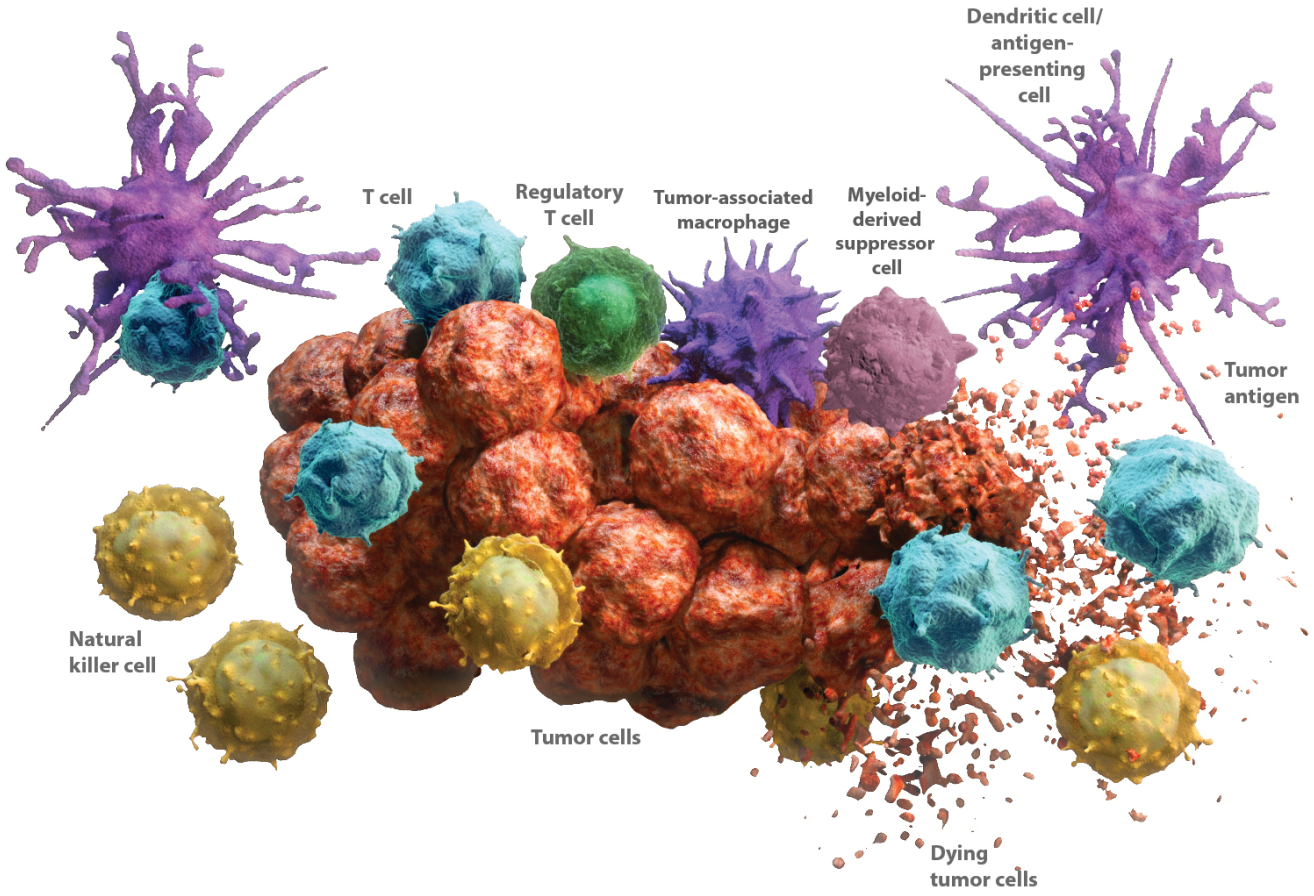
*Using the body's natural immune response to fight cancer*

## TABLE OF CONTENTS

# Revealing the Potential of the Immune System in Cancer

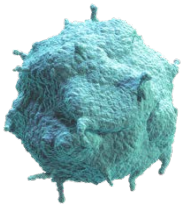
## Introduction to the tumor microenvironment and the immune response

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] 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.[1,6-8] It recognizes activating and inhibitory signals from target cells to distinguish self from nonself.[9-11]
**Natural Killer (NK) cells** are the main effector cells of innate immunity.[1]



**Adaptive immune response**
An antigen-specific response that is activated by recognition of tumor antigens (nonself).[1,8] Once activated, it can be sustained through a durable memory response.[12]
**Cytotoxic T cells** are the main effector cells of adaptive immunity.[1]

The antitumor activity of NK cells and cytotoxic T cells is regulated through a network of **activating** and **inhibitory** signaling pathways:[4,13,14]

**Activating Pathways:**
**Stimulating pathways trigger immune responses**

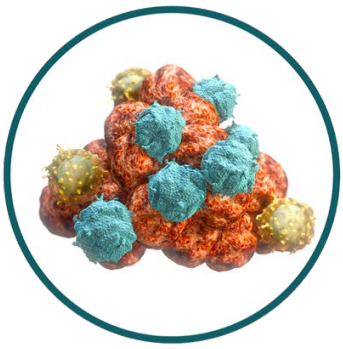
**Inhibitory Pathways:**
**Pathways that counterbalance immune activation**

The **balance between activating and inhibitory pathways** normally enables the immune system to attack tumor cells, while sparing healthy cells.[13]

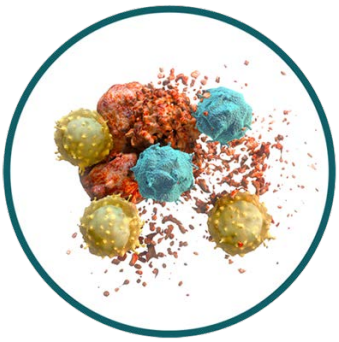
## Key stages of the antitumor immune response

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.[6,15]



### Infiltration
Tumor antigens and other factors attract immune cells to the tumor site, where they invade and attack.[15]



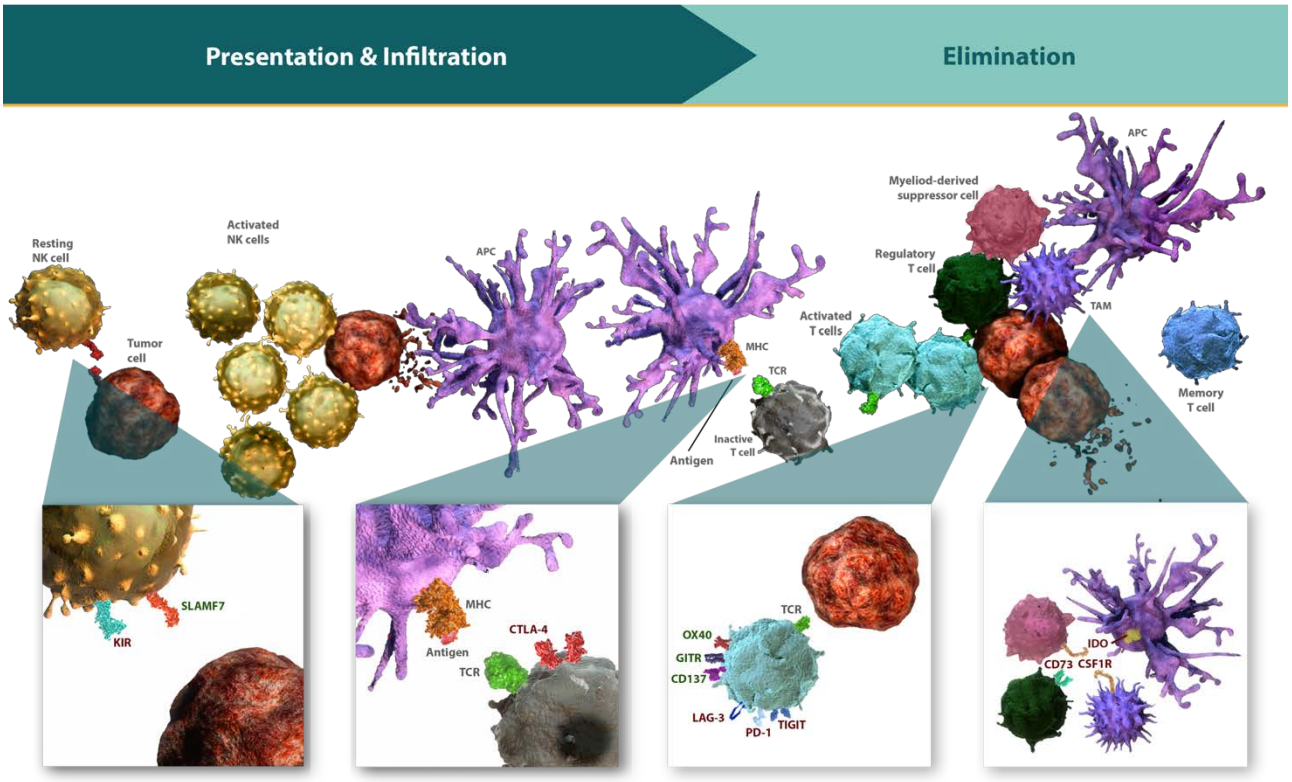
### Elimination
Activated cytotoxic T cells recognize tumor cells as the source of the antigen and target them for elimination.[15]

## 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. These mechanisms range from failing to **present** tumor antigens, to increasing expression of inhibitory proteins to prevent **elimination** by cytotoxic T cells.[16-20] The success of these strategies determines the ability of immune cells to react to the tumor.[21]

## Immune pathways combine to refine response

The three 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**.[4,14] Reestablishing the pathways that are impaired within tumors is a key focus of ongoing Immuno-Oncology research.




**Modulating immune pathways in combination may enhance the immune response, as suggested by preclinical data.[22-25]**

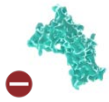
## Select pathways that modulate NK cell activity

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 pathway

**SLAMF7** is an activating receptor on the surface of NK cells and other immune cells.[26] When engaged, SLAMF7 activates NK cells, the rapid responders of the immune system and the body's first line of defense against cancer.[7,27]

### Inhibitory pathway



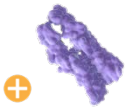
**KIR** is an immune checkpoint receptor on the surface of NK cells that acts to stop NK cells from killing normal cells.[10]

## 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.

### Activating pathways

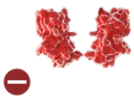
**CD137** is an activating receptor on the surface of NK cells and T cells that can stimulate them to reproduce and generate antitumor activity.[28,29]



**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.[30-32]

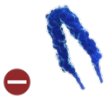
**OX40** is an activating receptor on the surface of activated cytotoxic T cells and Tregs.[33-35] OX40 plays a dual role in the immune response, both activating and amplifying T-cell responses.[36-39]

### Inhibitory pathways



**CTLA-4** is an immune checkpoint receptor on T cells that plays a key role in preventing T-cell overactivation.[40-43] CTLA-4 signaling diminishes the ability of memory T cells to sustain an immune response.[44]

**PD-1** is an immune checkpoint receptor on cytotoxic T cells that plays a key role in T-cell exhaustion and prevention of autoimmunity.[45-47]



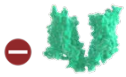
**LAG-3** is an immune checkpoint receptor on the surface of both activated cytotoxic and regulatory T cells (Tregs).[48,49] LAG-3 can negatively regulate T-cell proliferation and the development of lasting memory T cells.[50]

**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.[51,52] On all of these cells, TIGIT can play a role in immune suppression.[51-53]

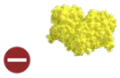
## Select pathways that modulate non-effector cell activity

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.

### Inhibitory pathways



**CD73** is a cell-surface enzyme on Tregs. 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.[54]



**IDO** is an intracellular enzyme that initiates the breakdown of tryptophan, an amino acid that is essential for T-cell survival.[55-57]

**CSF1R** is a receptor on the surface of macrophages and other cells of the myeloid lineage.[58] CSF1, the ligand for CSF1R, is a dominant regulator of macrophage differentiation and function.[59]

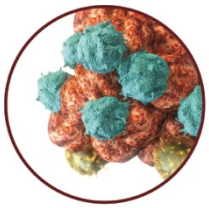
**Ongoing Immuno-Oncology research focuses on these select signaling pathways, either alone or in combination, to understand how they can be modulated to restore the body's natural ability to fight cancer.**

# Exploring Predictors of Response: Immune-Biomarkers

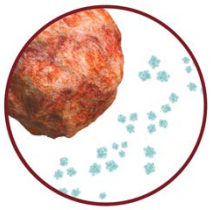
## Immune-biomarkers are indicators of immune activity

Immune-biomarkers are measures of activity within the tumor microenvironment, differing from established gene mutation biomarkers, such as BRAF and EGFR.[60-63]

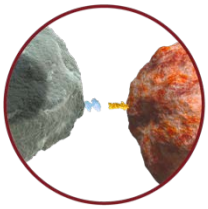
As components and regulators of the immune response, immune-biomarkers include:[60]



Tumor-infiltrating immune cells



Secreted peptides



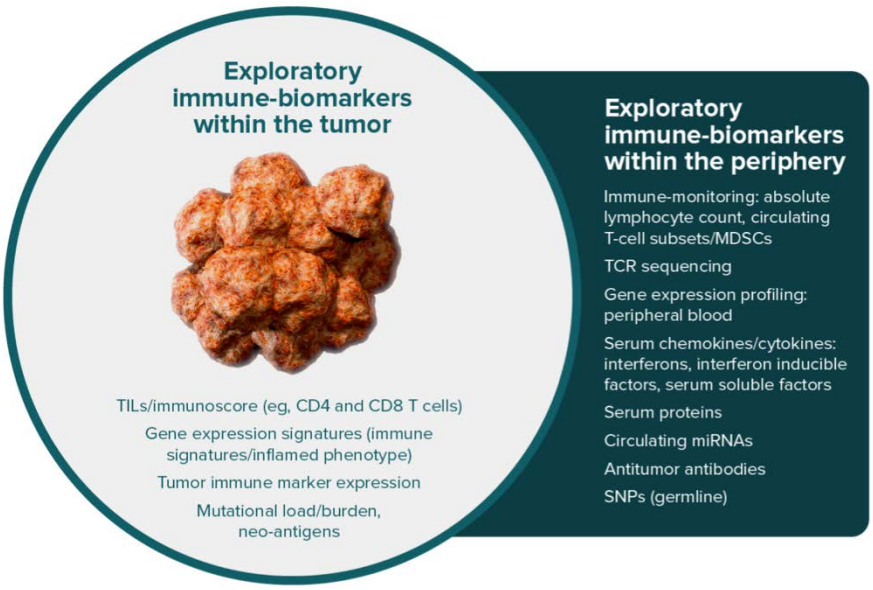
Cell surface proteins

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.[63,64]**

## Exploratory immune-biomarkers

New immune-biomarkers are now being investigated across tumor types:[65-76]




**The field of immune-biomarkers aims to characterize the ongoing interactions between the immune system and cancer.[60]**

# Evolving Clinical Expectations in Immuno-Oncology

## Immuno-Oncology is a different approach to fighting cancer

Immuno-Oncology seeks to activate the body's natural immune response to fight cancer. This is a fundamentally different approach to cancer treatment.

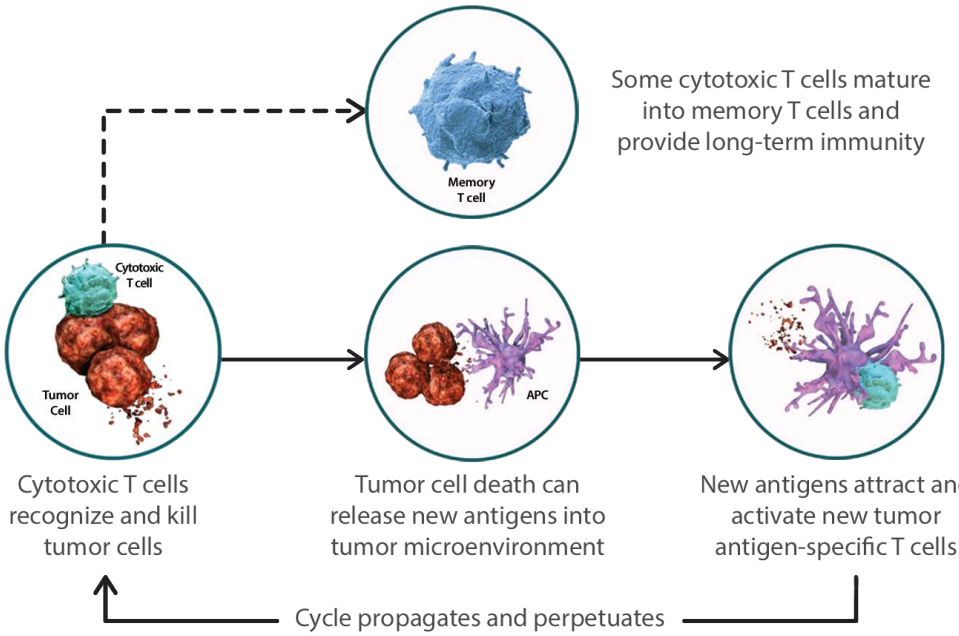
With this new approach comes unique considerations and distinctive characteristics that continue to be researched, such as:

- Immune responses have the potential to deepen and sustain over time
- Unique patterns of response, such as pseudo-progression
- Unique 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 intelligent nature of the immune response.[15]

Immune responses are dynamic and have the potential to improve and deepen over time .[77]

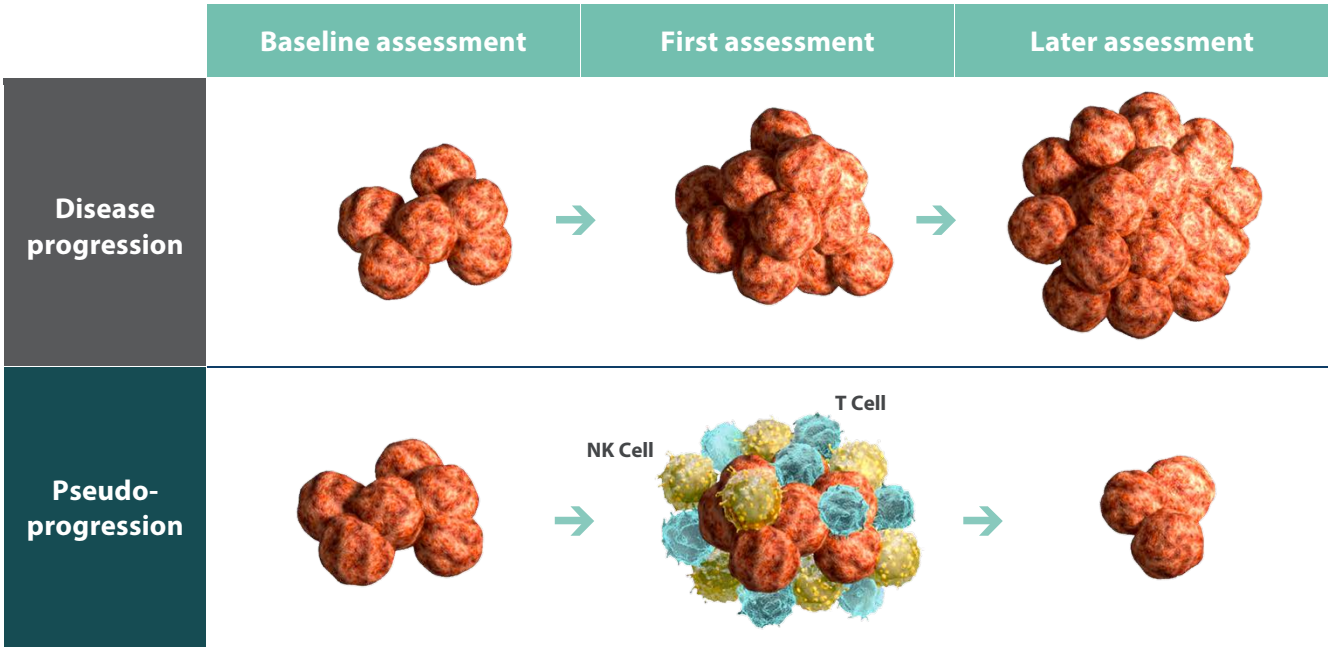



**As the immune response continues to expand, some cytotoxic T cells mature into memory T cells that may provide long-term immune protection, even if the original stimulus is no longer present.[12,78]**

## 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.[79] This is known as **pseudo-progression**. Pseudo-progression does not reflect tumor cell growth, but may be misclassified as disease progression.[79,80]

Tumors may **appear to grow or new lesions may appear when immune cells infiltrate the tumor site**.[79] Due to the time required to mount an adaptive immune response, pseudo-progression may also reflect continued tumor growth until a sufficient response develops.[79,81]




## 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.[81] Histologic confirmation is not always possible, but close monitoring of the following factors may help identify pseudo-progression: [79,82]

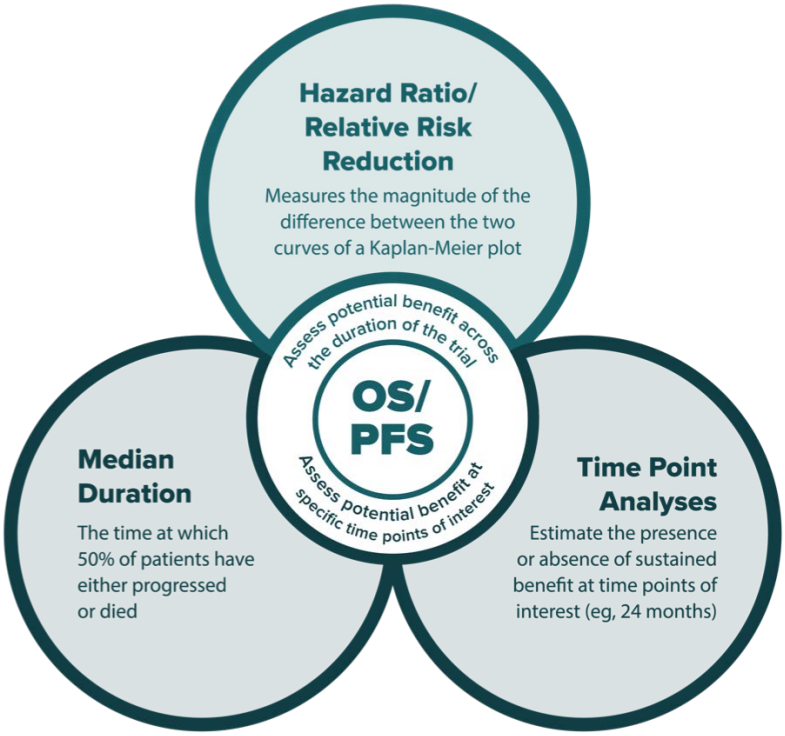
| | Disease progression | Pseudo-progression |
|---|---|---|
| **Performance status** | Deterioration of performance | Remains stable or improves |
| **Systemic symptoms** | Worsen | May or may not improve |
| **Symptoms of tumor enlargement** | Present | May or may not be present |
| **Tumor burden** | | |
| 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 Immuno-Oncology research

The criteria currently used to assess potential benefit of cancer therapies are based on surgery, radiation therapy, and chemotherapy.[83] However, for **Immuno-Oncology**, a different way to fight cancer, a more comprehensive approach to endpoint assessment may be needed to recognize potential benefit.[84-88]

**Overall survival (OS)**, **progression-free survival (PFS)**, and **response rate** are among endpoints used to measure outcomes in oncology research.[89,90] OS is the **gold standard** to assess therapeutic benefit when possible.[90]

In addition, key measures of response are **magnitude (size)**—measured as the proportion of patients with a predefined decrease in tumor burden, called the **Objective Response Rate (ORR)**—and **duration (time)**—assessed as the time from initial tumor response to disease progression, called the **Duration of Response (DoR)**.[89]




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.[85-87,91]

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

## Immune-mediated adverse reactions

Immuno-Oncology 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.[92]

**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 threatening[92]
- In addition, treatment algorithms are available for use by healthcare providers to assist them in managing immune-mediated adverse reactions[93]

**As research in immune system activation advances and more data are made available, understanding and appropriate management of immune-mediated adverse reactions will evolve.[94]**

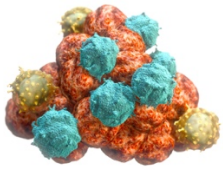
# Realizing the Potential of Immuno-Oncology Research

## 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 growth. This ability is known as **tumor immunogenicity**.[95,96] The body is able to recognize and attack cancer through the following mechanisms:

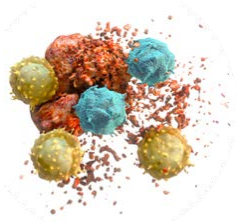
### Presentation

Traditionally immunogenic tumors are defined by a high rate of mutations.[97] These mutations create tumor antigens that can be recognized by the immune system, activating an antitumor immune response.[98]



### Infiltration

Tumor-infiltrating immune cells are present in the tumor microenvironment.[99-111] Their presence demonstrates their capacity to identify and migrate to tumor cells.[112]



### Elimination

Early in their development, some tumors display evidence of spontaneous regression.[113] 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.[113,114]

## Broad potential of Immuno-Oncology research

Evidence for tumor immunogenicity across a wide range of solid tumors and hematologic malignancies provides the rationale for the breadth of Immuno-Oncology research across tumor types: [115]

| Tumor Type | Evidence for tumor immunogenicity | | |
|---|---|---|---|
| | **PRESENTATION** Presence of somatic mutations | **INFILTRATION** Evidence of immune-cell infiltration | **ELIMINATION** Evidence of spontaneous regression |
| Bladder[97,109] | ● 97 | ● 109 | |
| Breast[111,116] | ● 116 | ● 111 | |
| Colorectal[110] | ● 110 | ● 110 | |
| Gastric/Esophageal[102,117] | ● 117 | ● 102 | |
| Glioblastoma[98,100] | ● 98 | ● 100 | |
| Head & Neck[103,118] | ● 118 | ● 103 | |
| Hepatocellular[107] | ● 107 | ● 107 | |
| Lung[97,102] | ● 97 | ● 102 | |
| Melanoma[97,102,113] | ● 97 | ● 102 | ● 113 |
| Ovarian[106,119] | ● 119 | ● 106 | |
| Pancreatic[110] | ● 110 | ● 110 | |
| Prostate[104,120] | ● 120 | ● 104 | |
| Renal[97,105] | ● 97 | ● 105 | ● 105 |
| Non-Hodgkin Lymphoma[99,121] | ● 121 | ● 99 | |
| Hodgkin Lymphoma[108,122] | ● 122 | ● 108 | |
| Leukemia[123] | ● 123 | | |
| Multiple Myeloma[124,101] | ● 124 | ● 101 | |

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