Looking deeper into the science of Immuno-Oncology

Using the body's natural immune response to fight cancer

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About

- These slides help explain key concepts about the rapidly evolving field of Immuno-Oncology (I-O). The information is separated into 5 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. **Discovering the possibilities of I-O biomarkers**

Topic 4. **Evolving clinical expectations in I-O**

Topic 5. **Realizing the potential of I-O research**

Topics covered

1 Essential principles of immunology

- Differentiating *self* from *nonself*
- Innate and adaptive immunity as complementary responses
- Innate immunity is rapid and antigen-independent
- APCs act as primary messengers between innate and adaptive immunity
- Adaptive immunity is durable and antigen-dependent
- T cells migrate throughout the body in search of antigens
- Select cells of the immune system

2 Revealing the potential of the immune system in cancer

- Introduction to the tumor microenvironment (TME) and the immune response
- Key stages of the antitumor immune response
- Evasion of immune activity by tumor cells
- Four modes of action that may enhance or inhibit the immune system's ability to fight off cancer
- Select pathways that modulate tumor detection, immunosuppression, effector cell function, and/or promote tumor cell growth

3 Discovering the possibilities of I-O biomarkers

- Biomarkers in I-O research and guiding clinical decisions
- I-O biomarkers as a dynamic and diverse subset of biomarkers
- Investigational I-O biomarkers
- Multiple I-O biomarkers needed to provide a more precise representation of the TME

4 Evolving clinical expectations in I-O

- I-O is a different approach that fights cancer by targeting the immune system
- Immune responses have the potential to deepen and sustain over time
- Resistance to immunotherapy
- Pseudoprogression
- Endpoint considerations for I-O research
- Immune-mediated adverse reactions

5 Realizing the potential of I-O research

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

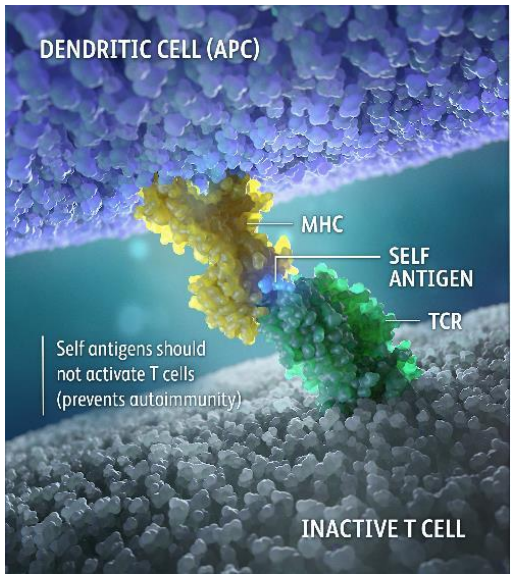
Topic 1: Essential principles of immunology

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

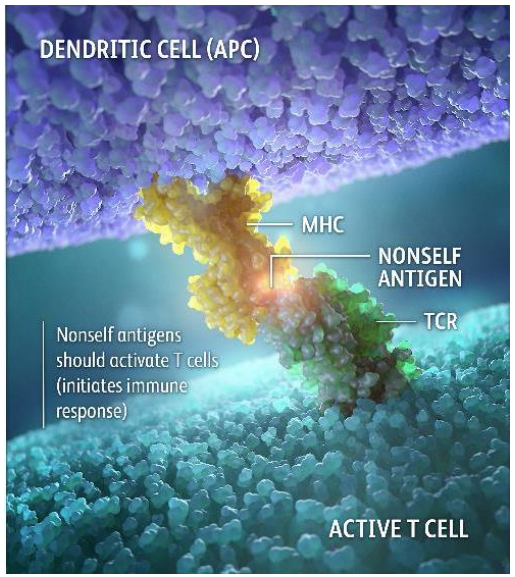
Differentiating self from nonself is a hallmark of the immune response

- 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 key elements in the process of distinguishing self from nonself[1]

Self[4]



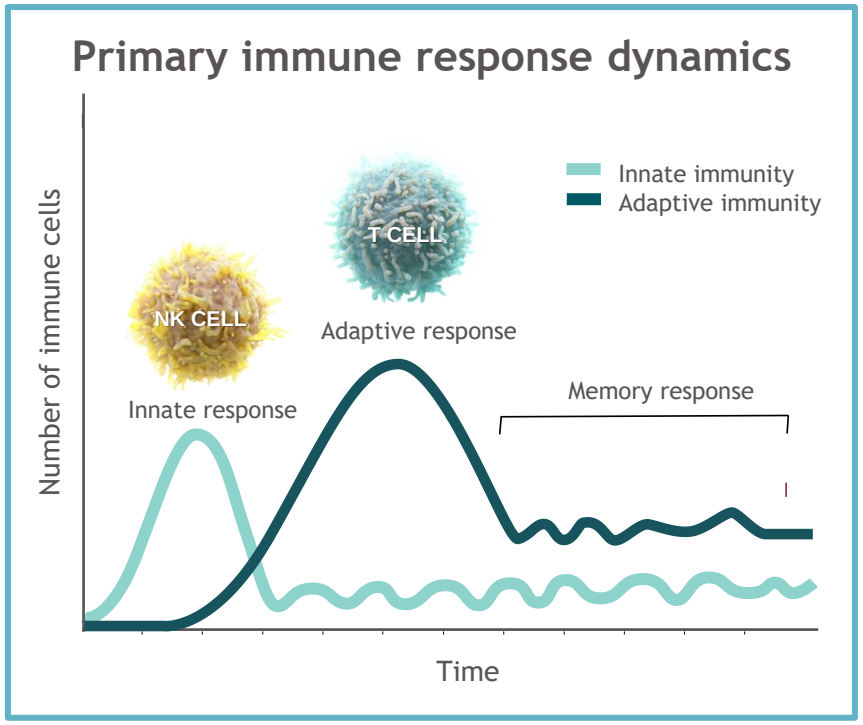
Nonself[1]



- **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 autoimmunity[2]
- 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]

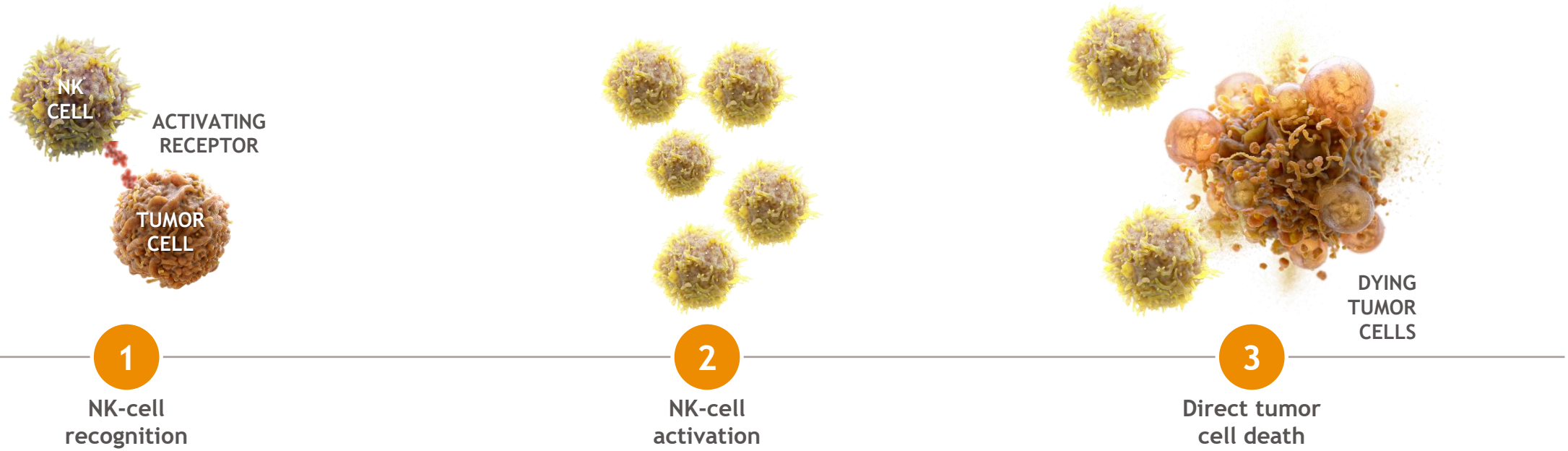


- The innate immune response is **rapid**, while the adaptive immune response is not as immediate but can produce a **durable response** through the development of memory cells, including memory T cells[1,6]

- 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[7-9]

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, NK cells, continually scan the body for abnormal cells to attack.[1,10,11]*



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.[12]

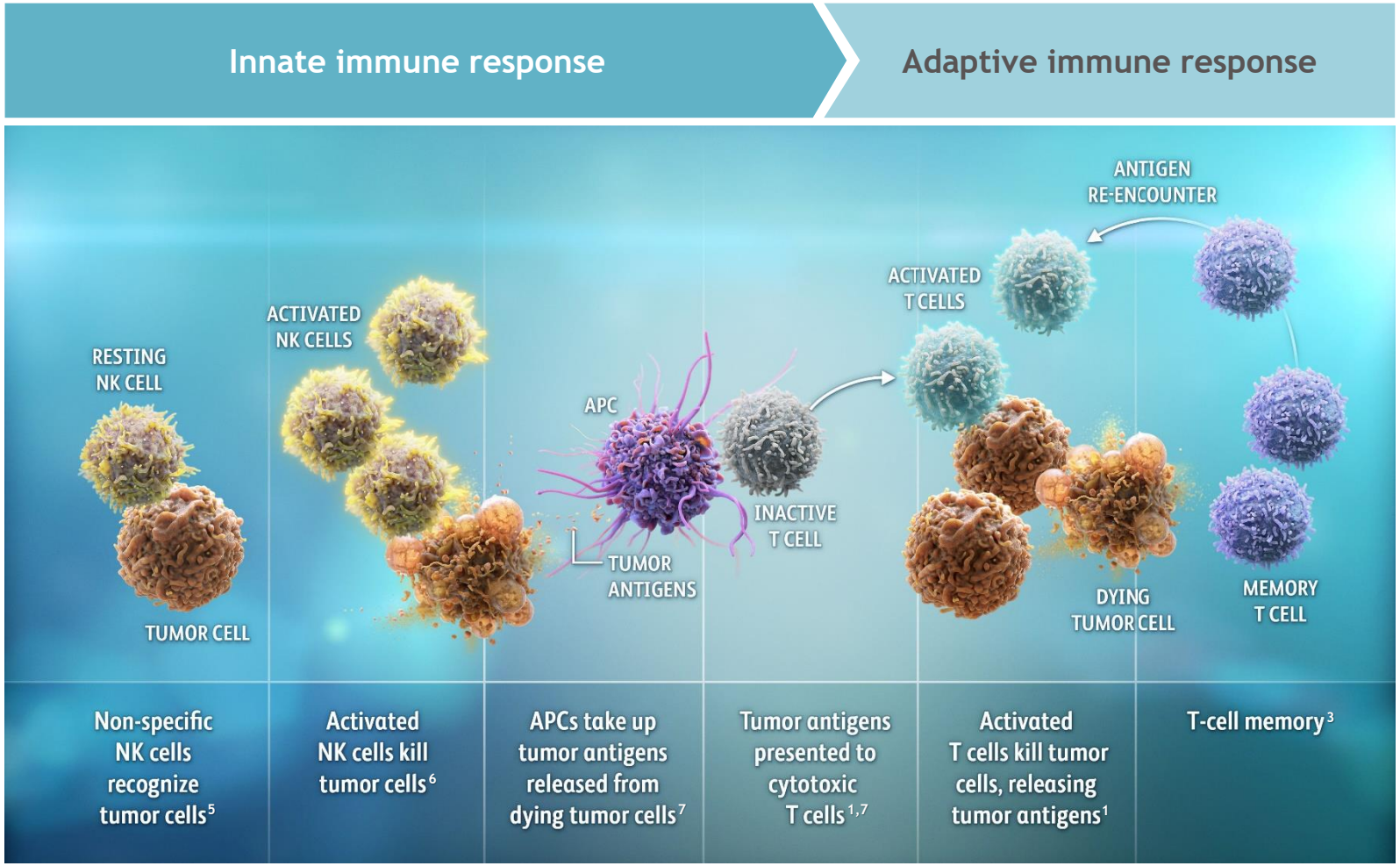
*Numerous cell types are involved with the innate immune response, including macrophages, neutrophils, dendritic cells, mast cells, basophils, eosinophils, NK cells, and lymphocytes (T cells).[1]

APCs act as central messengers between innate and adaptive immunity

- APCs are innate immune cells that can act as **central messengers between the innate and adaptive** immune responses.[1] Tumor cell death, which can be initiated by the innate immune system, can release signaling molecules, such as DNA, ATP, and proteins. These factors may cause APCs to initiate an adaptive immune response[13-16]

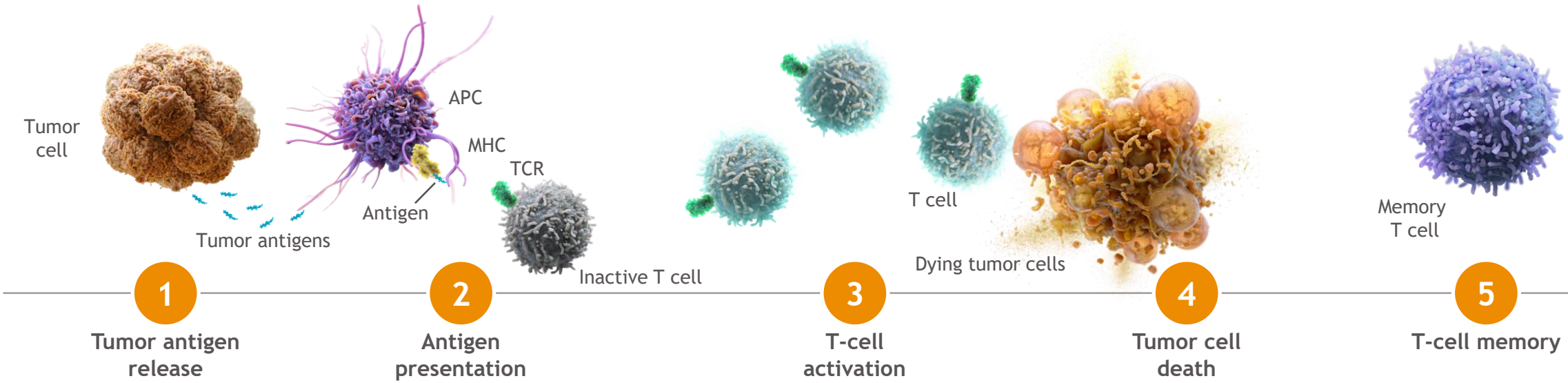
- DNA or ATP released by dying tumor cells stimulates APCs to produce proinflammatory cytokines, through the inflammasome, which can support antitumor function and survival in activated T cells involved in the adaptive immune response[16-19]

- Proteins released by dying tumor cells can be processed by APCs into tumor antigens.[20,21] APCs present these antigens to T cells, priming them to recognize tumor cells[1,21]



Adaptive immunity is durable and antigen-dependent

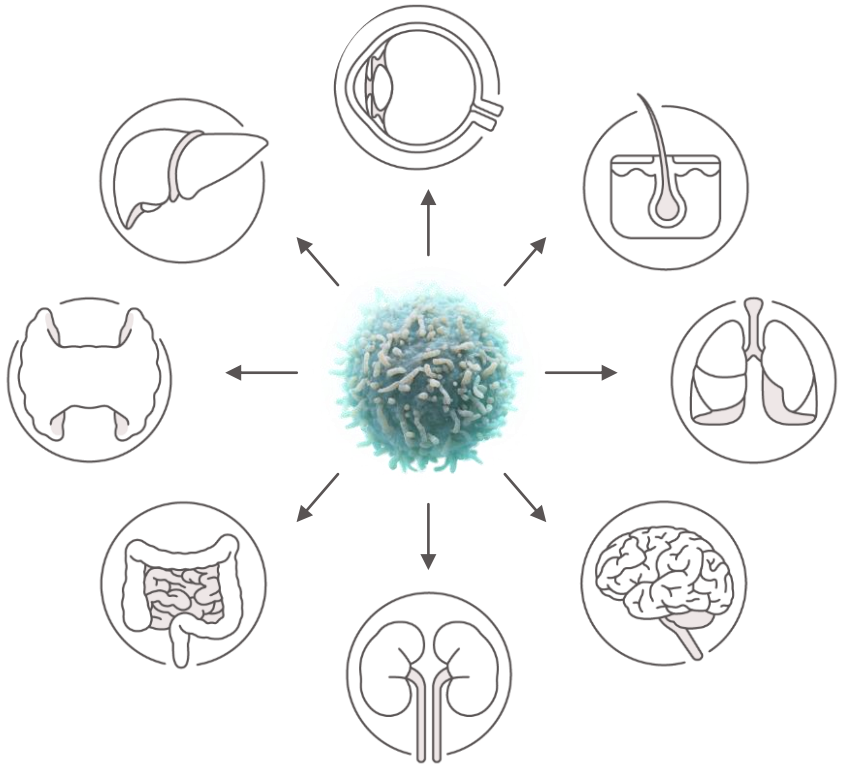
- Adaptive immunity is **antigen-dependent** and able to produce a **durable response.**[1] Cytotoxic T cells, the primary effector cells of the adaptive immune response, can be activated by the detection of tumor antigens.[1,22] Once activated, cytotoxic T cells proliferate, migrate to the location of the antigen, infiltrate it, and directly initiate cell death[23]



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[23,24]

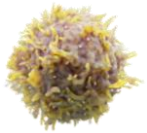


- To make this possible, activated T cells upregulate factors that enable them to recognize threats and **migrate through blood vessel walls**, into affected tissues[25,26]
- T-cell migration occurs across non-lymphoid tissues, with documented trafficking to even particularly **selective tissues such as the eye and brain**[27-33]
- After the activated cytotoxic T cell population diminishes, **memory T cells remain capable of trafficking to surrounding tissues** in the event of antigen reoccurence[28]

Select cells of the immune system

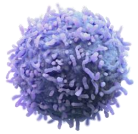
Effector cells:

Actively involved in the destruction of foreign pathogens and cancer.



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.[1,24]

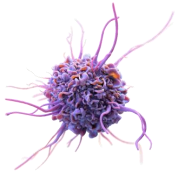
Cytotoxic T cells are the primary effector cells of the adaptive immune response. Following activation by recognition of antigens presented by MHC class I molecules, T cells directly kill pathogens and abnormal cells that express the respective antigen.[24,34]



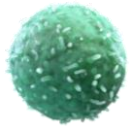
Memory T cells are derived from activated cytotoxic T cells and represent a long-lived population of antigen-experienced cells that can rapidly respond upon antigen reocurrence.[1,35]

Non-effector cells:

Directly or indirectly modulate the cytotoxic effector T-cell response. These cells cannot induce tumor cell death on their own.



APCs (such as dendritic cells) recognize, process, and present antigens to T cells through MHC molecules.[25,36,37]



Tregs are a unique subset of T cells that modulate the activation of other effector T cells to inhibit the immune response.[24,37]

TAMs are cells derived from the macrophage lineage that are recruited to the tumor microenvironment to promote tumor cell survival by driving immunosuppression.[38,39]

MDSCs are cells derived from the myeloid lineage that function to suppress T-cell responses.[38]

Stromal cells play an integral role in supporting the homeostasis of normal tissues and suppressing immune response in tumors.[40,41]

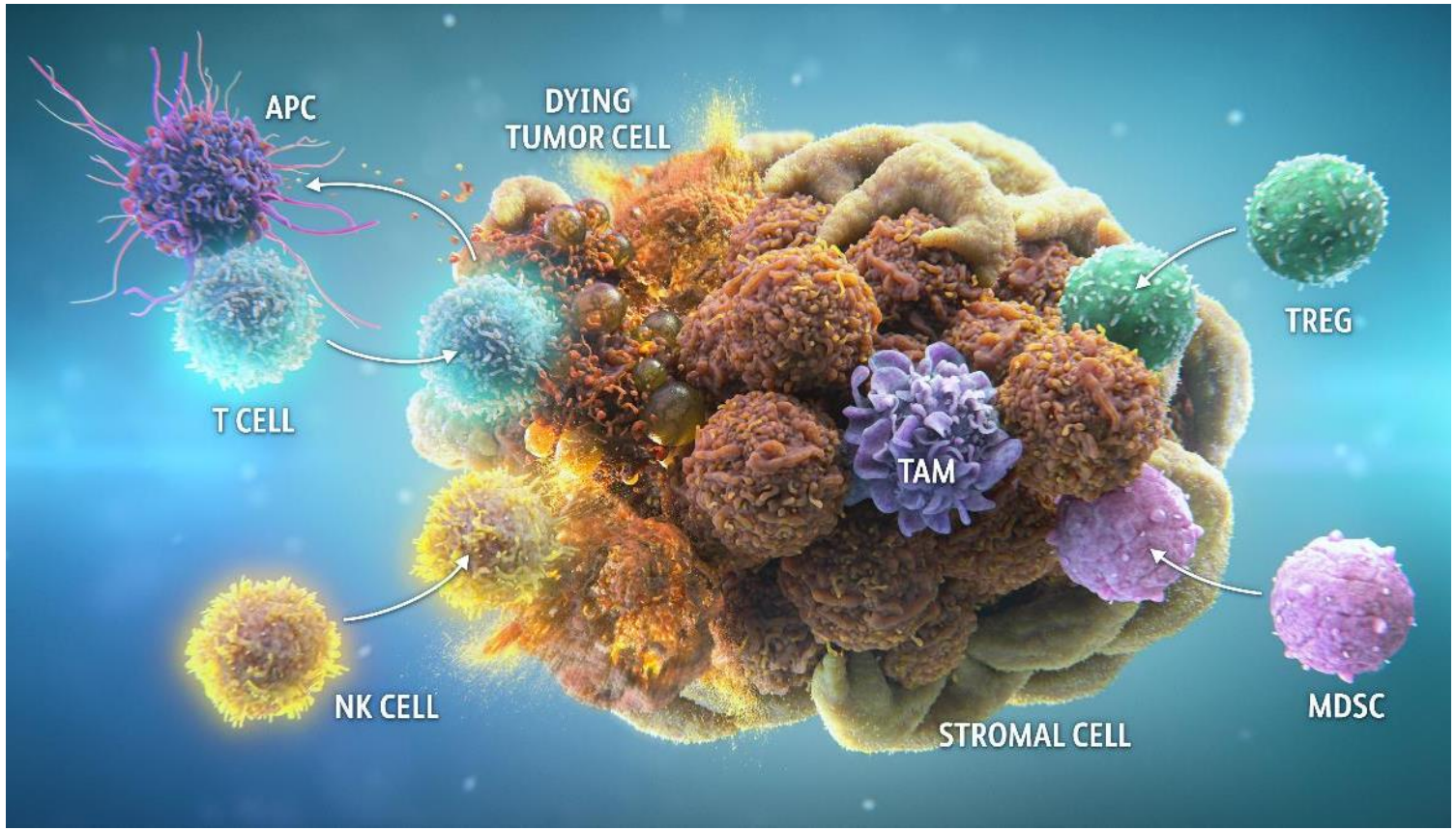
Topic 2:
Revealing the potential of the immune system in cancer

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

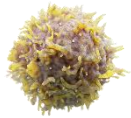
Introduction to the tumor microenvironment and the immune response

- Innate and adaptive immunity act as a complementary network of self-defense against foreign threats such as pathogens and cancer.[1]

- The immune system is able to recognize **foreign threats (nonself)** as distinct from **normal cells (self)**.[2-4] Despite originating from normal cells, tumor cells can be recognized as nonself through the production of tumor antigens.[3,5]

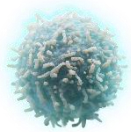


Antitumor activity of the innate and adaptive immune responses



Innate immune response

- The first line of defense, it rapidly identifies and attacks tumor cells without antigen specificity[1,6,7]
- It recognizes activating and inhibitory signals from target cells to distinguish self from nonself[8-10]
- **Natural killer (NK) cells** are the main effector cells of innate immunity[11,12]



Adaptive immune response

- The adaptive immune response is antigen-specific and produces durable responses[1,7]
- Once activated, it can be sustained through immune memory[13]
- **Cytotoxic T cells** are effector cells of the adaptive immune system[1]

The antitumor activity of NK cells and cytotoxic T cells is regulated through a network of **activating** and **inhibitory** signaling pathways[4,14,15]:

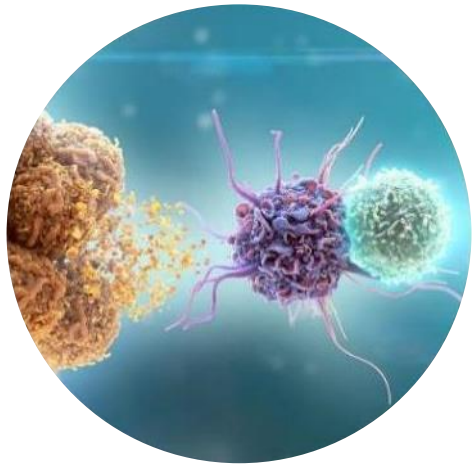
ACTIVATING
Pathways that trigger immune responses

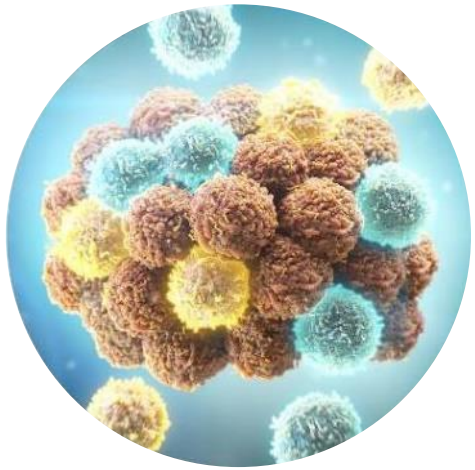
INHIBITORY
Pathways that counterbalance immune activation

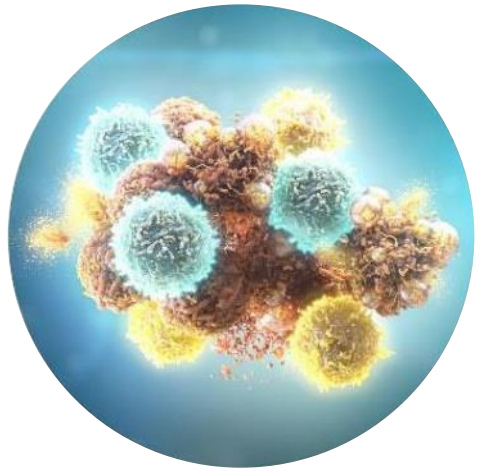
The **balance between activating and inhibitory pathways** normally enables the immune system to attack tumor cells, while sparing healthy cells.[15]

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]

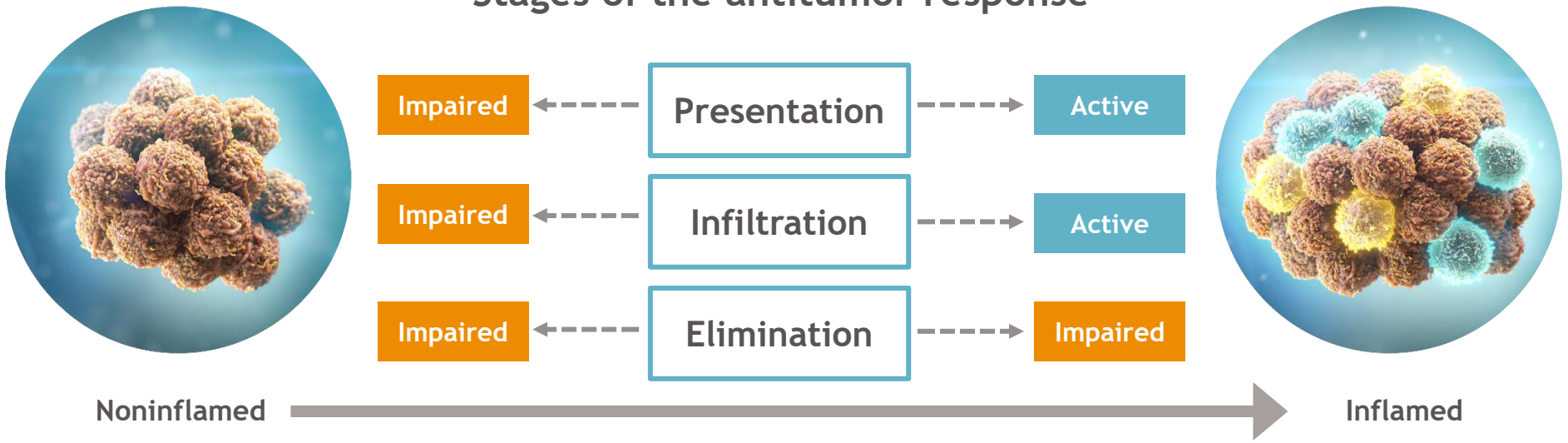
Elimination

- 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] The success of these strategies determines the ability of immune cells to react to the tumor.[19]
- The tumor microenvironment consists of different cell types that can 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.[22] Depending upon their degree of immune cell infiltration, tumors are defined on a range from **noninflamed** to **inflamed**.[19,23]

Stages of the antitumor response



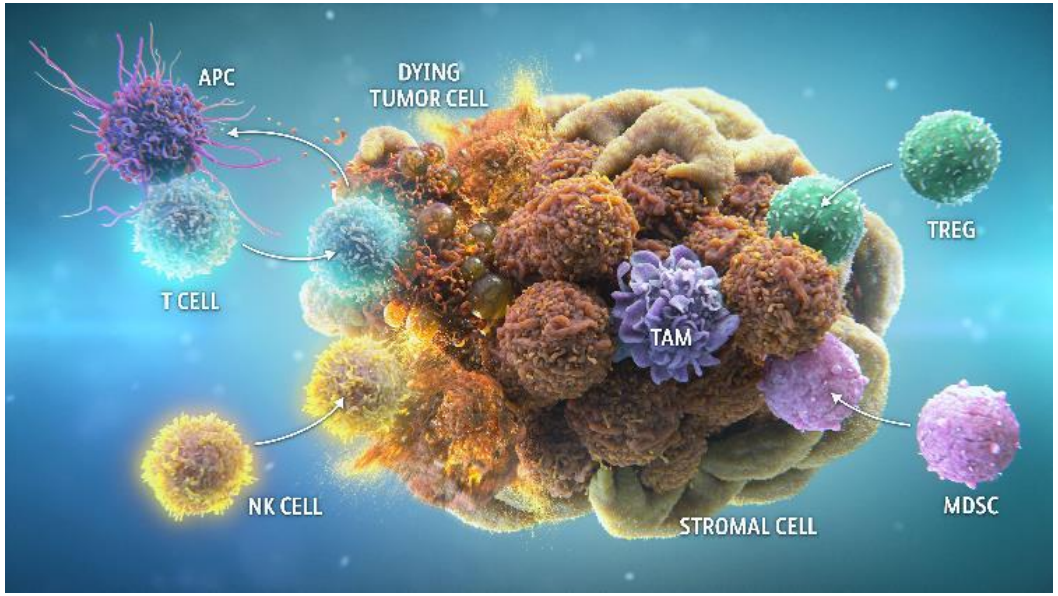
Characterized by poor presence of immune cells[19,21]

- Impaired ability to **present** tumor antigens to T cells or secrete key factors (chemokines)[19,24]
- Less able to direct tumor-specific T cells to the tumor and promote T cell **infiltration**, ultimately preventing tumor cell **elimination**[25,26]
- Ongoing research aims to promote inflammation within tumors to increase susceptibility to antitumor immunity

Characterized by presence of immune cells[19,25,27-29]

- Antigen **presentation** and expression of chemokines allow for **infiltration** of activated cytotoxic T cells[25,30-32]
- However, tumor cells may increase their expression of **inhibitory proteins** to prevent **elimination** by cytotoxic T cells[26,33]

Multiple pathways may be leveraged for tumor detection and elimination



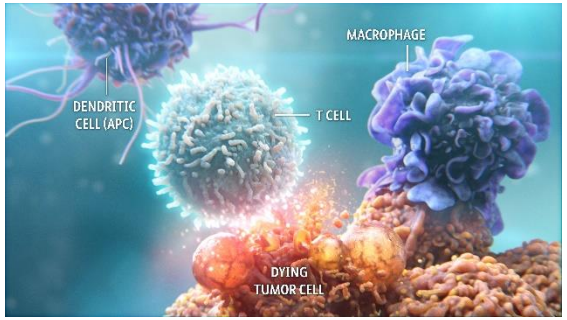
Pathways may be categorized into the following functions[17,34-36]

1. Tumor cell recognition[37]
2. Immunosuppression[21,27]
3. Effector cell function[37]
4. Tumor-intrinsic pathways[38,39]

- NK cells and cytotoxic T cells can migrate to the tumor site, and are key to destroying the tumor cells[40]
- These effector cells are regulated through a network of activating and inhibitory signaling pathways, with activating pathways triggering an immune response and inhibitory pathways providing a natural counterbalance to immune activation (eg, checkpoint pathways)[4,14,15]
- In addition, tumor-intrinsic signaling plays a key role in regulating the immunosuppressive tumor microenvironment and tumor immune escape[39]

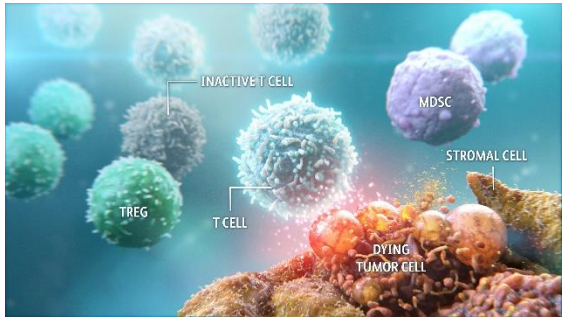
Empowering the immune system to fight cancer

- The immune system uses a **network of signaling pathways** to detect and eliminate tumor cells.[4,14,41,42] Ongoing Immuno-Oncology research aims to understand how modulating these pathways may overcome the mechanisms of tumor evasion to restore the body's natural ability to fight cancer. Pathways may be categorized in the following functions:



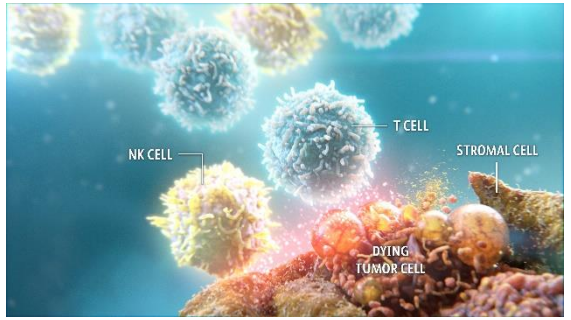
Tumor cell recognition

Tumors can adapt mechanisms to evade immune detection. Leveraging pathways, including those involved in antigen presentation and phagocytosis, may promote better tumor cell recognition.[37,43]



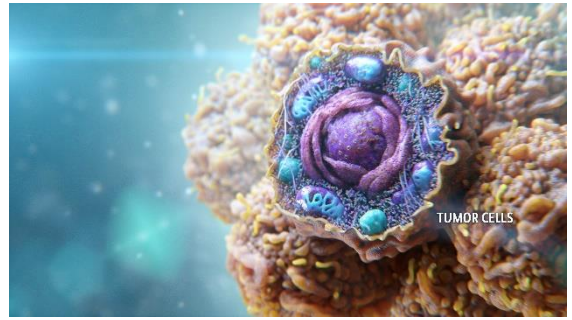
Immunosuppression

Some tumors can avoid destruction by thriving in an immunosuppressive environment and dampening the immune response. Modulating pathways that regulate immunosuppressive activity may increase anti-tumor activity.[44,45]



Effector cell function

Various components of the immune system and tumor microenvironment regulate an effector cell's ability to eliminate tumors. Modulating pathways involved in the regulation of effector cells may enhance their activity.[37,46]



Tumor-intrinsic pathways

Various signaling and metabolic pathways intrinsic to tumor cells can drive oncogenesis and tumor growth. Blocking these pathways may promote tumor cell death.[38,39]

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

Tumor Cell Recognition[37,43,47-53]

Increase antigen presentation, phagocytosis of tumor cells, and antibody-dependent tumor-cell death

- TLR8
- STING
- SIRPα
- FucGM1

Effector-Cell Function[33,37,46,54-83]

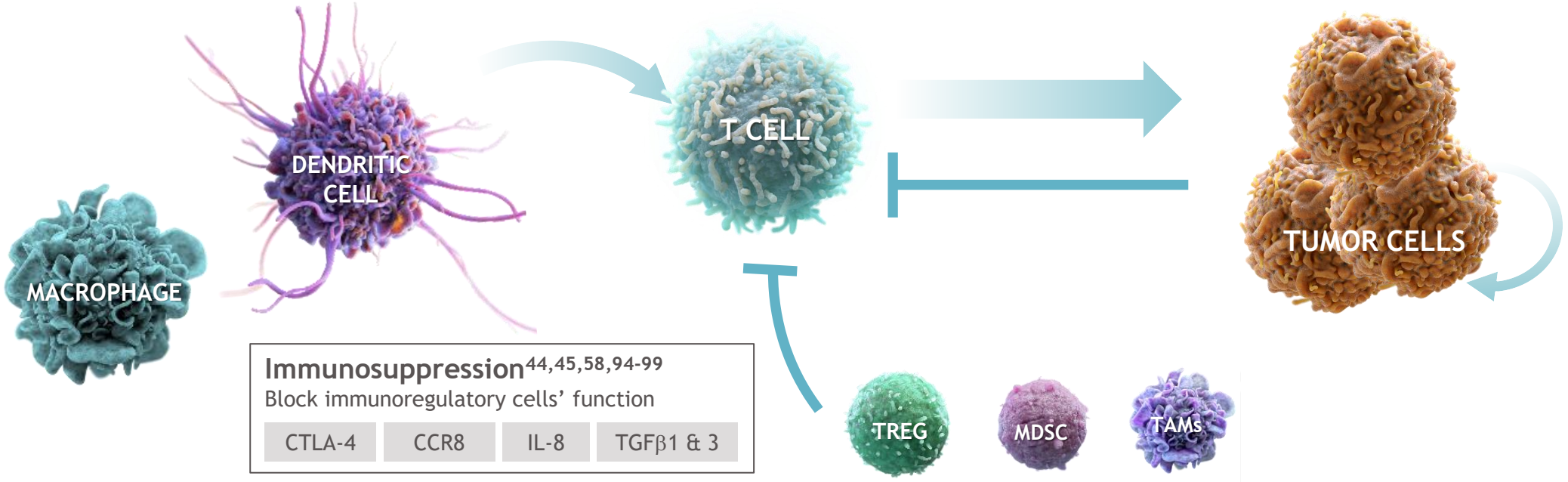
Block inhibitory immune checkpoints and stimulate effector-cell activation and proliferation

- PD-1
- CTLA-4
- LAG-3
- IL-2
- SLAMF7
- TIM-3
- TIGIT
- NKG2A
- IL-12
- OX40
- AHR
- PSCA
- IDO1

Tumor-Intrinsic Pathways[38,39,84-93]

Leverage protein degradation pathways and epigenetic drivers of oncogenesis

- BET
- UPP
- Folate receptor α (FRα)
- LSD1
- Androgen receptor degradation



Immunosuppression[44,45,58,94-99]

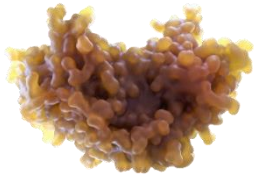
Block immunoregulatory cells' function

- CTLA-4
- CCR8
- IL-8
- TGFβ1 & 3

*Not a comprehensive list of immune pathways.

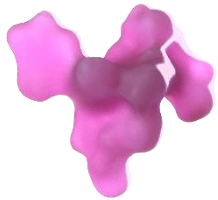
Select pathways that modulate tumor detection

- Current research is investigating modulation of pathways, including those involved in antigen presentation and phagocytosis, to promote better tumor cell recognition:[37,43]



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.[47,48] STING is triggered when an intracellular-sensing protein detects DNA from pathogens or dying tumor cells.[100,101]

Preclinical data suggest that activation of STING can increase priming of T cells, leading to increased T-cell activation and an inflamed tumor microenvironment.[101-104] Furthermore, mouse models indicate that STING activation, along with blockade of immune checkpoint receptors, may synergistically promote the antitumor immune response.[105,106]

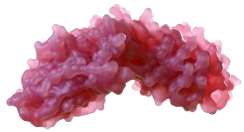


FucGM1 is a ganglioside, or cell surface glycosphingolipid, that enables cell-cell recognition, adhesion, and signaling transduction.[53] While FucGM1 is mostly expressed in neural tissue, with limited expression in normal tissues, it is also highly expressed on the surface of certain tumor cells.[53,107,108]

Preclinical data suggest that antibodies targeting FucGM1 promote compliment activation. FucGM1 antibodies may impart synergistic cytotoxic effects with other signaling pathways.[53]

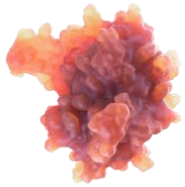
Select pathways that modulate immunosuppression

- Current research is investigating modulation of pathways that regulate immunosuppressive activity in order to increase anti-tumor response[44,45]:



CTLA-4 is an immune checkpoint receptor on activated T cells that inhibits their activation.[58,60] 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.[35,109] CTLA-4 signaling diminishes the ability of memory T cells to sustain a response, damaging a key element of durable immunity.[35,109]

Preclinical data suggest that treatment with antibodies specific for CTLA-4 can restore an immune response through increased accumulation, function, and survival of T cells and memory T cells and depletion of regulatory T cells.[34-36] One recent approach aims to improve the specificity of CTLA-4 blockade by using pro-antibodies, antibodies masked with a protein that can be removed by enzymes that are active primarily at the tumor site.[110,111]

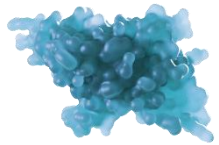


IL-8 is a chemokine produced by macrophages, monocytes, and stromal cells that promotes the recruitment of immunosuppressive MDSCs and activates the angiogenic response to generate new blood vessels during the normal healing process.[95,96,112,113] Both tumor and tumor-associated stromal cells can upregulate production of IL-8, causing MDSCs to migrate to the tumor microenvironment where they suppress the antitumor immune response.[96,113-116]

Preclinical data suggest that blockade of IL-8 signaling reduces angiogenesis and the recruitment of CXCR1- and CXCR2-expressing MDSCs to the stromal barrier and tumor microenvironment.[96,117,118]

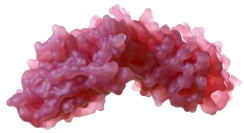
Select pathways that modulate effector cell function (1/5)

- Current research is investigating modulation of pathways involved in the regulation of effector cells in order to enhance their activity[37,46]:



PD-1 is an immune checkpoint receptor on cytotoxic T cells that plays a key role in T-cell exhaustion and prevention of autoimmunity.[54-56] Tumor-infiltrating T cells across solid tumors and hematologic malignancies display evidence of exhaustion, including upregulation of PD-1.[56]

Preclinical data suggest that PD-1 blockade reinvigorates exhausted T cells and restores their cytotoxic immune function.[119] Inhibiting both PD-1 ligands (PD-L1 and PD-L2) may be more effective at reversing T-cell exhaustion than inhibiting PD-L1 alone.[71]

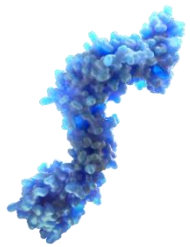


CTLA-4 is an immune checkpoint inhibitor that, in addition to being expressed on activated T cells, is also found on Tregs, where it is a key driver of their ability to suppress T-cell activity and counterbalance excessive immune activation.[15,41,58] Continuous expression of CTLA-4 on Tregs is critical for their suppressive activity.[59,120]

Preclinical data suggest that increased depletion of Tregs can improve cytotoxic T-cell activation and antitumor activity. One recent approach to regulate the degree of immune activity and increase the depletion of Tregs uses a specific type of CTLA-4 antibody with a modified Fc region known as a fucosylated antibody. This fucosylated antibody can bind to Tregs, identifying them for elimination by other immune cells.[34-36,121]

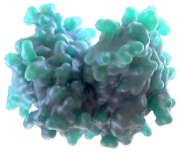
Select pathways that modulate effector cell function (2/5)

- Current research is investigating modulation of pathways involved in the regulation of effector cells in order to enhance their activity[37,46]:



LAG-3 is an immune checkpoint receptor on the surface of both activated cytotoxic and regulatory T cells (Tregs).[61,62,139] When bound to the antigen-MHC complex, LAG-3 can negatively regulate T-cell proliferation and the development of lasting memory T cells.[122] Repeated exposure to tumor antigen causes an increase in the presence and activity of LAG-3, leading to T-cell exhaustion.[123,124]

Preclinical data suggest that when the PD-1 pathway is blocked, LAG-3 may be upregulated to maintain tumor growth.[125] Research is ongoing to understand how dual inhibition of LAG-3 and other checkpoint pathways may synergistically increase T-cell antitumor activity compared with inhibition of either pathway alone.

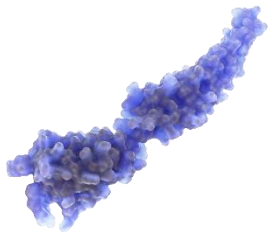


TIGIT is an immune checkpoint receptor expressed on the surface of cytotoxic, memory, and Tregs, as well as NK cells.[69,127] On cytotoxic T cells and NK cells, interaction of TIGIT with either of its ligands suppresses immune activation.[69,127] When TIGIT is expressed on Tregs, however, this interaction enhances their ability to suppress the immune response.[128]

Preclinical data suggest that the inhibition of TIGIT alone or in combination with other checkpoint inhibitors increases the proliferation and function of cytotoxic T cells.[70,128-130]

Select pathways that modulate effector cell function (3/5)

- Current research is investigating modulation of pathways involved in the regulation of effector cells in order to enhance their activity[37,46]:



TIM-3 is an immune checkpoint receptor involved in the suppression of both innate and adaptive immune cells.[67,131] 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] PS or HMGB1 interactions with TIM-3 on tumor-infiltrating DCs may lead to impaired ability of DCs to activate T cells and promote inflammation.[131-133]

Preclinical data suggest that the blockade of TIM-3 can rescue NK-cell activity, promote tumor antigen processing, and reinvigorate exhausted T cells, restoring their proliferation and function.[67,134,135] TIM-3 is often co-expressed with other immune checkpoint receptors. Preclinical studies suggest that the co-blockade of TIM-3 with another immune checkpoint receptor may further reinvigorate exhausted T cells.[134,136,137]

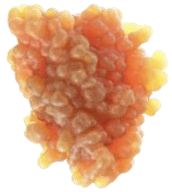
SLAMF7 is an activating receptor on the surface of NK cells and other immune cells.[66] When engaged, SLAMF7 activates NK cells, the rapid responders of the immune system and the body's first line of defense against cancer.[6,138]

Continuous activation of NK cells through pathways like SLAMF7 may initiate the development of long-term immunity.[11,16,139]

Preclinical data suggests that engagement of SLAMF7 may facilitate the interaction with NK cells to mediate the killing of tumor cells by promoting antibody-dependent cellular cytotoxicity (ADCC) through both CD16-dependent and –independent mechanisms[140,141]

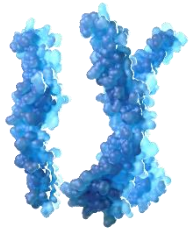
Select pathways that modulate effector cell function (4/5)

- Current research is investigating modulation of pathways involved in the regulation of effector cells in order to enhance their activity[37,46]:



IL-2 is a cytokine that binds to an activating receptor expressed on the surface of activated cytotoxic T cells, Tregs, NK cells, and other types of T cells.[63-65] The interaction of IL-2R and its ligand, IL-2, promotes the activation and proliferation of various immune cells.[65,142]

Preclinical data suggest that preferential binding to the dimeric IL-2R directly activates and expands effector T cells and NK cells over immunosuppressive Tregs, increasing the tumor-infiltrating lymphocyte proliferation and recruitment to the tumor microenvironment.[64,143,144]

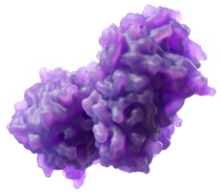


OX40 is an activating receptor on the surface of activated cytotoxic T cells and regulatory T cells (Tregs).[145,146] OX40 both activates and amplifies T cell responses, helping to create a tumor microenvironment more favorable to the antitumor immune response.[147-149]

Preclinical data suggest that OX40 signaling increases the number and activity of cytotoxic T cells and curtails the immunosuppressive impact of Tregs.[147-149]

Select pathways that modulate effector cell function (5/5)

- Current research is investigating modulation of pathways involved in the regulation of effector cells in order to enhance their activity[37,46]:



IDO1, an enzyme expressed in tumor cells and APCs, metabolizes tryptophan, an amino acid that is essential for cell survival, into immunosuppressive kynurenine.[81,82,150] Kynurenine normally acts as a counterbalance to suppress T-cell function and prevent overactivation of the immune response.[151,152] Tumors can hijack this immunosuppressive process and evolve to increase IDO1 expression in both tumor cells and APCs.[81,153-155]

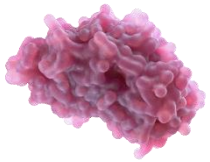
According to **preclinical studies**, IDO1 inhibition may reduce immunosuppressive Treg numbers and restore cytotoxic T-cell function.[156,157] Preclinical data also suggest that IDO1 inhibition alone or in combination with other checkpoint pathways, can reduce Treg accumulation and improve antitumor immune response.[156-160]

IL-12 is a proinflammatory cytokine released by antigen-presenting cells, such as dendritic cells, monocytes, macrophages, and B cells.[161,162] IL-12 stimulates the innate and adaptive antitumor immune response, mainly by increasing effector T cell and NK activity, as well as IFNγ production. By increasing IFNγ, IL-12 can promote Th1 and Th17 cell development, which are associated with antitumor immunity.[75,161,163] IL-12 can induce Treg apoptosis and attenuate immunosuppressive MDSCs.[164] IL-12 has also been associated with a decrease in EMT, angiogenesis, and metastasis.[75,161,164]

Preclinical studies suggest that IL-12 is a potent mediator in antitumor activity. Various experimental mice models suggest that IL-12 can stimulate different direct and indirect antitumor activities belonging to innate immunity, adaptive immunity, and non-immune mechanisms involving both solid and hematological tumors.[75,161,165,166]

Select tumor cell pathways (1/2)

- Current research is investigating modulation of various signaling and metabolic pathways intrinsic to tumor cells in order to promote tumor cell death:



BET is a family of epigenetic reader proteins that recognizes acetyl groups in the histone tail and is involved in recruiting factors to activate gene transcription.[167-169] BET can upregulate the transcription of oncogenes such as *c-Myc*.[167-171]

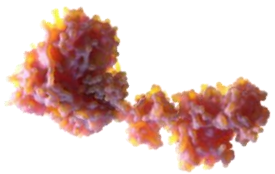
Preclinical studies suggest that inhibition of BET can suppress expression of PD-L1, which may lead to increased activity of cytotoxic T cells.[169,171] Preclinical studies also suggest that inhibition of BET, in combination with other checkpoint pathways, may have greater antitumor activity than blockade of BET alone.[171]

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.[172-174] LSD1 binds to enhancer and promoter regions of genes and regulates stemness, cell motility, and differentiation, among other critical processes in cells.[175-177]

Preclinical data suggest that inhibition of LSD1 elicits anti-tumor immunity characterized by T cell infiltration and newly obtained immunogenicity in previously low or non-immunogenic tumors. Combinatorial use with checkpoint inhibitors suggests a synergistic effect and currently being studied.[178]

Select tumor cell pathways (2/2)

- Current research is investigating modulation of various signaling and metabolic pathways intrinsic to tumor cells in order to promote tumor cell death:



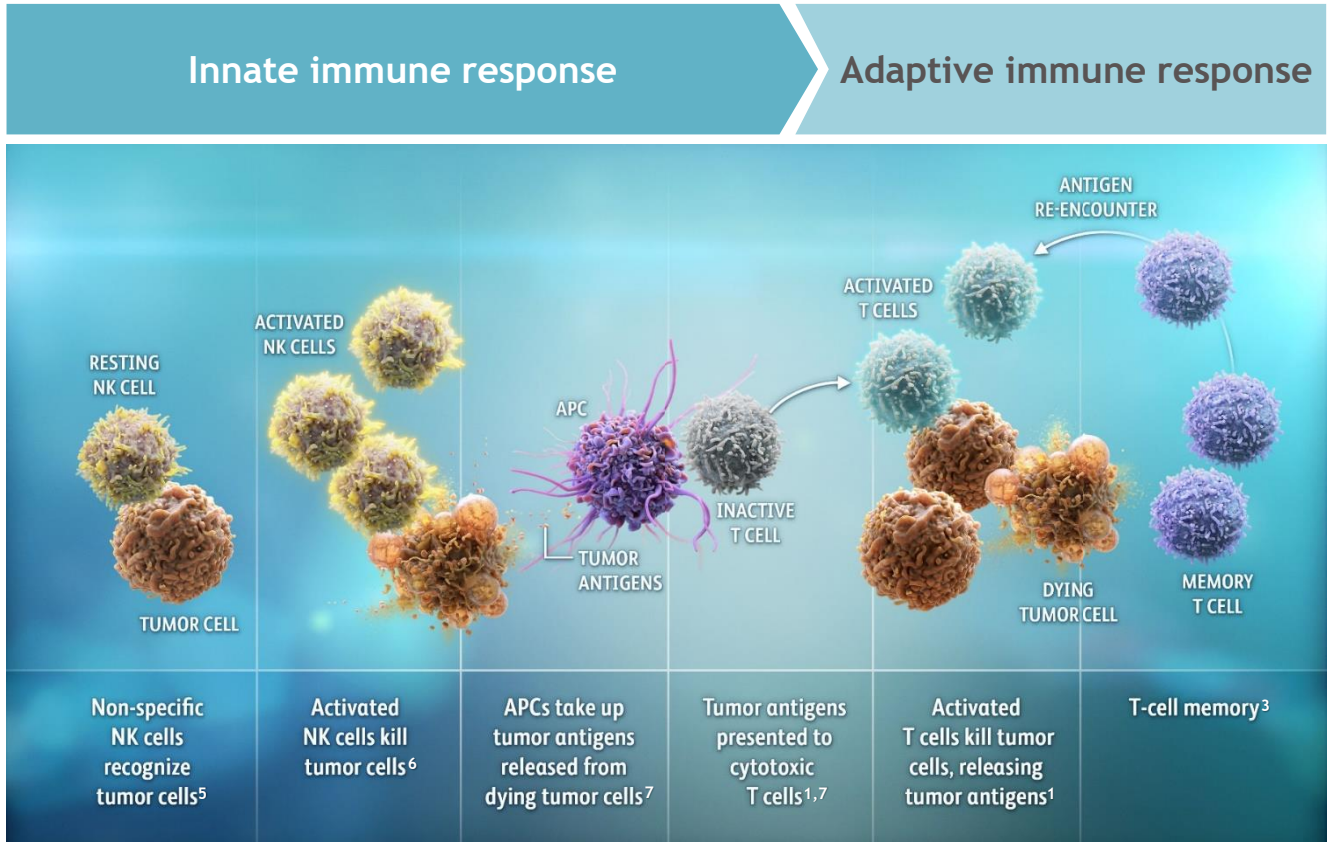
BCR-ABL is a tyrosine kinase fusion protein, formed as a result of the chromosomal translocation that produces the Philadelphia chromosome.[179] BCR-ABL is constitutively active in cancers such as CML, ALL, and occasionally AML.[180-182] BCR-ABL expression promotes tumor-cell proliferation and increases resistance of tumor cells to apoptosis.[183]

Preclinical evidence suggests that inhibiting BCR-ABL expression may suppress anti-apoptotic activity. Preclinical studies also suggest that the inhibition of BCR-ABL and other signaling pathways, such as MAPK, may enhance tumor cell regression and promote an antitumor immune response.[184]

Immune pathways combine to refine response

- Activating and inhibitory signaling pathways **combine to maintain immune balance** by regulating the 3 key stages of the immune response: presentation, infiltration, and elimination.[54,185,186]

- Once an immune response is initiated, each stage can potentiate or limit the activity of subsequent stages.[187]



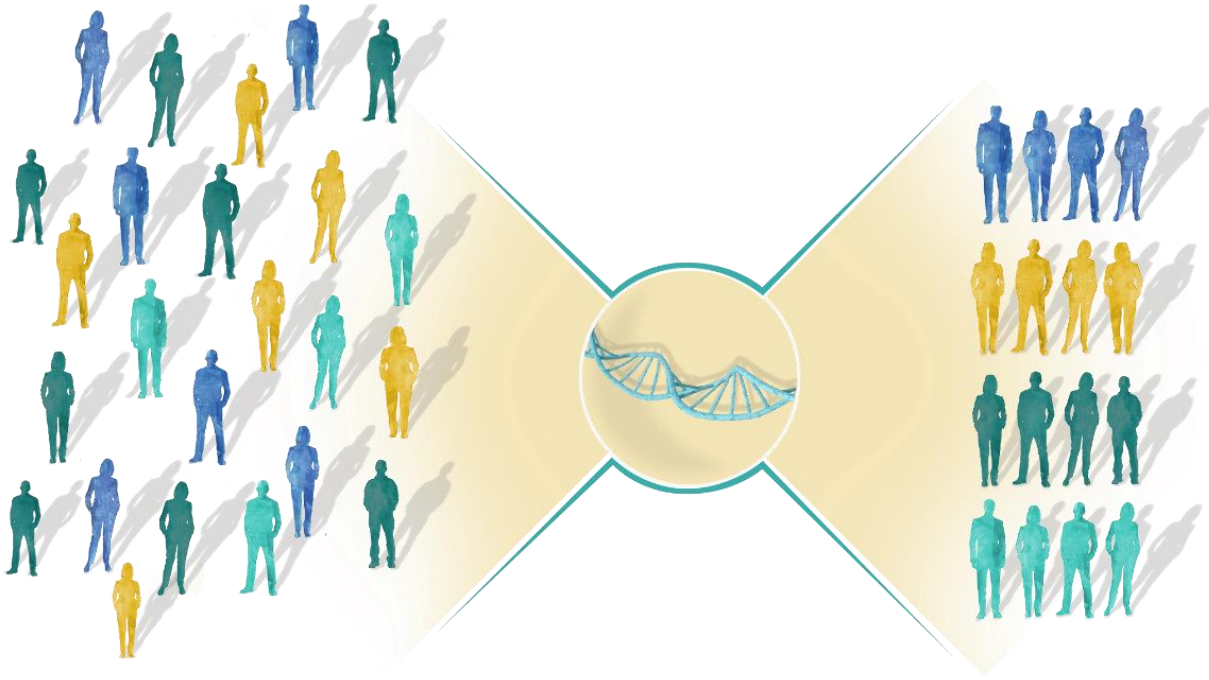
Modulating signaling pathways in combination may enhance the antitumor immune response, as suggested by preclinical data.[188-192]

Topic 3:
Discovering the possibilities of I-O biomarkers

Research in the field of I-O biomarkers seeks to characterize the relationship between the immune system, the tumor and its microenvironment, and the host.

Biomarkers in I-O research

- For each patient, the interaction of the immune system, cancer, and therapy is complex and unique.[1]
- 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.[2,3]



A goal of I-O biomarker testing is to help enable a more personalized approach to treatment by identifying patients who are likely to respond to specific immunotherapies.[1,4,5]

Biomarkers can help guide clinical decisions

- I-O biomarkers are a class of biomarker that can help evaluate an active antitumor immune response within the body.[6] They can be prognostic, predictive, or pharmacodynamic[7-10]:

PROGNOSTIC BIOMARKERS

Prognostic biomarkers may identify the likelihood of a clinical event, such as disease progression, disease recurrence, or death, independent of the therapy received.[7,8]

PREDICTIVE BIOMARKERS

Predictive biomarkers may identify whether individuals are more likely to experience a favorable or unfavorable response to treatment (eg, a mutation in the *EGFR*, *BRAF,* or *KRAS* genes).[7,8,11]

PHARMACODYNAMIC BIOMARKERS

Pharmacodynamic biomarkers may show that a biologic response has occurred in an individual who has received treatment.[8,9]

I-O biomarkers are a dynamic and diverse subset of biomarkers*

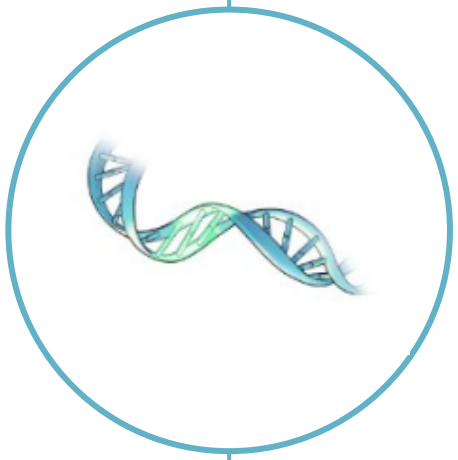
- I-O biomarker research aims to further characterize the unique interplay between the immune system and tumor cells in the following categories:

Circulating biomarkers[12-15]	• IL-8 • ctDNA • MRD
Immune modulators[5,16]	• TILs • Tregs • MDSCs • PD-L1 • LAG-3
Digital technologies[17,18]	• Digital pathology • AI-based signatures
Genomic features[5,16]	• TMB • MSI-H/dMMR • Immune gene signatures

*Not a comprehensive list of biomarkers.

Investigational I-O biomarker: genomic features

- Proteins released by dying tumor cells can be processed by APCs into tumor antigens. APCs present these antigens to T cells, priming them to recognize tumor cells.[19-21]



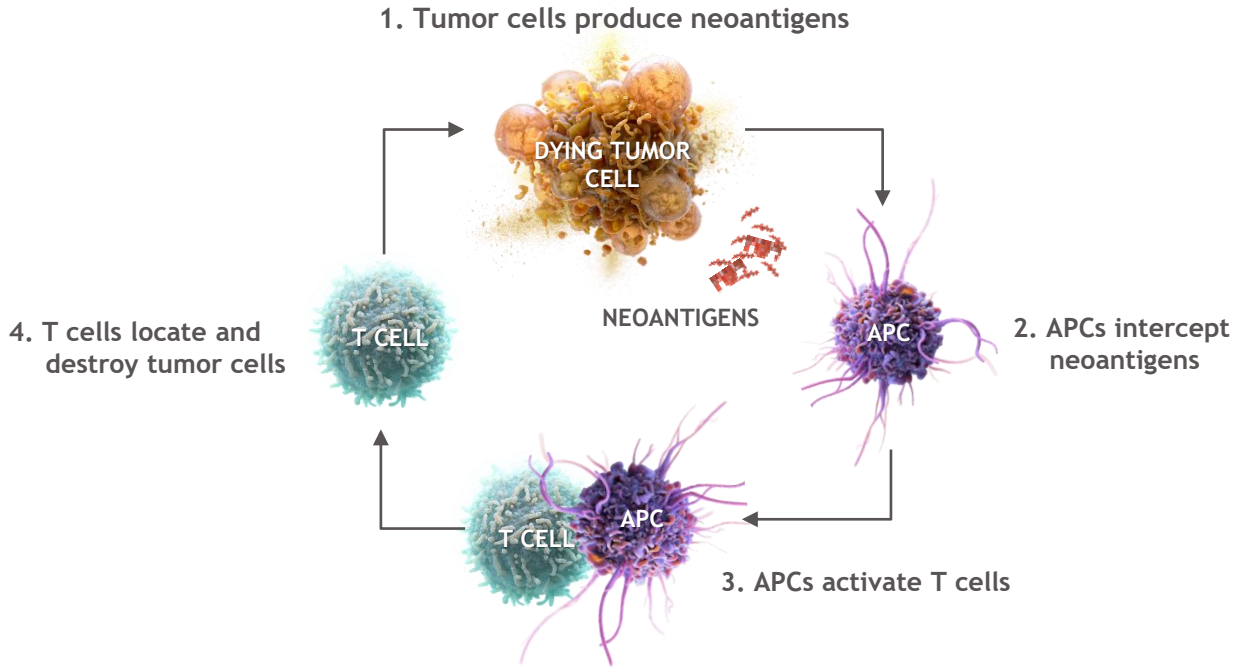
- **Tumor mutational burden (TMB):** The collective number of somatic (acquired) mutations in the tumor genome[22,23]
- **Microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR):** Indicators of genomic stability[24,25]
- **Immune gene signatures:** Specific type of gene expression profile providing a holistic view of cellular function[26,27]

Several I-O biomarkers related to genomic features are currently under investigation.*

*Not a comprehensive list of genomic features.

TMB may be a surrogate for neoantigens

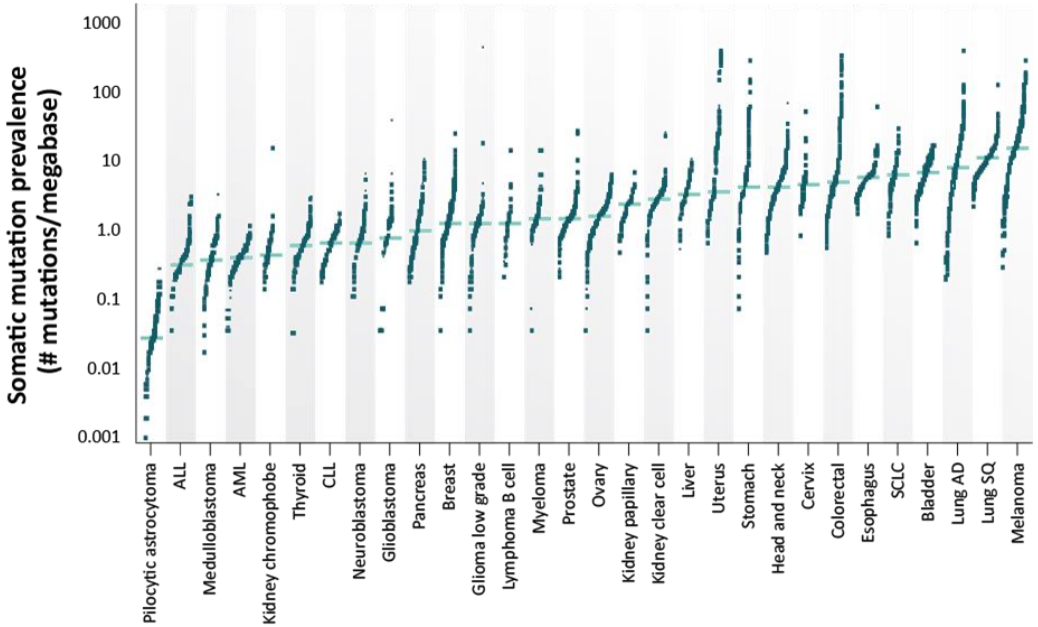
- Neoantigens are a class of tumor antigen derived from the unique mutations in tumor DNA that differentiate tumors from normal tissue. Neoantigens are thus unique to the tumor and recognizable as nonself by the immune system. They can initiate the adaptive immune response, a process known as immunologic priming.[1,28-31]



Tumors with a high burden of neoantigens are more sensitive to immunotherapy, indicating that neoantigens may be a potential I-O biomarker.[32] As immunogenic neoantigens can be challenging to identify directly, TMB may potentially be used as a surrogate to indirectly assess neoantigen load.[1,31]

Investigational I-O biomarker: tumor mutational burden

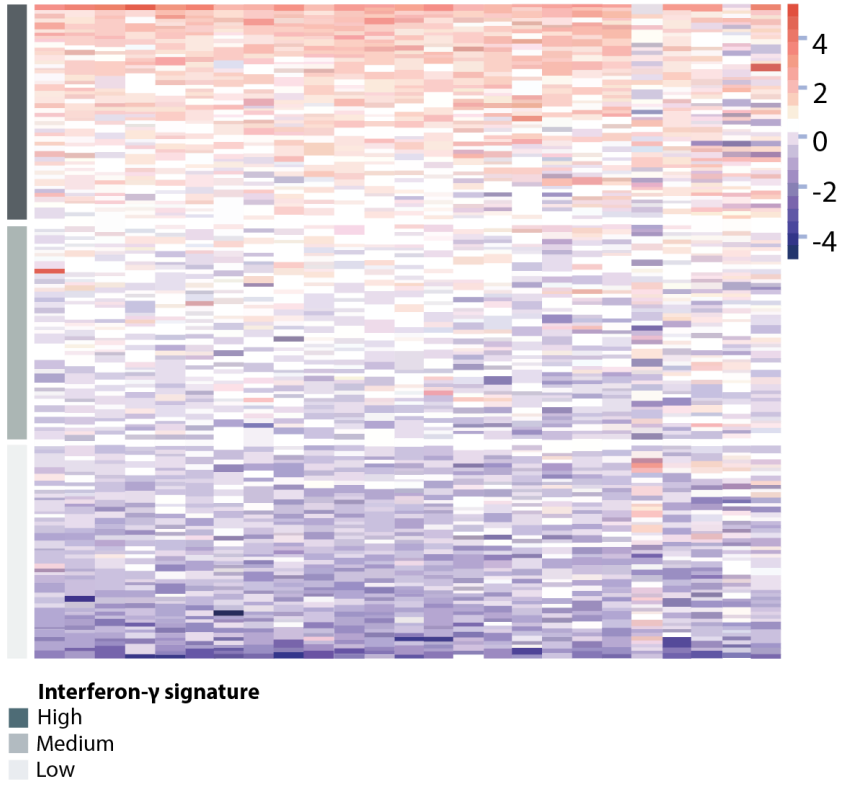
- Tumor mutational burden (TMB) is defined as the number of somatic (acquired) mutations in the tumor genome.[22,23] The number of mutations can vary across different tumor types.[31,36,37] High TMB has been shown to be associated with infiltration of cytotoxic T cells into the tumor microenvironment, supporting its use as a neoantigen surrogate.[38,39]
- TMB is assessed using next-generation sequencing (NGS), a method in which tumor DNA can be read and analyzed for mutations against a reference genome.[40,41]



TMB is an emerging biomarker that may predict the likelihood of an immune response against cancer cells, which could help inform individualized treatment across tumor types.[1,42]

Investigational I-O biomarker: inflammation gene signatures

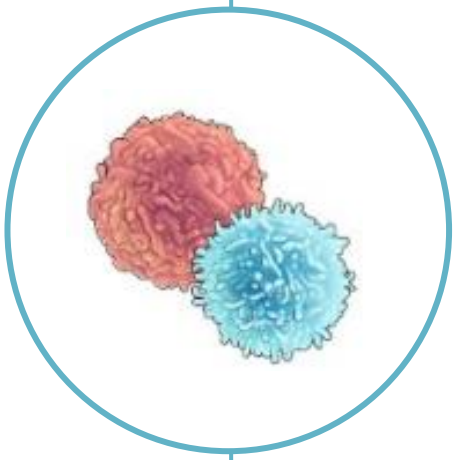
- Inflammation gene signatures are a specific type of gene expression profile. GEP measures the expression of mRNA across thousands of genes. This can create a distinct molecular profile (or gene signature), providing a holistic view of cellular function. Inflammation gene signatures vary across tumor types and may be a powerful diagnostic tool.[43-45]



Inflammation gene signatures are being investigated as a potential I-O biomarker.

Investigational I-O biomarker: immune modulators

- Inflamed tumors show evidence of immune-cell infiltration and activation in the tumor microenvironment.[46,47]

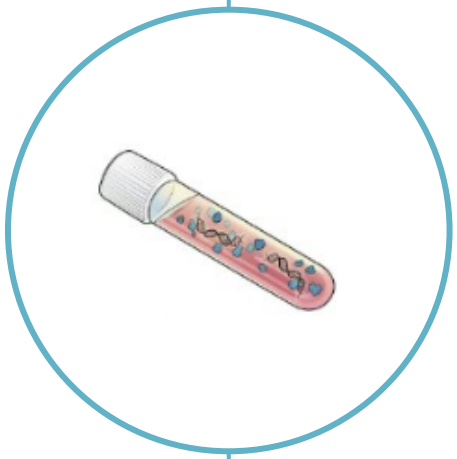


- **Programmed death ligand 1/programmed death ligand 2 (PD-L1/PD-L2):** Ligands for the immune checkpoint receptor PD-1 expressed on the surface of immune cells, including cytotoxic T cells[48]
- **Tumor-infiltrating lymphocytes (TILs):** Immune cells that enter the tumor and its microenvironment to mediate an antitumor immune response[49,50]
- **Lymphocyte-activation gene 3 (LAG-3):** Immune checkpoint receptor expressed on activated cytotoxic T cells and Tregs[51,52]
- **Regulatory T cells (Tregs):** Cells that suppress the immune response by modulating the activation of effector T cells[53,54]
- **Myeloid-derived suppressor cells (MDSCs):** Cells recruited to the tumor microenvironment to suppress effector-cell responses[55]

Several I-O biomarkers related to immune modulators are currently under investigation.*

*Not a comprehensive list of immune modulators.

Investigational I-O biomarker: circulating biomarkers

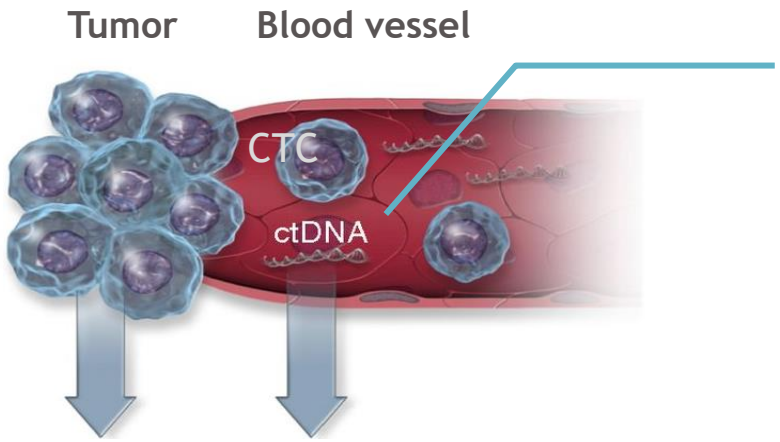


- **Circulating tumor DNA (ctDNA):** A liquid biopsy analyte for surveying biomarkers and monitoring disease[12,13]
- **Minimal residual disease (MRD):** Tumor cells that persist after initial therapy and are a potential source of metastatic relapse at distant sites[14]
- **Interleukin-8 (IL-8):** A chemokine secreted by tumor cells that promotes immune evasion by recruiting immunosuppressive neutrophils and MDSCs[15,56,57]

Several I-O biomarkers exist that are reflective of circulating biomarkers.*

*Not a comprehensive list of circulating biomarkers.

Additional advances in diagnostic testing have also led to minimally invasive approaches to biomarker testing that are being explored in various tumor types



ctDNA is a liquid biopsy analyte for surveying biomarkers, including predicting treatment response[12,13]

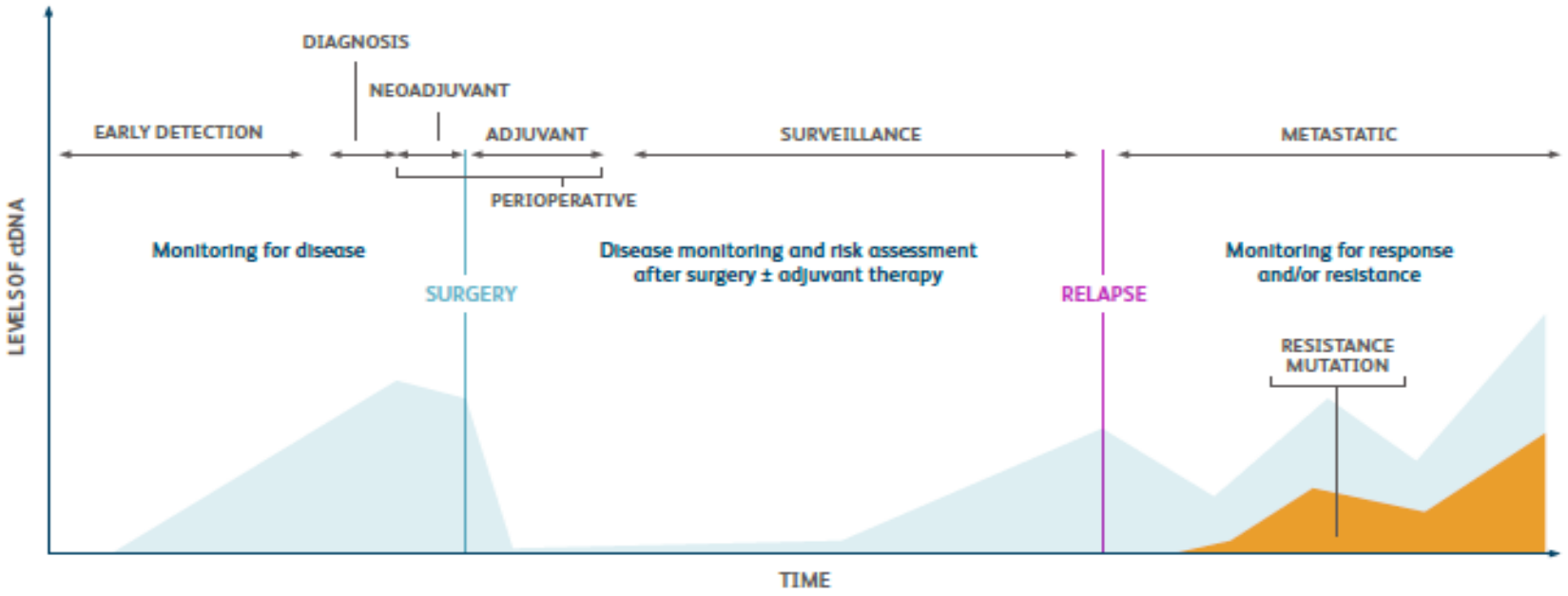
Clinical applications may include:

- Diagnostic purposes (eg, screening)[60]
- Assessing markers of early progression, recurrence, and resistance[60,61]
- Predicting response to treatment by monitoring biomarkers prior to and during treatment[60]
- Determining the molecular landscape of the tumor and assessing the heterogeneity of metastatic cancer[60]
- Observing genomic alterations and evolution over time (eg, clonal evolution)[60,61]

Figure adapted from Roschewski M. *Blood*. 2016;128(2):149-150.

ctDNA as a liquid biopsy analyte is an emerging approach that may be used to help monitor disease and tumor response to I-O

ctDNA concentrations can be detected at different stages of the cancer treatment continuum, including **early detection, surveillance after resection,** and **metastatic relapse**[62-65]



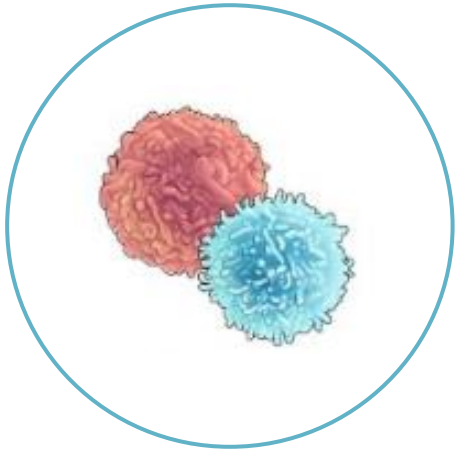
- Studies suggest that ctDNA levels **may correlate with antitumor response**[62-64,66]
- ctDNA can detect minimal residual disease (not captured by conventional imaging modalities) and **may predict relapse**[14,62,64,67,68]
- ctDNA can help with disease monitoring including assessing molecular disease relapse, resistance, or treatment response[14,69]

Figure adapted from Cabel L et al.

A comprehensive view of biomarkers enhances our understanding of tumor interaction with the immune system

- The presence or absence of any single biomarker may not provide a complete understanding of the diverse interactions occurring in the tumor environment[4,70]

Genomic features



Immune modulators

Circulating biomarkers

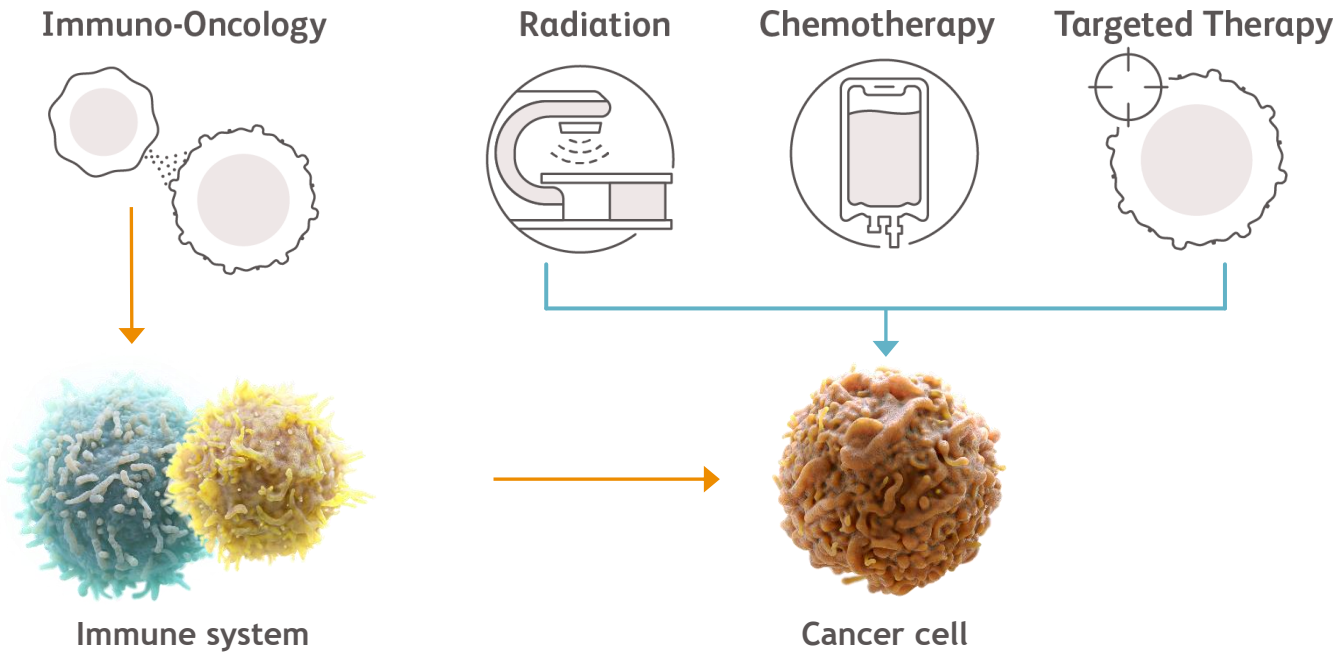
- A composite biomarker approach may provide a more precise representation of the tumor microenvironment[70,71]
- Research is underway to identify mechanisms of resistance and corresponding biomarkers to better inform treatment options[1,72-75]

Topic 4:
Evolving clinical expectations in I-O

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

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. Chemotherapy, radiation, and targeted therapy are all directed toward killing tumor cells.[1-4] In contrast, I-O seeks to activate the body's natural immune response to fight cancer.[5] This is a fundamentally different approach to cancer treatment.

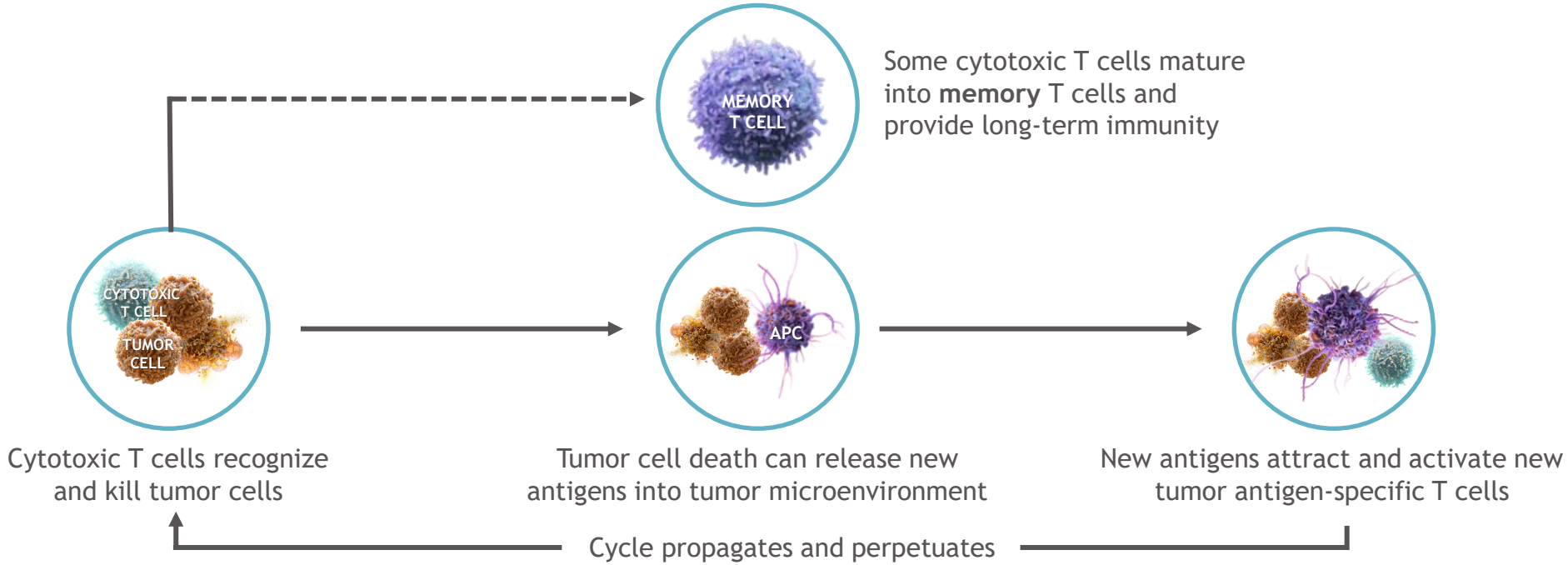


With an I-O approach come unique considerations and distinctive characteristics that continue to be researched, such as:

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

Immune responses have the potential to deepen and sustain over time

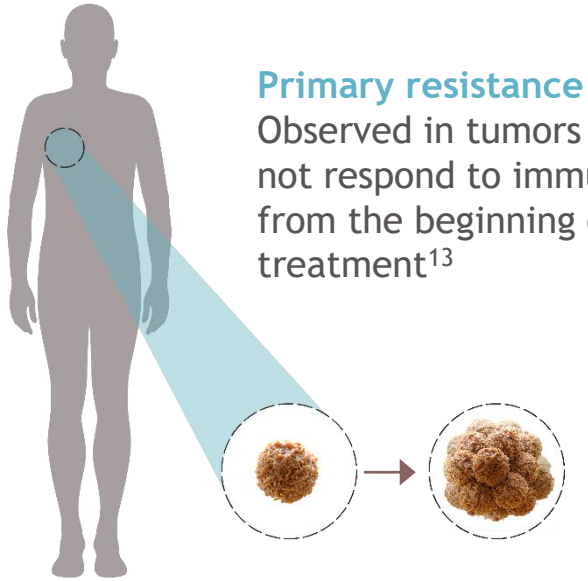
- The immune response **evolves and expands over time** by constantly recognizing and remembering tumor antigens. This ability—to propagate and perpetuate—suggests the adaptive nature of the immune response. Immune responses are dynamic and have the potential to improve and deepen over time.[6-8]



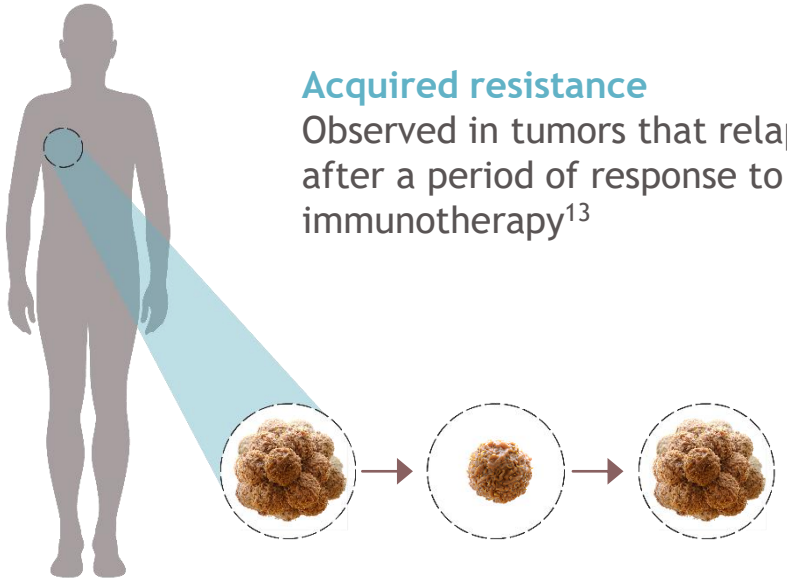
As the immune response continues to expand, some cytotoxic T cells mature into memory T cells that may provide long-term immune protection, even if the original stimulus is no longer present.[8-10]

Tumors that are resistant to I-O therapy may either have existing mechanisms of resistance or exploit evasive methods to overcome I-O treatment

Tumors may have primary resistance or acquired resistance to immunotherapy[11-13]:



Primary resistance
Observed in tumors that do not respond to immunotherapy from the beginning of the treatment[13]



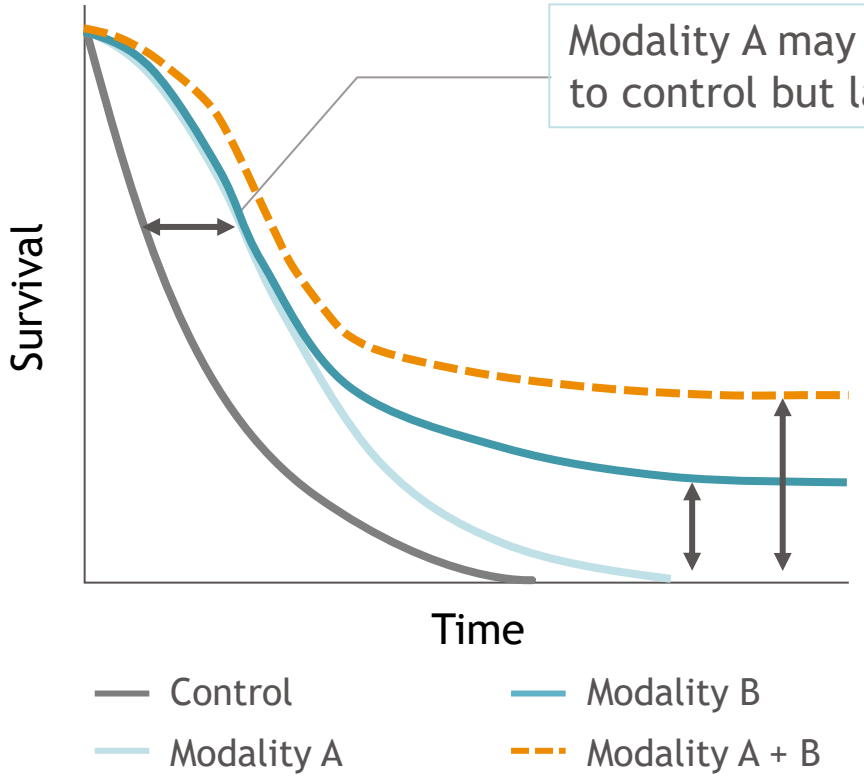
Acquired resistance
Observed in tumors that relapse after a period of response to the immunotherapy[13]

Research is underway to identify underlying mechanism of primary and secondary acquired resistance or exploit evasive methods to overcome I-O treatment[14,15]

I-O=Immuno-Oncology.

Combining immunotherapies with other treatment modalities may enhance the antitumor response[16,17]

- From a mechanistic standpoint, it is possible that combining immunotherapies with other treatment modalities may result in induction of immune memory, leading to longer duration of response than what is achievable with either modality alone



Modality A may have improved survival compared to control but lacks duration of response

Research is ongoing to assess the possibility for improved survival with longer duration of response for more patients with combination A + B

Modality B can have improved survival and longer duration of response in a fraction of patients

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

Adapted from Sharma P et al. *Cell*. 2015;161(2):205-214.

Preclinical studies suggest modulating multiple immune pathways may augment antitumor activity[18-20]*

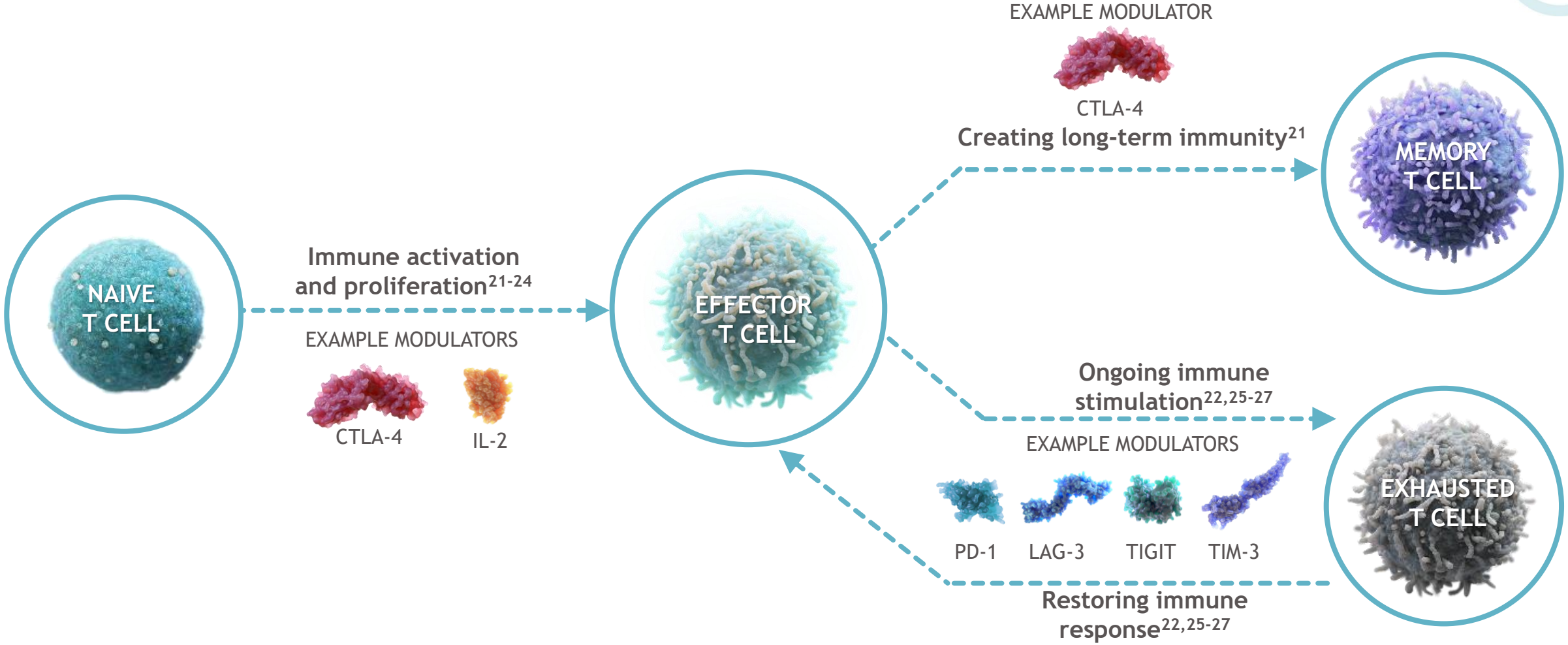
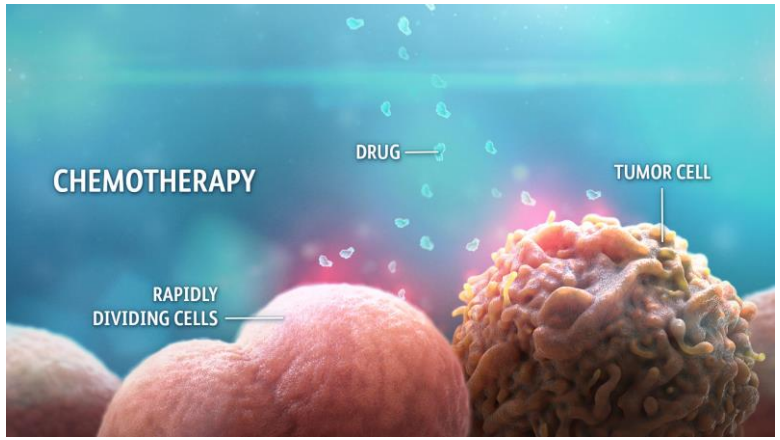
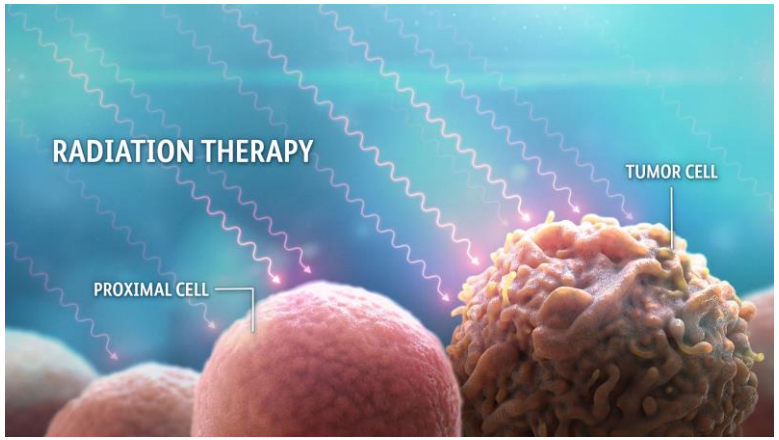


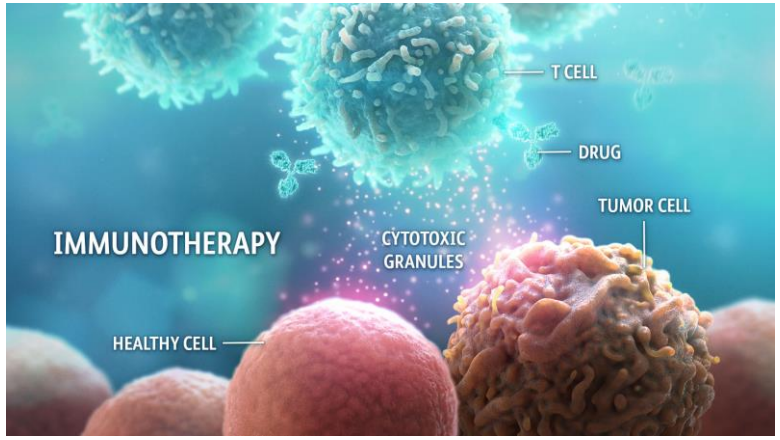
*Image intended to provide examples of pathways that may promote/inhibit T cells and long-term immunity.

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

- Preclinical studies suggest that chemoradiation combined with immunotherapy may augment the antitumor response by generating cytotoxic T-cells against tumor cells[28-31]

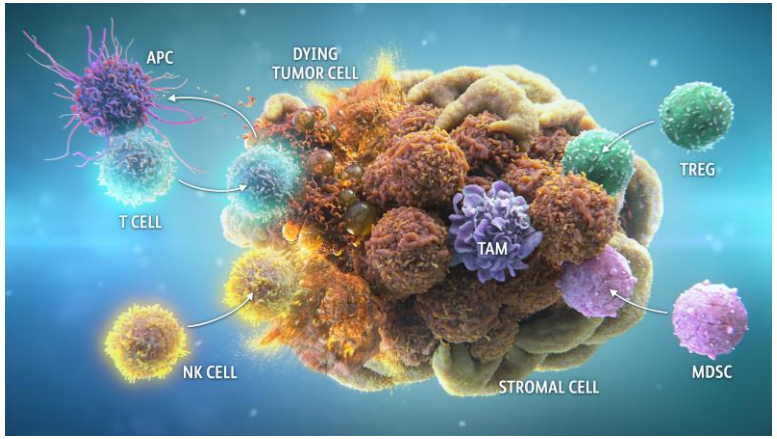


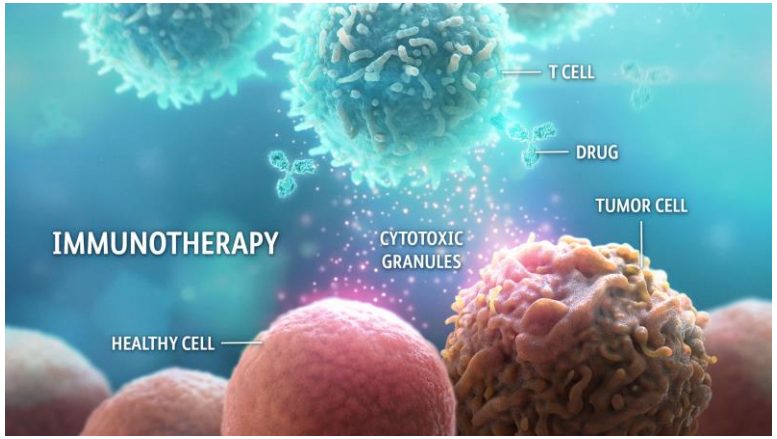




Research is ongoing to explore the potential synergistic antitumor effects of immunotherapy in combination with targeted therapies

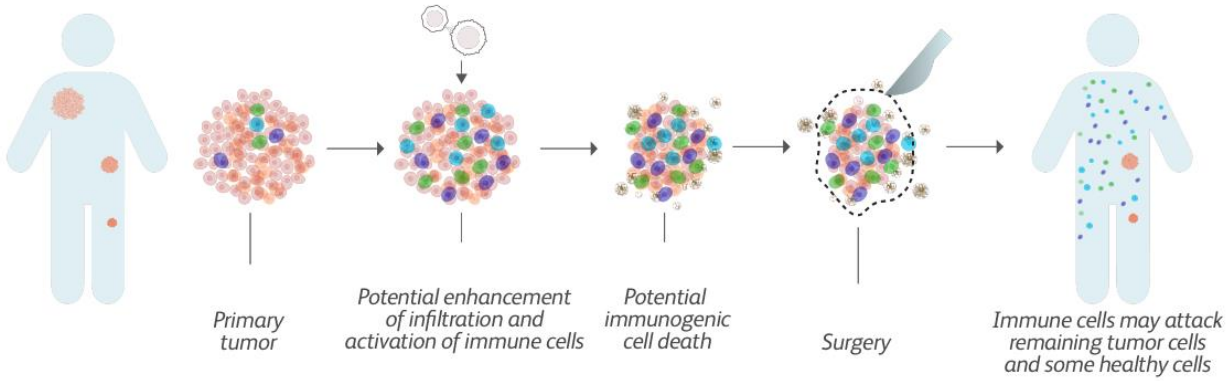
- Tumors may leverage a multitude of non–immune-related mechanisms to create a microenvironment conducive to tumor growth and survival[32-34]
- Combining immunotherapy with the blockade of pathways essential for tumor survival and growth may increase antitumor response[35,36]



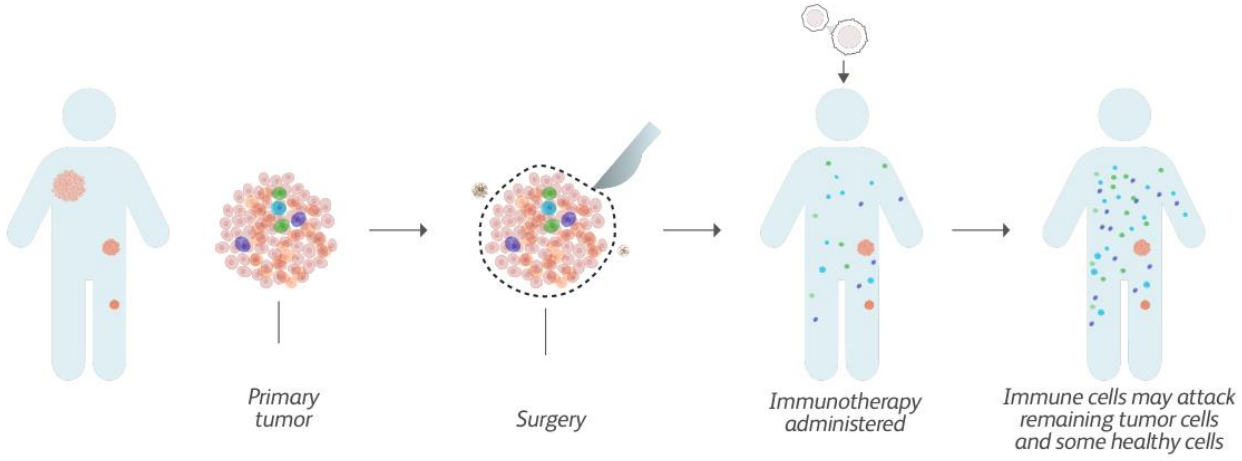


Research aims to explore the potential of I-O to target and eliminate tumor cells in earlier stages of cancer[37-41]

- In earlier stages of cancer, the immune system may be more intact and responsive[42]



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[38-40]

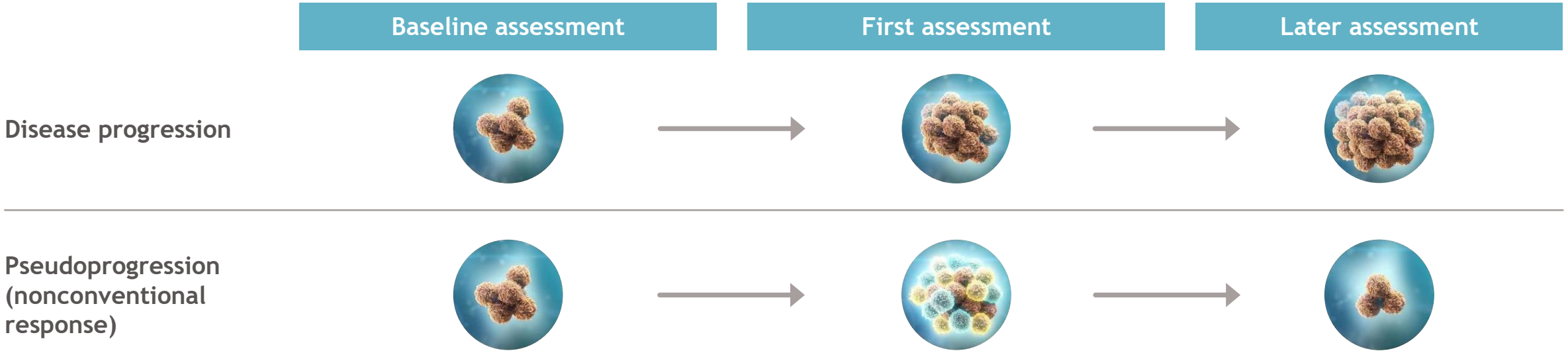


In the adjuvant setting, primed T cells, specific to tumor antigens, may develop into protective memory T cells after surgical excision of the primary tumor[43]

Pseudoprogression (1/2)

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.[44,45] This is known as **pseudoprogression**. Pseudoprogression does not reflect tumor cell growth but may be misclassified as disease progression[46-49]
- Tumors may **appear to grow, or new lesions may appear when immune cells infiltrate the tumor site.**[46] Due to the time required to mount an adaptive immune response, pseudoprogression may also reflect continued tumor growth until a sufficient response develops.[46,50]



Pseudoprogression (2/2)

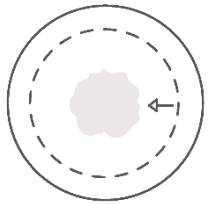
Pseudoprogression should be considered until disease progression can be confirmed

- While uncommon, pseudoprogression **is an important consideration** when evaluating response to Immuno-Oncology therapies.[50] Histologic confirmation is not always possible, but close monitoring of the following factors may help identify pseudoprogression[46,49,51]:

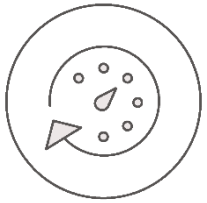
	Disease progression	Pseudoprogression (nonconventional response)
Performance status	Deterioration of performance	Remains stable or improves
Systemic symptoms	Worsen	May or may not improve
Symptoms of tumor enlargement	Present	May or may not be present
Tumor burden		
Baseline	Increase	Initial increase 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

Endpoint considerations for I-O research (1/3)

- The criteria currently used to assess potential benefit of cancer therapies are based on surgery, radiation therapy, and chemotherapy.[52] However, for **Immuno-Oncology**, a different way to fight cancer,[53] a more comprehensive approach to endpoint assessment may be needed to recognize potential benefit.[54-57]
- Response can be assessed by both **magnitude (size)** and **duration (time)**.[58]



Overall response rate (ORR) is the proportion of patients with a predefined decrease in tumor burden.[58] ORR reflects solely the magnitude of response, and is generally defined as a sum of partial and complete responses.[58]

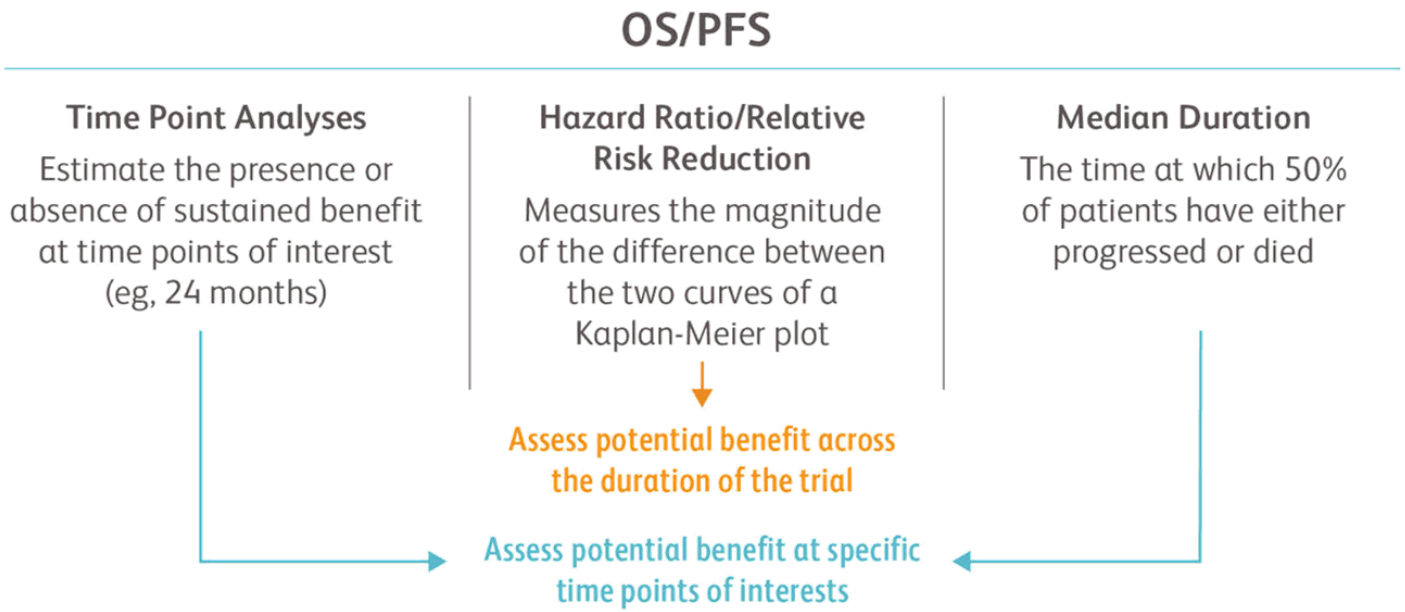


Duration of response (DOR) measures the time from initial tumor response to disease progression. As our understanding of research continues to evolve, the DOR may prove even more relevant to potential benefit than the magnitude of tumor reduction.[58,59]

Because responses range in both size and duration, these measures should be evaluated together to more accurately assess advances in Immuno-Oncology research.[58]

Endpoint considerations for I-O research (2/3)

- **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.[58,59]

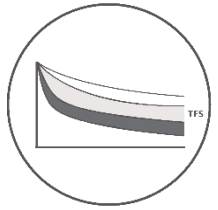


Assessing multiple measures can illustrate the full scope of clinical benefit.[55-57,60]

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.[55-57,60]

Endpoint considerations for I-O research (3/3)

Other measures may provide additional information regarding clinical benefit of a treatment

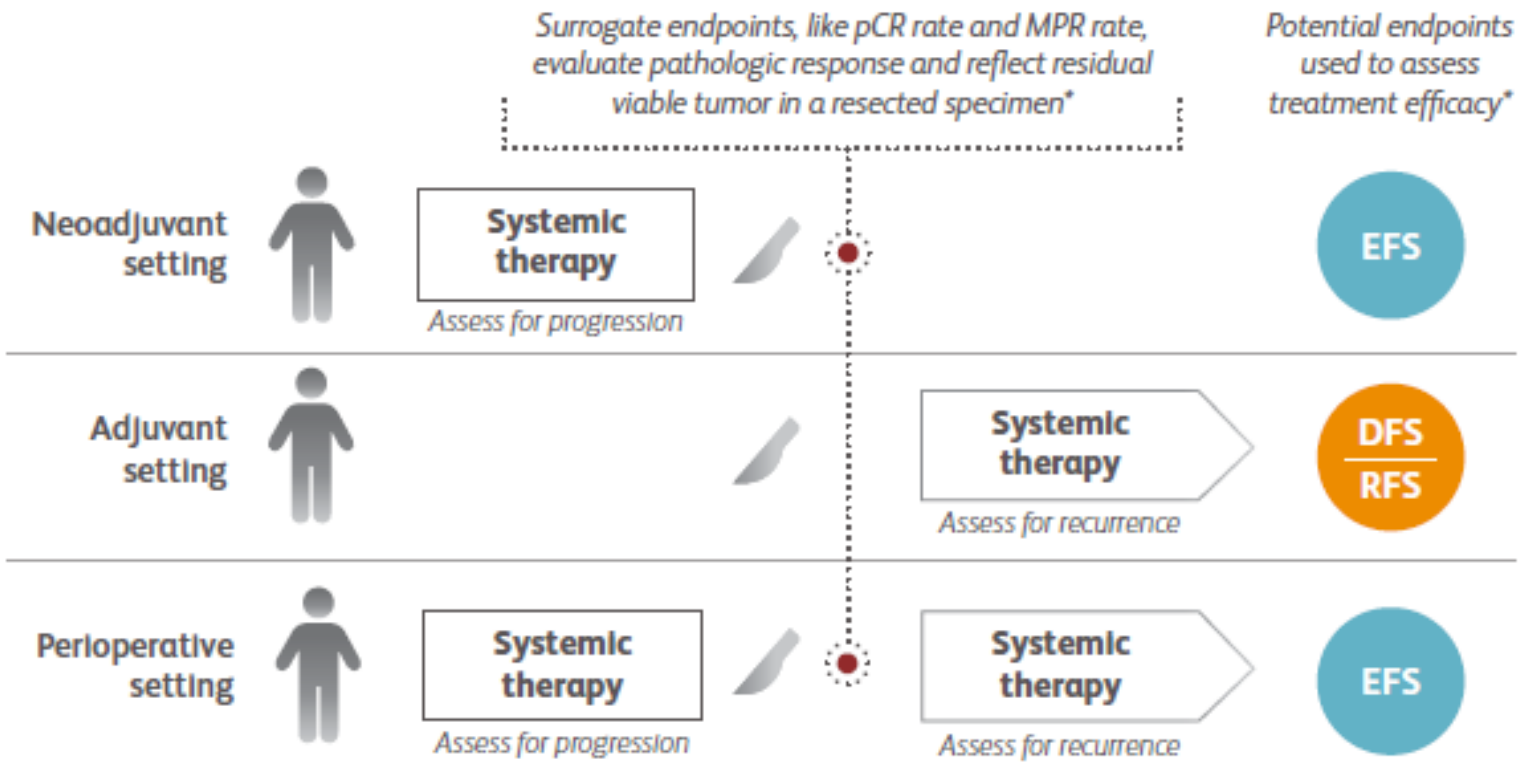


Treatment-free survival (TFS) is the time that patients in a given treatment arm spent off treatment prior to initiating a subsequent therapy.[61,62] TFS may integrate patient quality of life and toxicities experienced during the treatment-free period.[61,62]

Patient-reported outcomes (PROs) assess a patient's HRQOL (physical, psychological, and social) as experienced by the patient without the interpretation of a clinician.[63,64] The prominence of this measure is increasing as both a primary and secondary endpoint.[63-65]

TFS and PROs are other measures to obtain more information about the clinical benefits of a treatment.

Surrogate endpoints for survival may help to assess the efficacy of treatment in the neoadjuvant, adjuvant, and perioperative settings[66-75]



While OS is a common endpoint in oncology, it requires a longer follow-up period.[66] Surrogate endpoints may potentially correlate with OS[71,76-78]

BMS is investigating OS and surrogate endpoints to assess treatment efficacy in earlier stages of cancer[79-87]

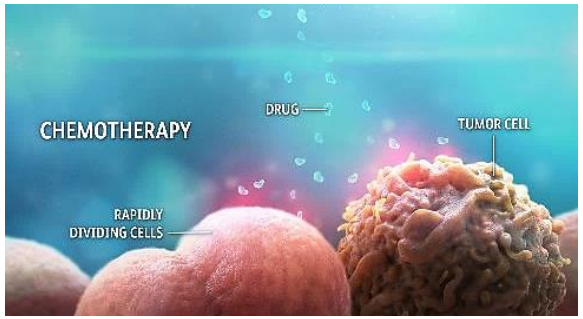
Immune-mediated adverse reactions (1/3)

Both traditional cancer therapies and immunotherapy can lead to adverse reactions

- Traditional therapies may affect healthy cells, in addition to the target cells, leading to adverse reactions. Immunotherapies can also affect healthy cells resulting in IMARs, a specific type of adverse reaction.[6,88-92]

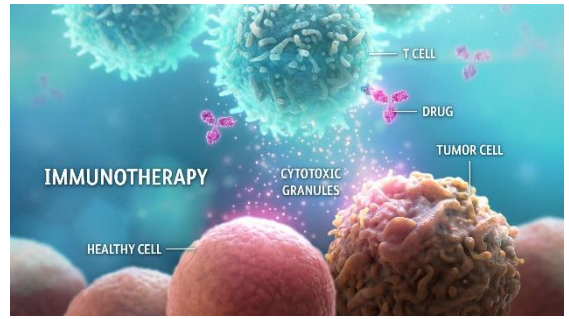
Mechanism of action for each treatment approach leads to adverse reactions

Radiation



Chemotherapy

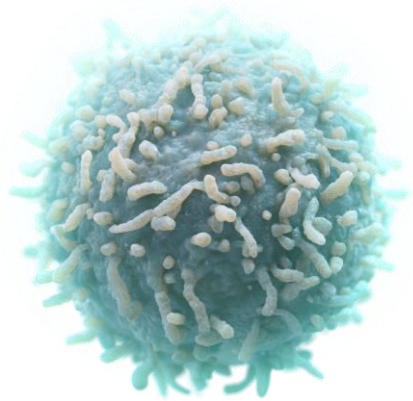
Targeted therapy



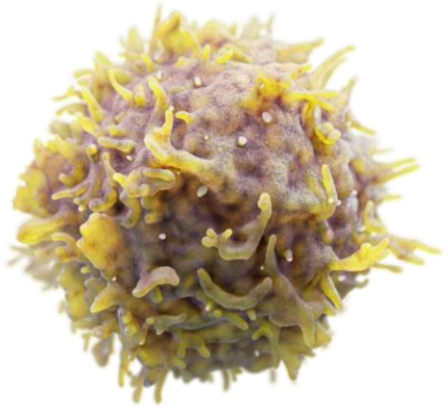
Immunotherapy

Immune-mediated adverse reactions (2/3)

- I-O therapies that modulate immune pathways **may enable the immune system to attack healthy cells** along with tumor cells resulting in immune-mediated adverse reactions.[6,91] The link between immune activation and IMARs is an area of ongoing research. T cells, NK cells, and certain immune pathways have been associated with IMARs.[93,94]



T cells: T-cell activation has been linked to immune attack on normal cells and the development of IMARs in certain organ systems.[91]



NK cells: Studies have shown that NK cells may protect healthy cells from being attacked by the immune system.[95-97]

As research in immunotherapy advances and more data are made available, understanding and appropriate management of immune-mediated adverse reactions will evolve.[98]

Immune-mediated adverse reactions (3/3)

Monitoring and vigilance of IMARs

- IMARs can occur at any point during and after the treatment continuum. Hence, early detection and management of IMARs is essential.[99-103]

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[91,99]
- In addition, treatment algorithms are available for use by healthcare providers to assist them in managing immune-mediated adverse reactions[104,105]
- Recent guidelines have been published that provide consensus recommendations for the management of immune-mediated adverse reactions.[100,104-106] Specific guidance for managing immune-mediated adverse reactions for an individual product can be found in the accompanying FDA-approved prescribing information

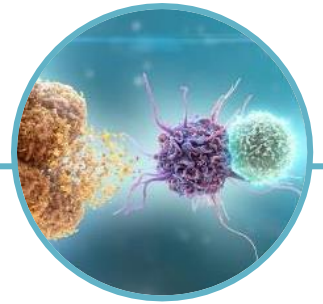
As research in immunotherapy advances and more data are made available, understanding and appropriate management of immune-mediated adverse reactions will evolve.[98]

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.[22]

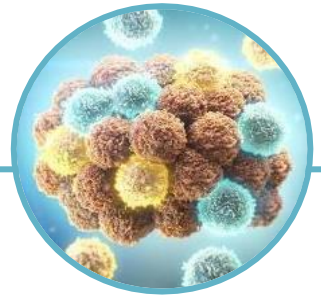
Depth of evidence for the immune response to cancer

- 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**.[1,2] The body can recognize and attack cancer through the following stages of immune response:



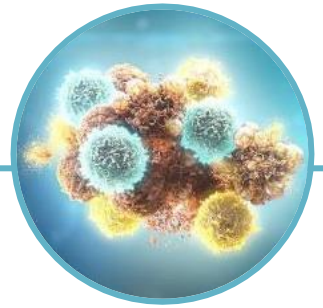
Presentation

Traditionally, immunogenic tumors are defined by a high rate of mutations.[3] These mutations create **neoantigens that can be recognized** by the immune system, activating an antitumor immune response.[4]



Infiltration

Tumor-infiltrating immune cells are present in the tumor microenvironment. Their presence demonstrates their capacity to **identify and migrate to tumor cells.**[5-18]



Elimination

Early in their development, some tumors display evidence of spontaneous regression.[19] 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.[20]

Broad potential of I-O research

There is evidence of immunogenicity across a wide range of malignancies[21]:

Tumor type*	Evidence for tumor immunogenicity		
	PRESENTATION Presence of somatic mutations	INFILTRATION Evidence of immune-cell infiltration	ELIMINATION Evidence of spontaneous regression
Bladder[3,15]	●	●	
Breast[17,22]	●	●	
Colorectal[16]	●	●	
Gastric/esophageal[8,23]	●	●	
Glioblastoma[3,4,6]	●	●	
Head and neck[9,24]	●	●	
Hepatocellular[13]	●	●	
Lung[3,8]	●	●	
Melanoma[3,8,25]	●	●	●
Ovarian[12,26]	●	●	
Pancreatic[16]	●	●	
Prostate[10,27]	●	●	
Renal[3,11]	●	●	●
Non-Hodgkin lymphoma[5,28]	●	●	●
Hodgkin lymphoma[14,29]	●	●	
Leukemia[30]	●		
Multiple myeloma[3,7,31]	●	●	

*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
- Exploring the potential of I-O by modulating multiple immune pathways to augment antitumor activity in the treatment of earlier stages of cancer
- Identifying I-O biomarkers that clarify the unique interplay between the immune system and the tumor and 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 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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Abbreviations (1 of 2)

ADCC=antibody-dependent cellular cytotoxicity
AE=adverse event
AHR=aryl hydrocarbon receptor
AI=artificial intelligence
ALL=acute lymphoblastic leukemia
AML=acute myeloid leukemia
APC=antigen-presenting cell
ATP=adenosine triphosphate
BCR-ABL=breakpoint cluster region-Abselon
BET=bromodomain and extraterminal domain
BRAF=B-raf proto-oncogene
CCR=chemokine (C-C motif) receptor
CML=chronic myelogenous leukemia
CTC=circulating tumor cell
ctDNA=circulating tumor DNA
CTLA-4=cytotoxic T-lymphocyte antigen 4
CXCR1=chemokine (C-X-C motif) receptor 1
CXCR2=chemokine (C-X-C motif) receptor 2
DC=dendritic cell
DFS=disease-free survival
dMMR=mismatch repair deficient
DOR=duration of response
EFS=event-free survival
EGFR=epidermal growth factor receptor
EMT=epithelial-mesenchymal transition
Fc=fragment, crystallizable
FucGM1=fucosyl GM1
GEP=gene expression profile
HMGB1=high mobility group box 1
HRQOL=health-related quality of life
IDO1=indoleamine 2,3-dioxygenase 1
IFN=interferon
Ig=immunoglobulin
IL=interleukin
IMAR=immune-mediated adverse reaction
I-O=immuno-oncology
ITIM=immunoreceptor tyrosine-based inhibitory motif
KRAS=Kirsten rat sarcoma
LAG-3=lymphocyte-activation gene 3
LSD1=lysine-specific demethylase 1
MAPK=mitogen-activated protein kinase
MDSC=myeloid-derived suppressor cell
MHC=major histocompatibility complex
MPR=major pathologic response
MRD=minimal residual disease
mRNA=messenger RNA
MSI-H=microsatellite instability-high
NGS=next-generation sequencing
NK=natural killer
NKG2A=NK group 2 member A
NLRP3=nucleotide-binding oligomerization domain-like receptor family, pyrin domain containing 3

Abbreviations (2 of 2)

ORR=overall response rate

OS=overall survival

pCR=pathologic complete response

PD-1=programmed death receptor-1

PD-L1=programmed death ligand 1

PD-L2=programmed death ligand 2

PFS=progression-free survival

PGE2=prostaglandin E2

PRO=patient-reported outcomes

PS=phosphatidylserine

PSCA=prostate stem cell antigen

RFS=recurrence-free survival

SCLC=small cell lung cancer

SIRPα=signal-regulatory protein alpha

SLAMF7=signaling lymphocytic activation molecule family member 7

STING=stimulator of interferon genes

TAM=tumor-associated macrophage

TCR=T-cell receptor

TFS=treatment-free survival

TGF=transforming growth factor

Th=helper T cell

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