ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

www.immunoscienceacademy.be

Understanding immunoscience

A guide for specialists working with immunotherapies

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Immunotherapy for malignancies

Immunotherapy for malignancies

Click on a chapter below to start learning

Click on the ISA logo of a slide to return to the chapter homepage

Introduction

Immunotherapy for malignancies

Immunotherapy for malignancies: introduction

- Immunotherapy is a therapeutic modality that harnesses the body's own immune system to fight cancer[1–3]
- Tumor cells can be recognized and killed by the immune system, mostly by the adaptive immune system[3]
- Understanding the modalities of increasing this antitumor activity has led to the development of novel therapeutic agents[4]
- Immunotherapy has changed the treatment landscape for a variety of solid tumors and hematologic malignancies and is helping to improve outcomes for patients[3-4]
- Currently, there is great interest in developing predictors of response to immunotherapy and rational combination therapies that can enhance efficacy by overcoming primary and acquired resistance in comparison with monotherapy treatment[5]

1. Murphy. Oncology 2010;4:67–80. 2. Kirkwood et al. CA Cancer J Clin 2012;62:309–35. 3. Borghaei et al. Eur J Pharmacol 2009;625:41–54. 4. Chen & Mellman. Immunity 2013;39:1–10. 5. Meric-Bernstam et al. Lancet. 2021;397:1010-1022.

Principles of immuno-oncology

Immunotherapy for malignancies

The **dual role** of the immune system in cancer[1,2]

- The immune response to tumors can vary between continuous activation and suppression, with tumor progression favored when the immune response is suppressed[1,2]

- 'Cancer immunoediting' is a three-stage model that helps us to understand the host-protective and tumor-sculpting actions of immunity during cancer[1,2]

Elimination (or immunosurveillance)
Transformed cells are destroyed by a capable immune system (innate and adaptive)[1]

Equilibrium
The immune system retains the tumor in a state of functional dormancy[2]

Escape
The immune system is no longer able to restrict tumor growth; the disease becomes clinically apparent[1,2]

1. Dunn et al. Annu Rev Immunol 2004;22:329–60. 2. Mittal et al. Curr Opin Immunol 2014;27:16–25.

Key scientific concepts of current immunotherapy for cancer

- The main effector cells against tumor cells are **cytolytic T lymphocytes**
  Patients can mount spontaneous antitumor T-cell responses; mounting such a response is a multistep process
- Cytolytic T lymphocytes can recognize **tumor-specific antigens** on the surface of tumor cells
- The **activity of T lymphocytes** can be increased by stimulatory or inhibitory **surface coreceptors**
- In addition to cytolytic T lymphocytes, the immune system can kill tumor cells through **other modalities**
- Tumors have several **mechanisms of resistance** to host antitumor immunity responses

Professor P. Coulie, personal communication.

Key scientific concepts that underpin current immunotherapy for cancer

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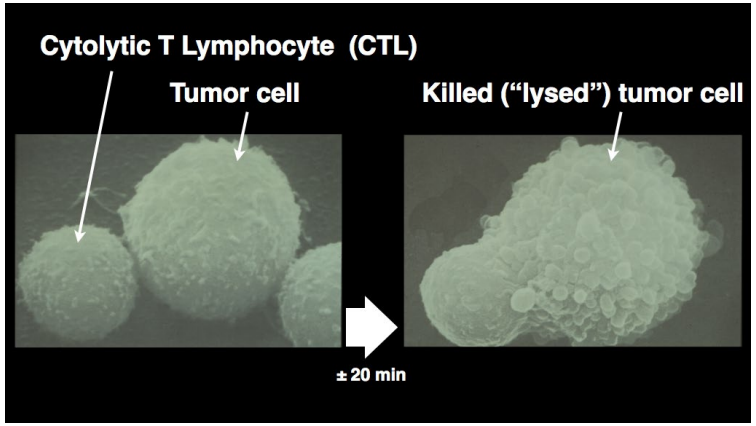
Tumor-specific cytolytic T lymphocytes

- Immunological memory is the immune system's ability to **respond more rapidly** to a previously encountered pathogen[1]
- This occurs owing to the pre-existence of clonally expanded antigen-specific lymphocytes[1]
- After an immune attack, cytotoxic T cells will either die or differentiate into memory T cells[2]
- Memory T cells remain in the body and recognize the antigen again to support a further immune response[3]
- Cytotoxic and memory T cells recognize their unique activating antigen (presented via APCs) and migrate to the relevant tissue in the event of antigen recurrence[3]
- In cancer, TAAs are one of the main triggers of the T-cell immune response against tumorigenesis[4]



Killing capacities[5]

Absolute tumor **specificity**

Memory

Unique therapeutic modality

Long-lasting, tumor-specific activity

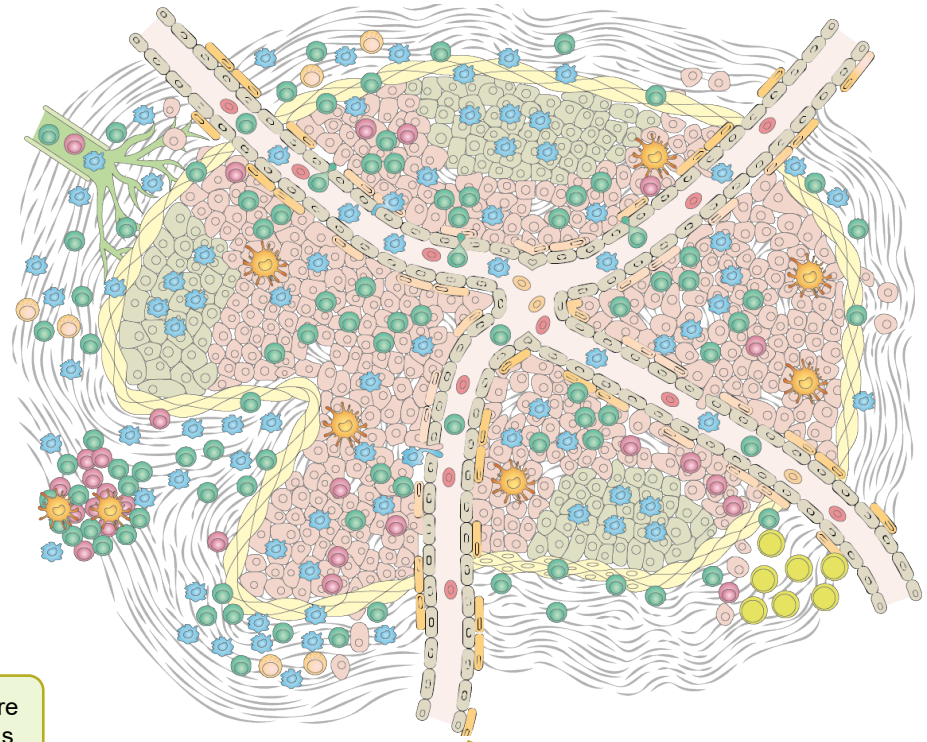
APC, antigen presenting cell; TAAs, tumor-associated antigens.

1. Immunobiology: The Immune System in Health and Disease. 5th edition. Available from: https://www.ncbi.nlm.nih.gov/books/NBK27158/ Accessed Jul 22 2022. 2. Masopust & Schenkel. Nat Revs Immunol 2013:13;309–20. 3. Woodland & Kohlmeier. Nat Rev Immunol 2009;9:153–61. 4. Spurrell & Lockley. Ecancer medical science. 2014;8:441. 5. Professor P. Coulie, personal communication. Image provided by Professor P. Coulie, personal communication.

Spontaneous antitumor T-cell responses

- Tumors contain a complex network of structures (such as blood vessels and connective tissue), cells and chemical signals[1]
- The genetic alterations characteristic of tumors can result in the expression of numerous tumor antigens, allowing the immune system to **differentiate tumor cells from normal cells**[1]
- **Evidence for spontaneous antitumor T-cell responses**
  - Antitumor CTLs are present in cancer patients prior to any treatment, including in blood and within tumors[1]
  - There is a higher incidence of tumors reported in immunosuppressed patients[2]
  - There is downregulation of surface HLA molecules in some types of tumors (most likely as a result of immunoselection)[3]
  - The prognostic or predictive value of TILs is related to the enrichment of tumor-specific T cells[3]
- These responses are insufficient (Darwinian selection of resistant tumors)[3]

The tumor microenvironment[4]



Learn more about TILs

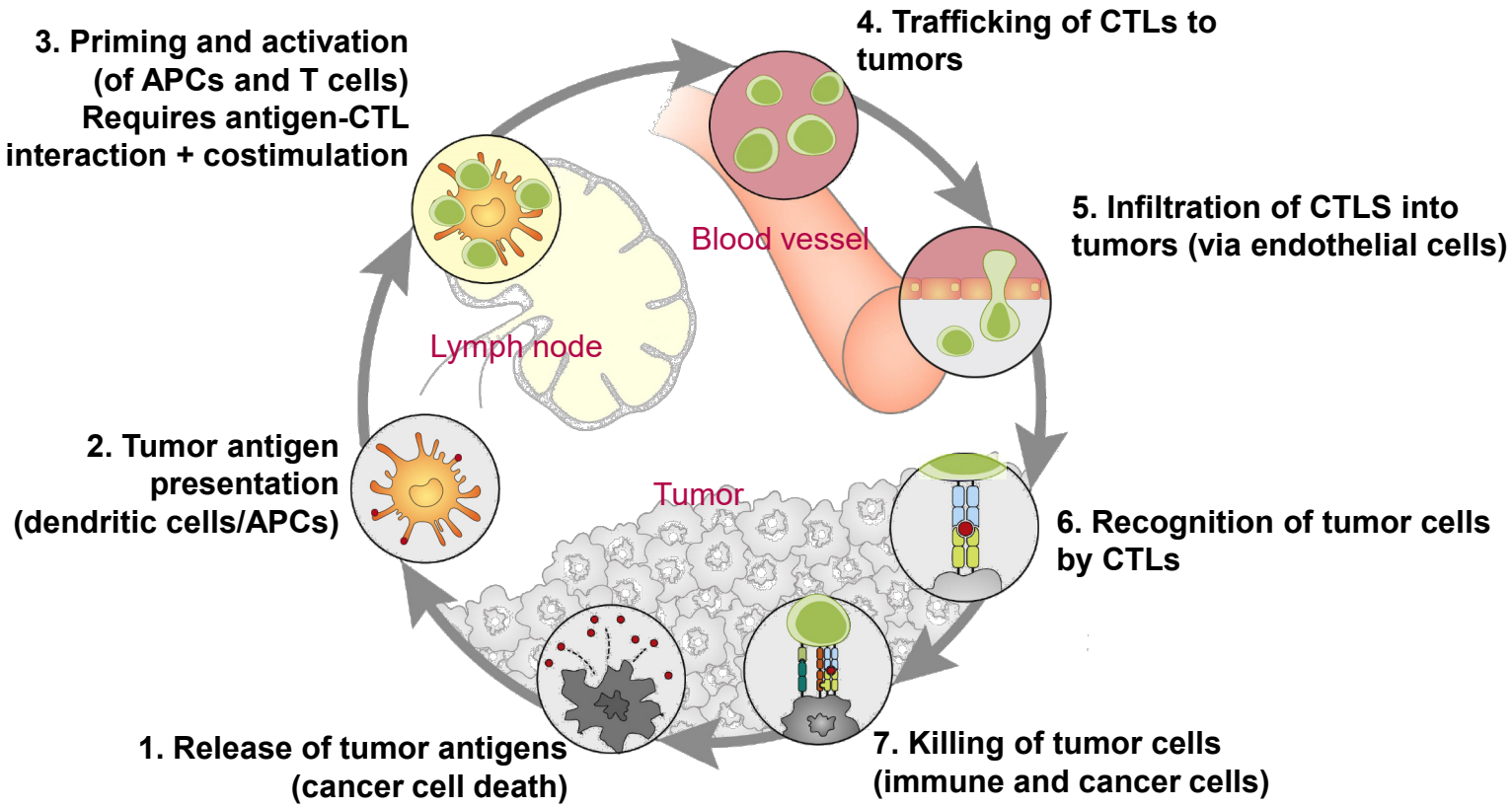
Learn more about the TME

CTL, cytolytic T lymphocyte; HLA, human leukocyte antigen; TIL, tumor-infiltrating lymphocyte; TME, tumor microenvironment.

1. Spurrell & Lockley. Ecancermedicalscience 2014;8:441. 2. Schulz. Int J Cancer 2009;125:1755–63. 3. Professor P. Coulie, personal communication. 4. Balkwill et al. J Cell Sci 2012;125:5591–6.

Mounting antitumor T-cell responses

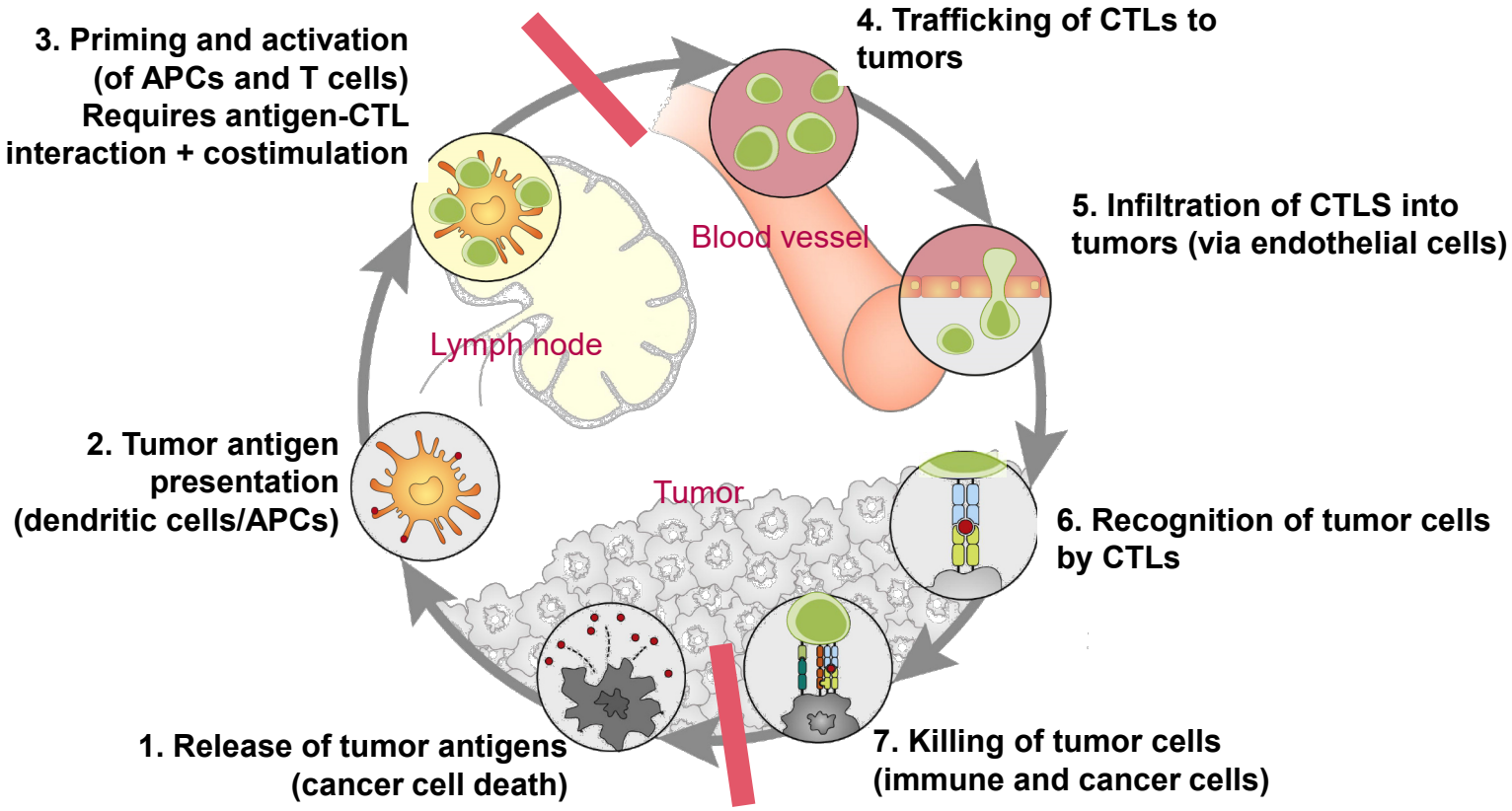
- **Immune surveillance**: identification and elimination of cancer cells by the immune system can be seen as a cyclic series of stepwise events[1]



APC, antigen presenting cell; CTL, cytotoxic T lymphocyte.
Figure adapted from 1. Chen & Mellman. Immunity 2013;39:1–10.

Mounting antitumor T-cell responses

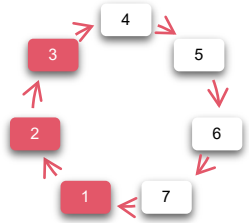
- Each step in the cycle is necessary but not sufficient to eliminate the tumor[1]
- Targeting more than one element of a defective cycle is likely to enhance the immune activity in patients compared with a single point of intervention alone, and is the premise of combination immunotherapy[1]



APC, antigen presenting cell; CTL, cytotoxic T lymphocyte.

1. Professor P. Coulie, personal communication. Figure adapted from 2. Chen & Mellman. Immunity 2013;39:1–10.

Key scientific concepts that underpin current immunotherapy for cancer



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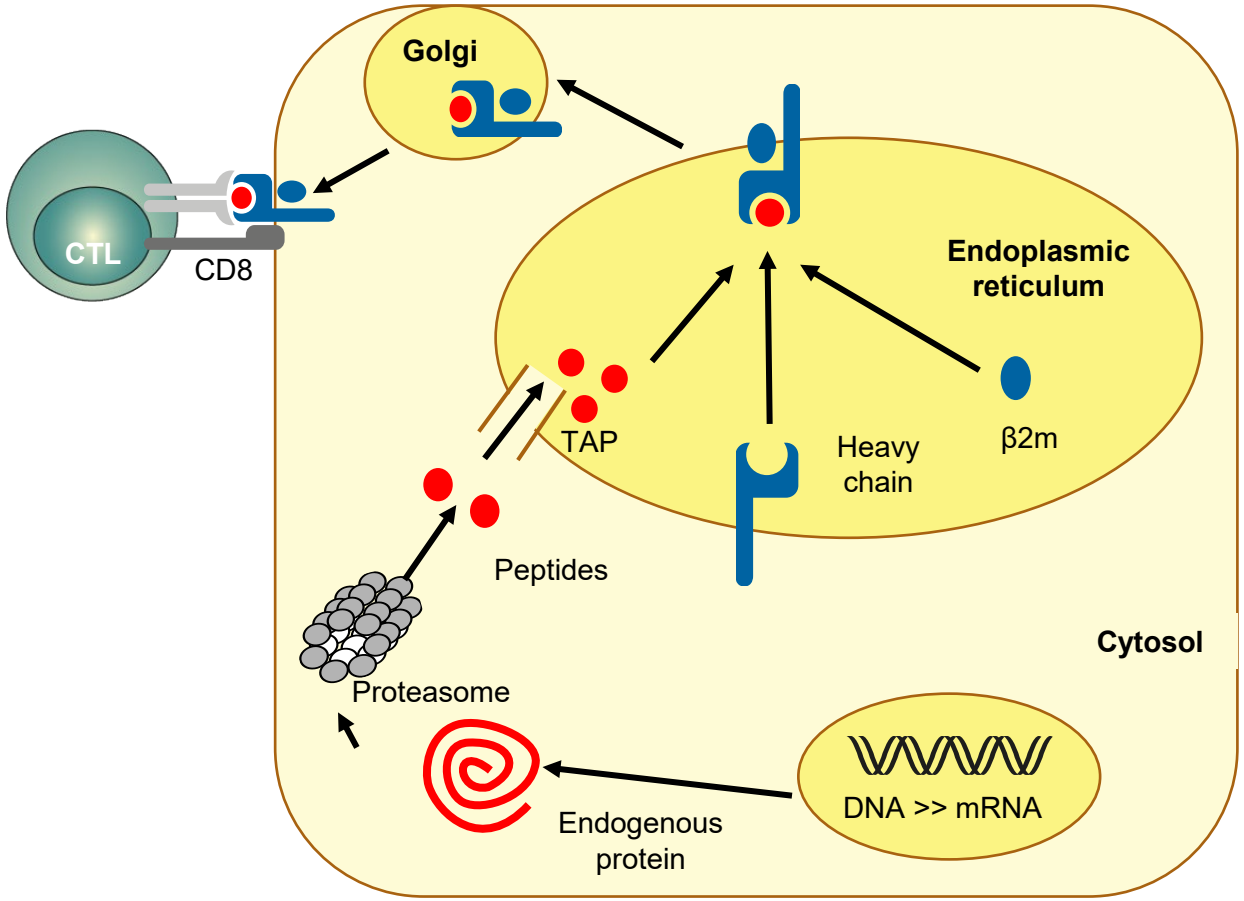
Professor P. Coulie, personal communication

Cytolytic T lymphocytes can recognize tumor-specific antigens on the surface of tumor cells

- Tumor antigens resulting from tumor cell mutations that arise during oncogenesis are released and captured by APCs such as dendritic cells for processing[1]
- Proteins are processed and antigen presentation occurs via HLA class I molecules[2]
  - Proteins are degraded by the proteasome
  - Next, the resultant peptides are translocated by TAP into the ER lumen and loaded onto HLA class I molecules
  - The peptide–HLA class I complexes are then released from the ER and transported via the Golgi to the plasma membrane
- The antigenic tumor peptide is presented to CTLs ($CD8^+$ T cells)[1]

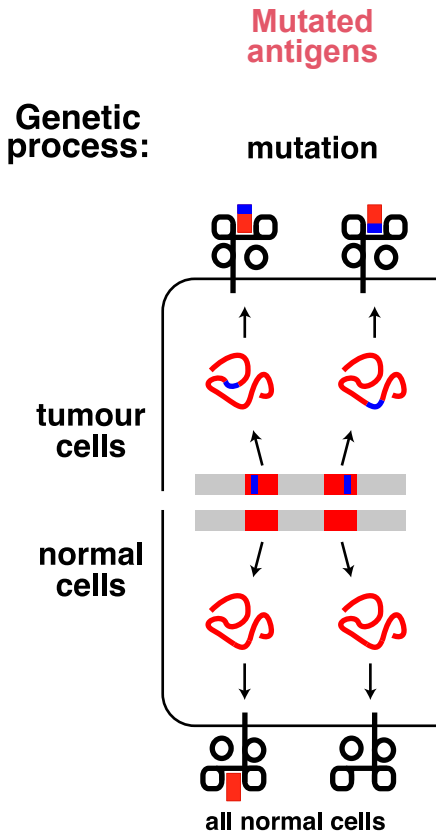


APC, antigen presenting cells; ß2m, beta2 microglobulin; CD, cluster of differentiation; CTL, cytolytic T lymphocyte; ER, endoplasmic reticulum; HLA, human leukocyte antigen; TAP, transporter associated with antigen presentation.

1. Chen & Mellman. Immunity 2013;39:1–10. 2. Neefjes et al. Nat Rev Immunol 2011;11:823–36.

Tumor antigen recognition by T lymphocytes

Five distinct genetic mechanisms lead to the expression of tumor-specific (for the first three mechanisms) or tumor-associated (for the last two) antigens recognized by T cells



DNA mutations and mutated antigens

- Mostly nonsynonymous single-nucleotide variations leading to an amino acid change in a protein
- Mostly occur at random: passenger mutations
- Sometimes occur in oncogenes (KRAS)
- Chromosomal translocations that result in chimeric proteins that are foreign to the host immune system
- A peptide that contains a mutated amino acid can be presented by HLA molecules and recognized by CTLs
- Mutated antigens are also known as 'neoepitopes' or 'neoantigens'

ALL, acute lymphocytic leukemia; CML, chronic myeloid leukemia; CTL, cytolytic T lymphocyte; EML4-ALK, echinoderm microtubule associated protein like 4; HLA, human leukocyte antigen; NSCLC, non-small-cell lung carcinoma.

Coulie et al. Nat Rev Cancer 2014;14:135–46.

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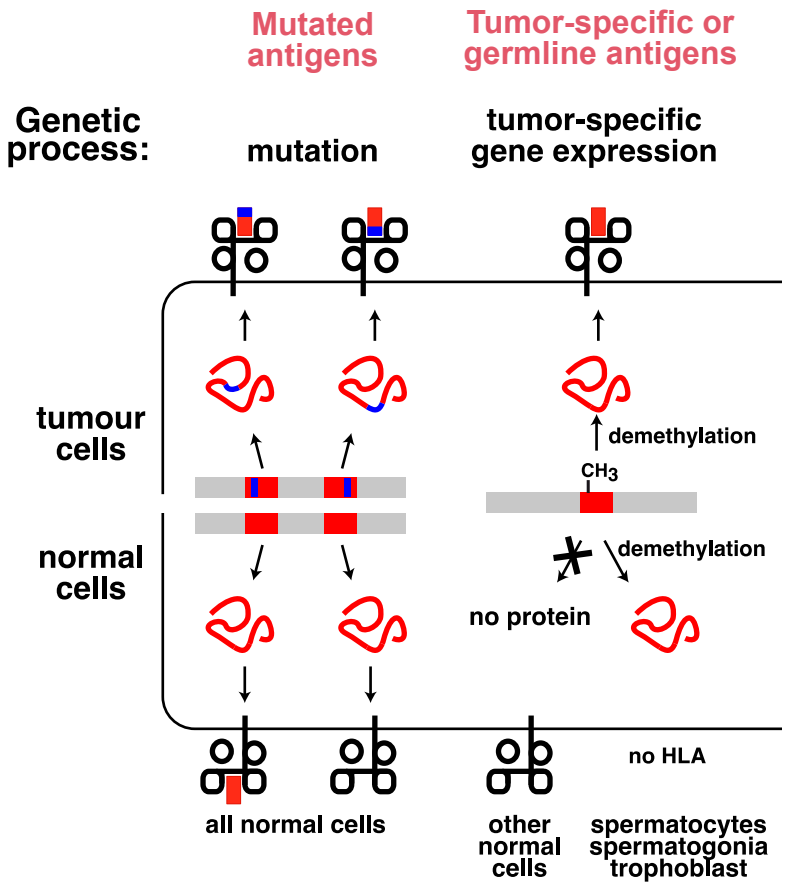

Tumor-specific or germline antigens

- Cancer-germline genes are expressed in tumors
- Most of them are silent in normal adult tissues, except for male germline cells (HLA-negative)
- The reason for this pattern of expression is DNA methylation

HLA, human leukocyte antigen; MAGE, melanoma antigen gene; MAGE-A1, MAGE family member A1.
Coulie et al. Nat Rev Cancer 2014;14:135–46.

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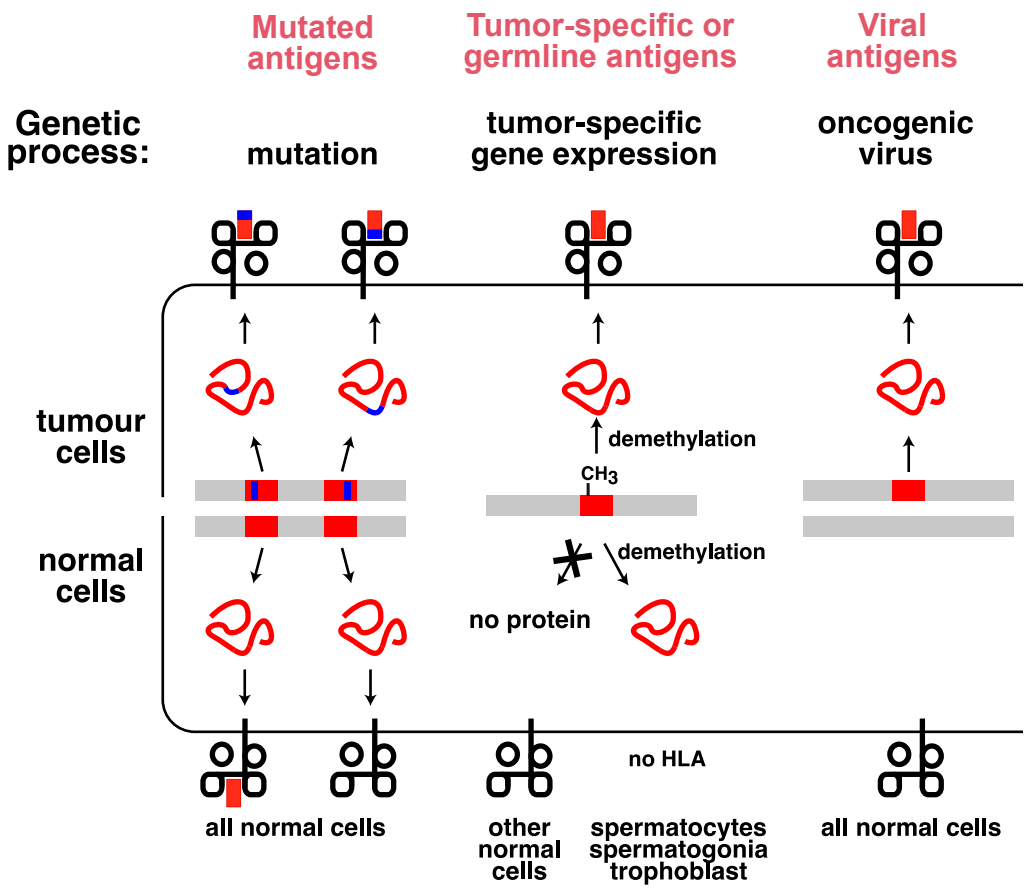

Viral antigens

- A **viral** protein is an antigen specified by the **viral** genome that can be detected by a specific immunological response
- A **viral** antigen is a protein encoded by the **viral** genome
- **Viral** antigens arise in cancer cells from oncogenic viral proteins

HLA, human leukocyte antigen; MAGE, melanoma antigen gene.
Coulie et al. Nat Rev Cancer 2014;14:135–46.

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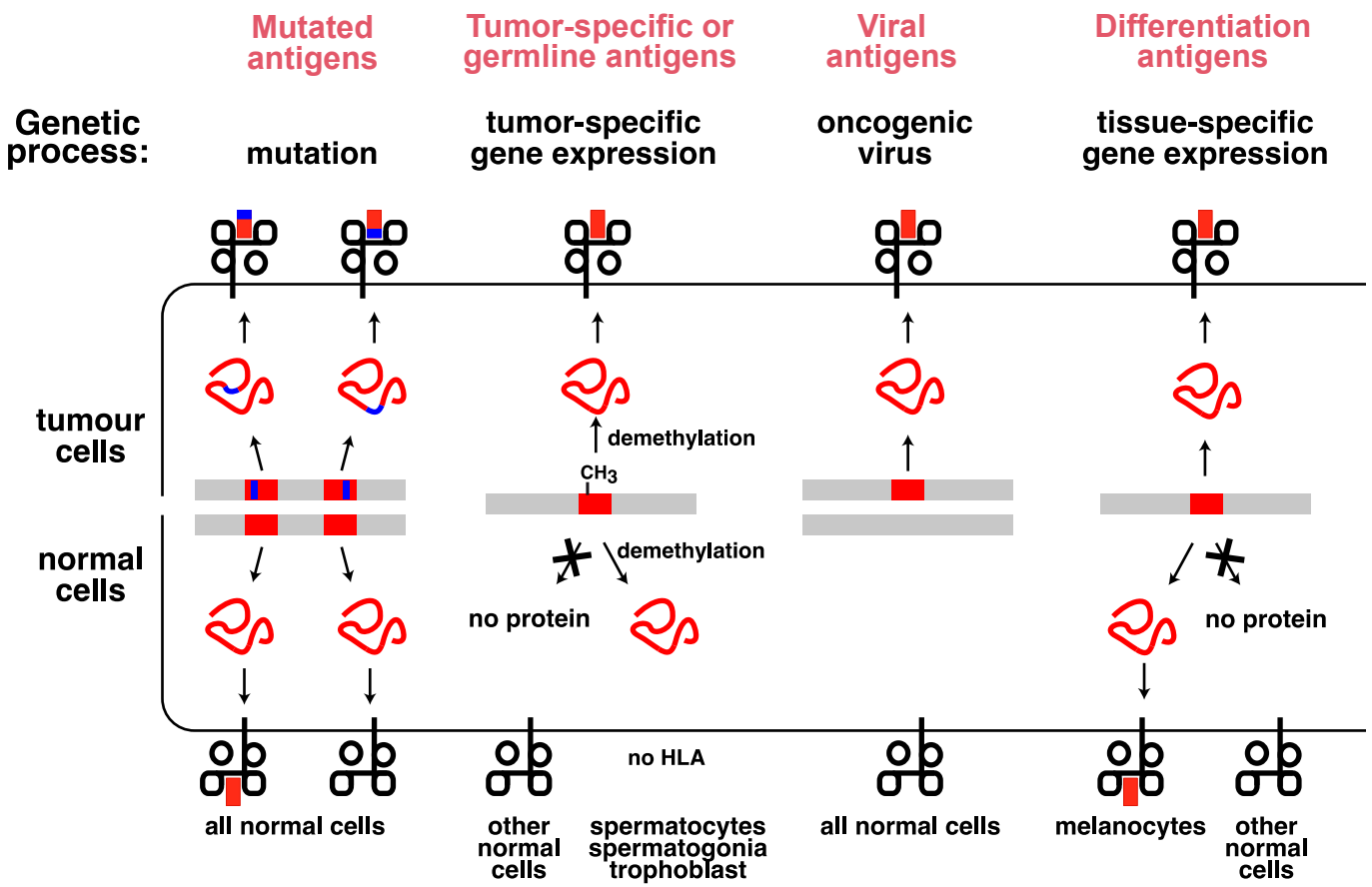


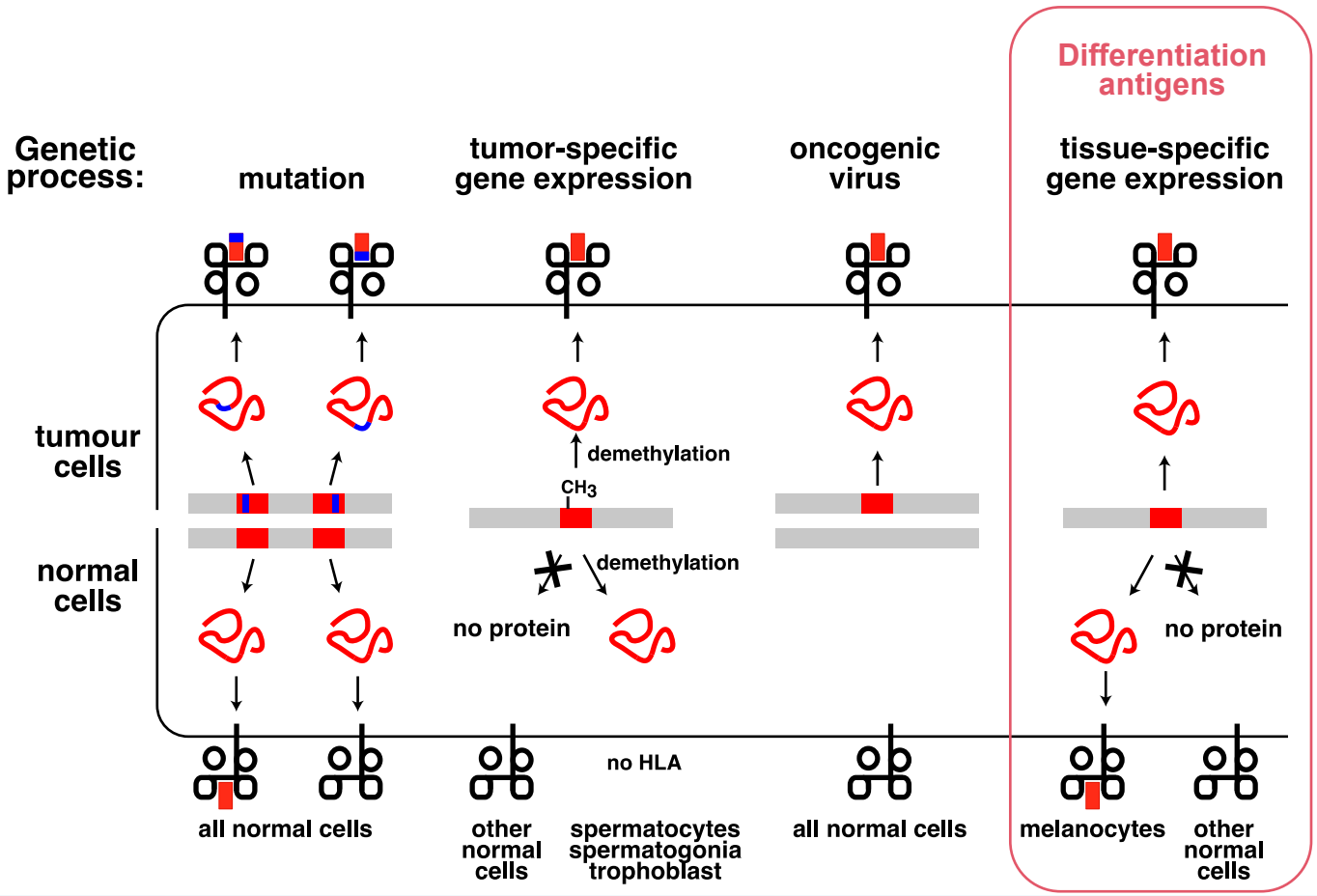
Differentiation antigens

- Differentiation antigens are expressed by both the tumor and the normal tissue from which the tumor arose

CEA, carcinoembryonic antigen; gp100, glycoprotein 100; HLA, human leukocyte antigen; MAGE, melanoma antigen gene; PSA, prostate-specific antigen.
Coulie et al. Nat Rev Cancer 2014;14:135–46.

Clinical relevance

Tumor antigen recognition by T lymphocytes



Selected examples of approved immunotherapies that target differentiation tumor antigens

- Sipuleucel-T (anti-PAP vaccine for prostate cancer)
- Blinatumomab (CD19–CD3 bispecific antibody for ALL)
- Rituximab (CD20 for CLL)
- Ofatumumab (CD20 for CLL)
- Obinutuzumab (CD20 for CLL and FL)
- Daratumumab (CD38 for MM)
- Elotuzumab (SLAMF7 for MM)

ALL, acute lymphocytic leukemia; CLL, chronic lymphocytic leukemia; CD, cluster of differentiation; FL, follicular lymphoma; HLA, human leukocyte antigen; MAGE, melanoma antigen gene; MM, multiple myeloma; PAP, prostatic acid phosphatase; SLAMF7, signaling lymphocytic activation molecule F7.

Coulie et al. Nat Rev Cancer 2014;14:135–46.

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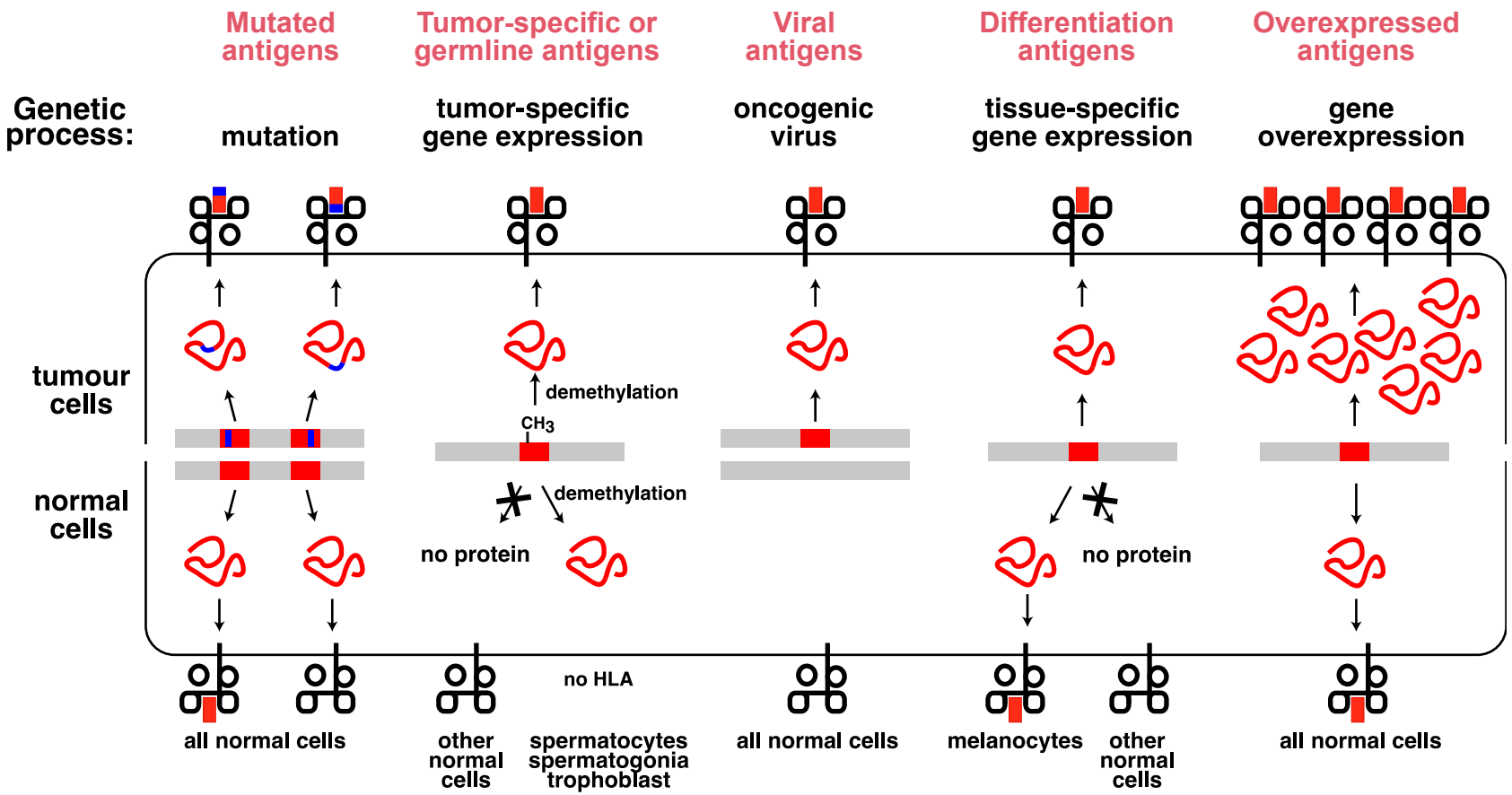

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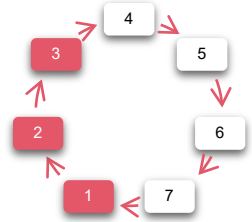
Adaptive immunity and controlling tumor growth



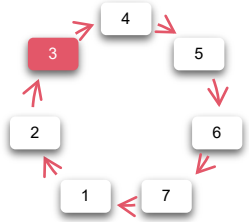
- **TAAs** are important triggers of the immune response, and are recognized by T-cells[1]

TAA	Mechanism of immune activation	Examples[1]
Mutated antigens[1] (also known as neoantigens)[2]	Arise as a result of genetic mutations or splicing aberrations, which leads to the generation of a protein that is foreign to the host immune system[1] In certain tumors, chromosomal location can result in the fusion of distant genes, and the expression of an abnormal **fusion protein** that is foreign to the host immune system[2]	• Individual **KRAS** mutations in colon, pancreatic and other cancers • **BCR-ABL** in CML and some ALL • **EML4-ALK** in NSCLC
Tumor-specific antigens[1]	Mutations in the tumor genome can cause tumors to express mutant proteins. They are not expressed on normal cells	• **MAGE** (melanoma-associated antigen) • **BAGE** (B melanoma antigen) **GAGE** (G antigen) • **LAGE1** = NY-ESO-1
Viral antigens[2]	Arise in cancer cells from oncogenic viral proteins[2]	• **HPV oncoproteins E6** and **E7** in HPV-associated cancers of the cervix, anus and oropharynx
Differentiation antigens[1]	Expressed by the tumor and the normal tissue from which the tumor arose[1]	• **CEA** – expressed in embryonic tissues and overexpressed in colorectal cancer • **PSA** – expressed in normal prostate and overexpressed in prostate cancer; • **gp100** – expressed in melanocytes and melanoma
Overexpressed antigens[1]	Expression levels in normal tissues is below the required threshold for T-cell activation. Overexpression by malignant cells therefore overrides the tolerance and triggers T-cell activation[1]	• **HER2** – overexpressed in breast cancer • **AFP** – overexpressed in HCC and some germ cell tumors

AFP, alphafetoprotein antigen; ALL, acute lymphoblastic leukaemia; CEA, carcinoembryonic antigen; CML, chronic myeloid leukaemia; EML4-ALK, echinoderm microtubule associated protein like 4 – anaplastic lymphoma kinase, gp100, glycoprotein 100; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; NSCLC, non-small-cell lung carcinoma; PAP, prostatic acid phosphatase; PSA, prostate-specific antigen; TAA, tumor-associated antigens.

1. Spurrell & Lockley Ecancermedicalscience. 2014;8:441. 2. Yarchoan et al. Nat Rev Cancer 2017;17:209–22.

Key scientific concepts that underpin current immunotherapy for cancer



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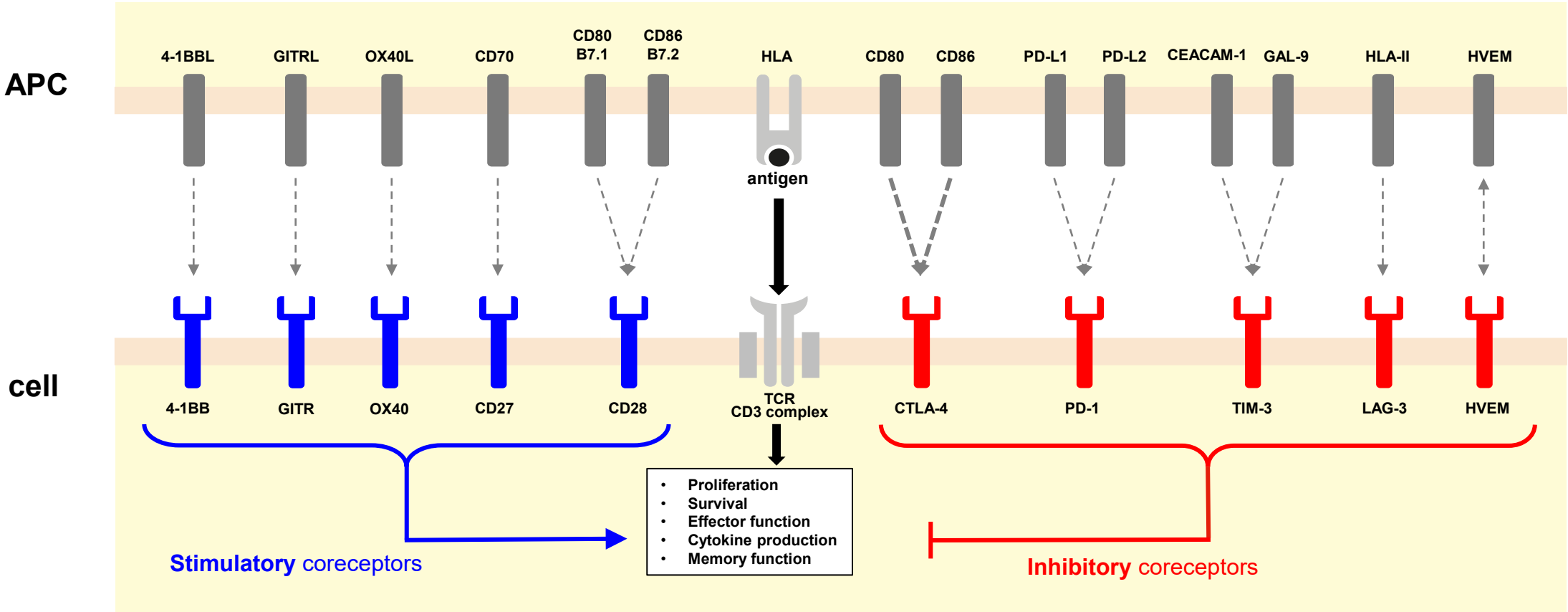
Professor P. Coulie, personal communication.

The activity of T lymphocytes can be increased by stimulatory or inhibitory surface coreceptors

Stimulatory and inhibitory T-cell coreceptors

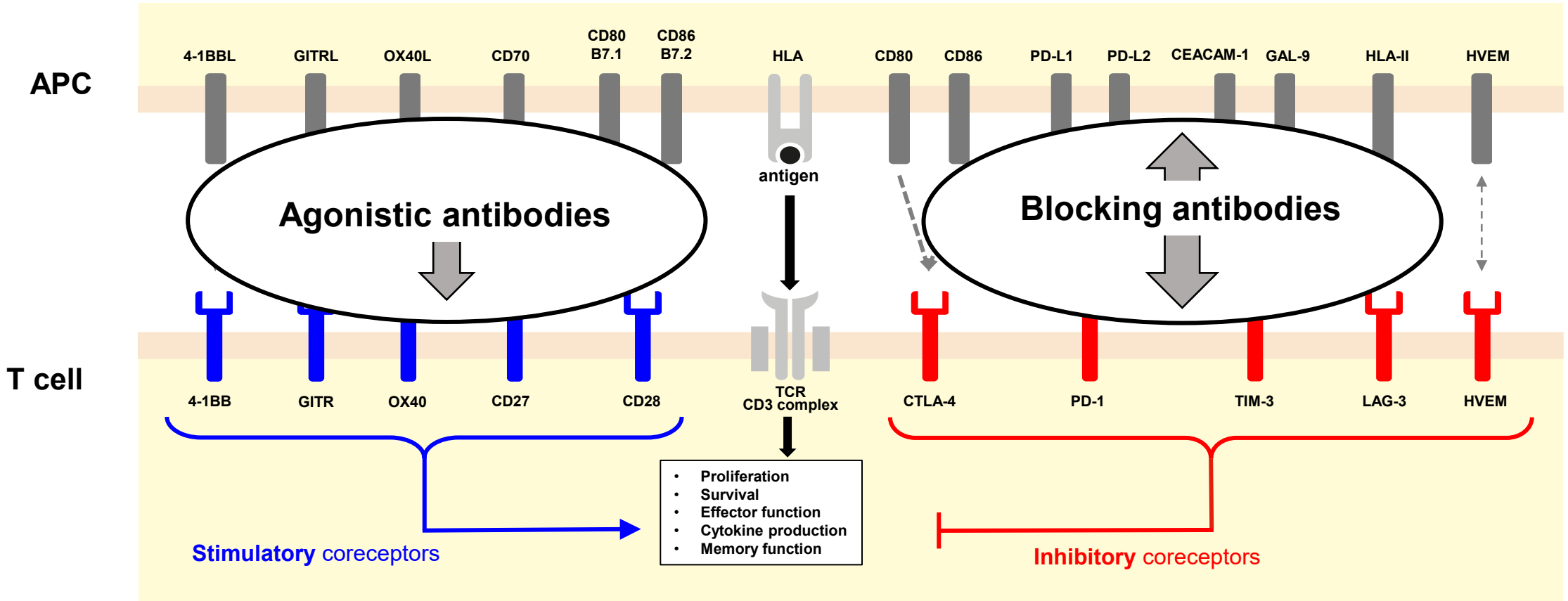


APC, antigen-presenting cell; CD, cluster of differentiation; CEACAM-1, carcinoembryonic antigen-related cell adhesion molecule 1; CTLA-4, cytotoxic T-lymphocyte associate protein 4; GAL-9, galectin 9; GITRL, glucocorticoid-induced TNF receptor ligand; HLA, human leukocyte antigen; HVEM, herpesvirus entry mediator; LAG-3, lymphocyte activating 3; PD-L1/2, programmed death-ligand 1/2; TCR, T-cell receptor; TIM-3, T cell immunoglobulin and mucin domain 3; TNF, tumor necrosis factor.

Adapted from Kershaw et al. Nat Rev Cancer 2013;13:525–41.

Manipulation of T-cell regulatory pathways by the use of antibodies can increase T-cell activity

- **Blocking** the effects of inhibitory coreceptors or **activating** stimulatory coreceptors promotes T-cell activation; this has been shown to have **clinical antitumor effects** in cancer patients



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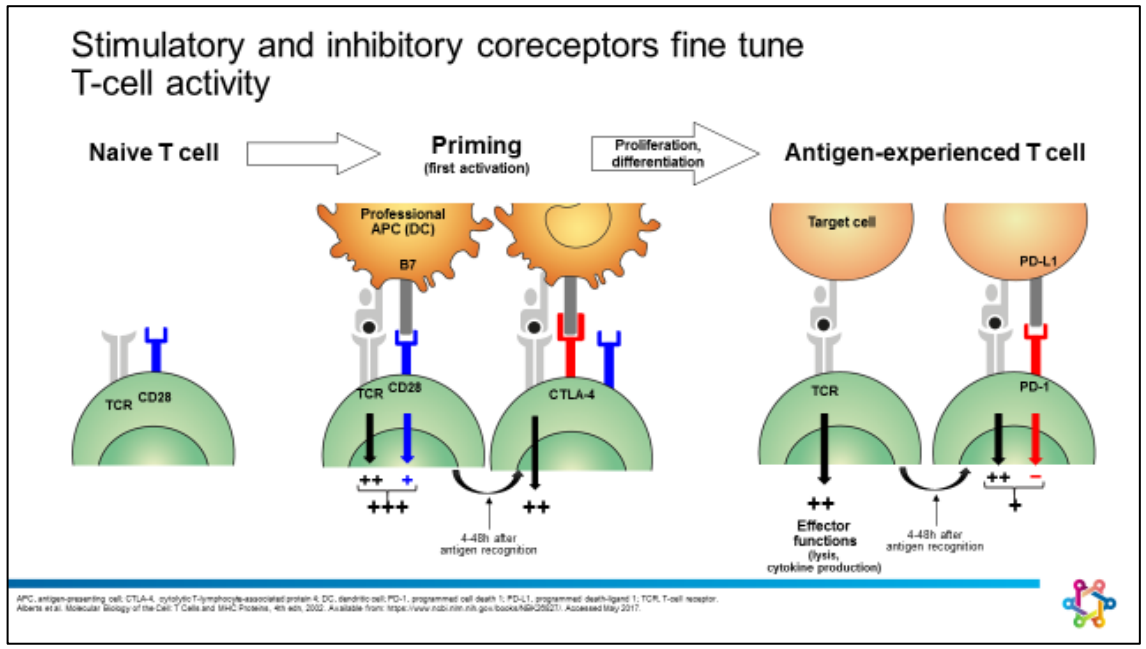
Clinical relevance
Modulation of T-cell activity



➢ Checkpoint inhibitors

Monoclonal antibodies that block T-cell inhibitory coreceptors to increase T-cell activity and are used in oncology

- **Anti-CTLA-4 antibodies**

  Ipilimumab, indicated for melanoma, RCC, NSCLC, mesothelioma, CRC and OSCC

- **Anti-PD-1 antibodies**

  Nivolumab, indicated for melanoma, NSCLC, RCC, cHL, SCCHN, urothelial carcinoma, mesothelioma, CRC, oesophageal/GEJ cancer and Gastric/Oesophageal/GEJ adenocarcinoma

  Pembrolizumab, indicated for melanoma, NSCLC, cHL, urothelial carcinoma, SCCHN, RCC, OS, triple-negative breast cancer, endometrial carcinoma, cervical cancer and MSI-H cancers (CRC, endometrial carcinoma and gastric cancer)

- **PD-L1 antibodies**

  Atezolizumab, indicated for urothelial carcinoma, NSCLC, breast cancer and hepatocellular carcinoma

  Avelumab, indicated for Merkel cell carcinoma, urothelial carcinoma and RCC

  Durvalumab, indicated for NSCLC and ES-SCLC

  Cemiplimab, indicated for NSCLC, BCC and CSCC

- **Anti-PD-1 antibody + Anti-Lag-3[a1]**

  Nivolumab + **Relatlimab**, indicated for melanoma

[a]Positive CHMP opinión on July 2022

BCC, basal cell carcinoma; cHL, classical Hodgkin lymphoma; CRC, colorectal cancer; CSCC, cutaneous squamous cell carcinoma; CTLA-4, cytolytic T-lymphocyte-associated protein 4; ES-SCLC, extensive-stage small cell lung cancer; GEJ, gastro-esophageal junction; NSCLC, non-small-cell lung cancer; OS, oesophageal squamous; OSCC, oesophageal squamous cell carcinoma; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; PI, prescribing information. RCC, renal cell carcinoma; SCCHN, squamous cell cancer of the head and neck. 1. EMA, CHMP, Summary of opinion, July 2022: 2https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-opdualag_en.pdf Always refer to the SmPC. All SmPCs are available from http://www.ema.europa.eu/ema/. Accessed August 1, 2022

Key scientific concepts that underpin current immunotherapy for cancer

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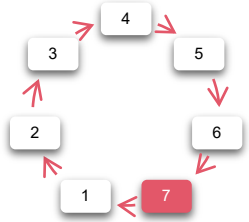
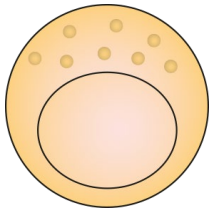
Professor P. Coulie, personal communication.

Other modalities of tumor cell killing by the immune system



Innate immune system

NK cells



- With antibodies (antibody-dependent cellular cytotoxicity)
- Without antibodies

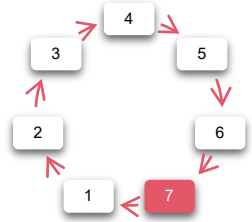
Adaptive immune system

Antibodies

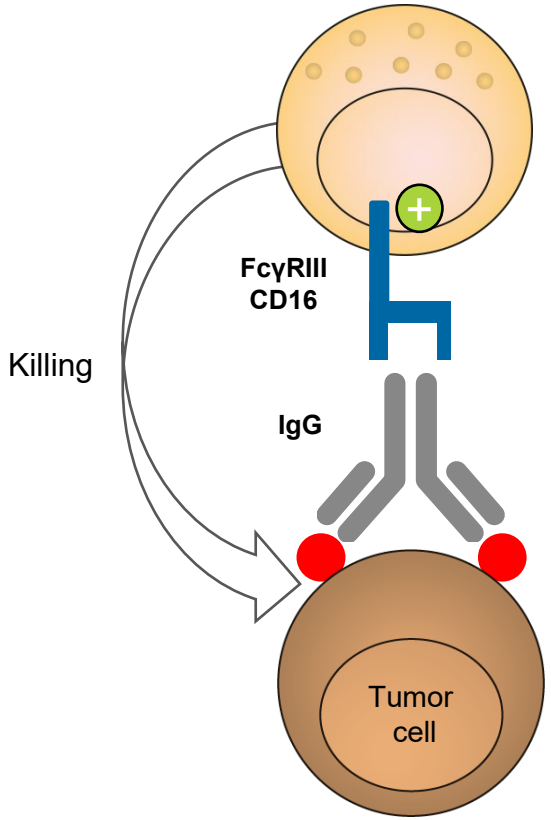
- Through NK cells (antibody-dependent cellular cytotoxicity)
- Through complement-mediated cytotoxicity

NK, natural killer.
Professor P Coulie, personal communication.

Tumor cell killing by NK cells with antibodies



Antibody-dependent cellular cytotoxicity



NK cells target cells recognized by IgG antibodies for destruction

Part of the anticancer activity of the following monoclonal antibodies is mediated by NK cells:

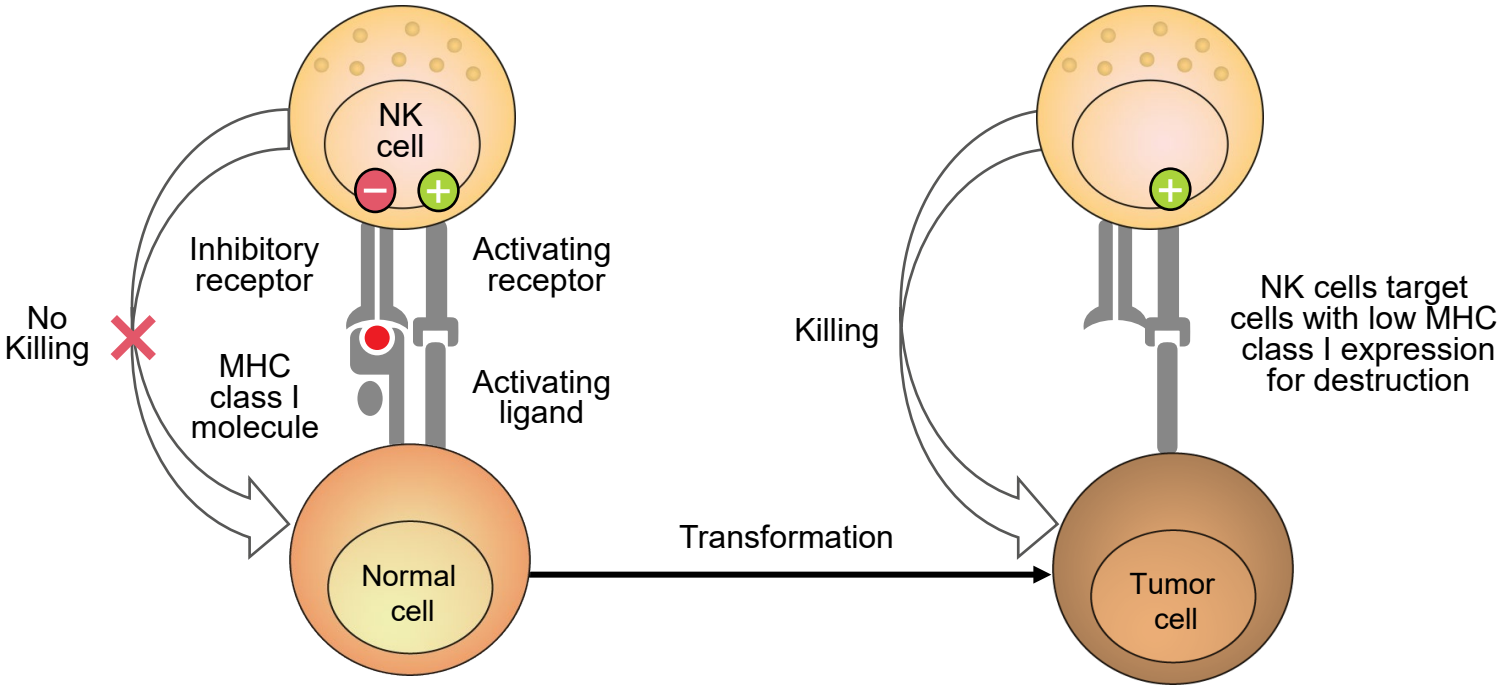
- Rituximab
- Trastuzumab

The Fc part of IgG antibodies can be engineered to allow or abrogate binding to FcγRIII and NK cell activation

CD, cluster of differentiation; Ig, immunoglobulin; NK, natural killer.
Boyerinas et al. Cancer Immunol Res 2015;3:1148–57.

Tumor cell killing by NK cells without antibodies

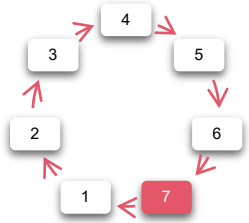
- NK cell activation is controlled by a balance between signals mediated via activating and inhibitory receptors[1]
- During tumor progression, tumor variants that upregulate ligands for inhibitory receptors and/or lose ligands for activating receptors may evolve, potentially allowing tumors to escape NK-cell-mediated recognition[1]



MHC, major histocompatibility complex; NK, natural killer.

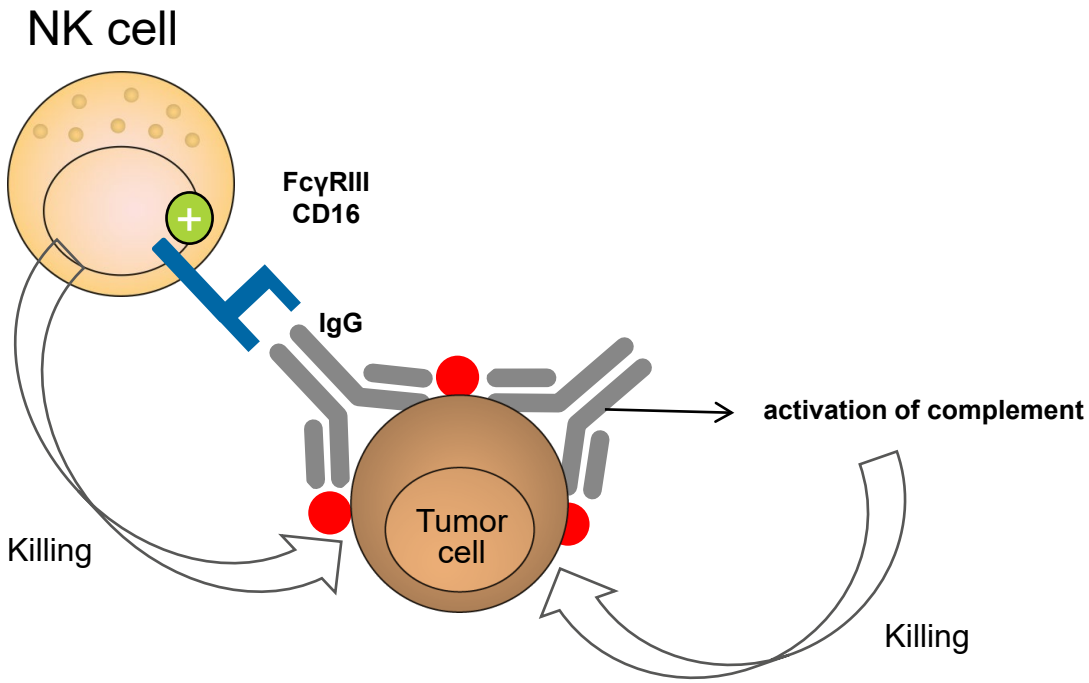
1. Ljunggren & Malmberg. Nat Rev Immunol 2007;7:329–39. 2. Pandya et al. J Immunol Res 2016;2016:4273943.

Tumor cell killing by the adaptive immune system

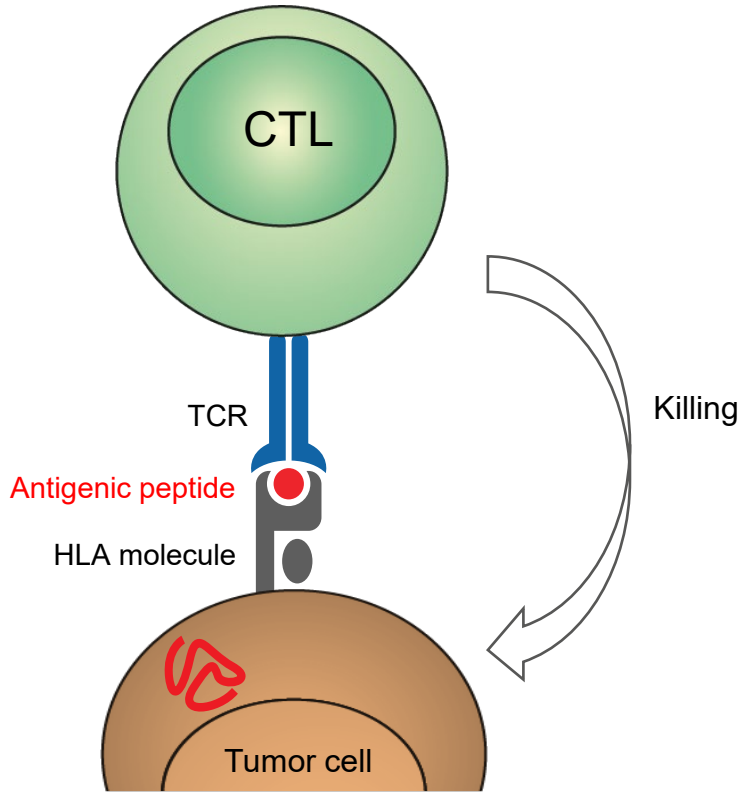


Direct recognition of **extracellular** tumor antigens by antibodies

(**CAR-T** cells are another modality of direct recognition of extracellular tumor antigens)

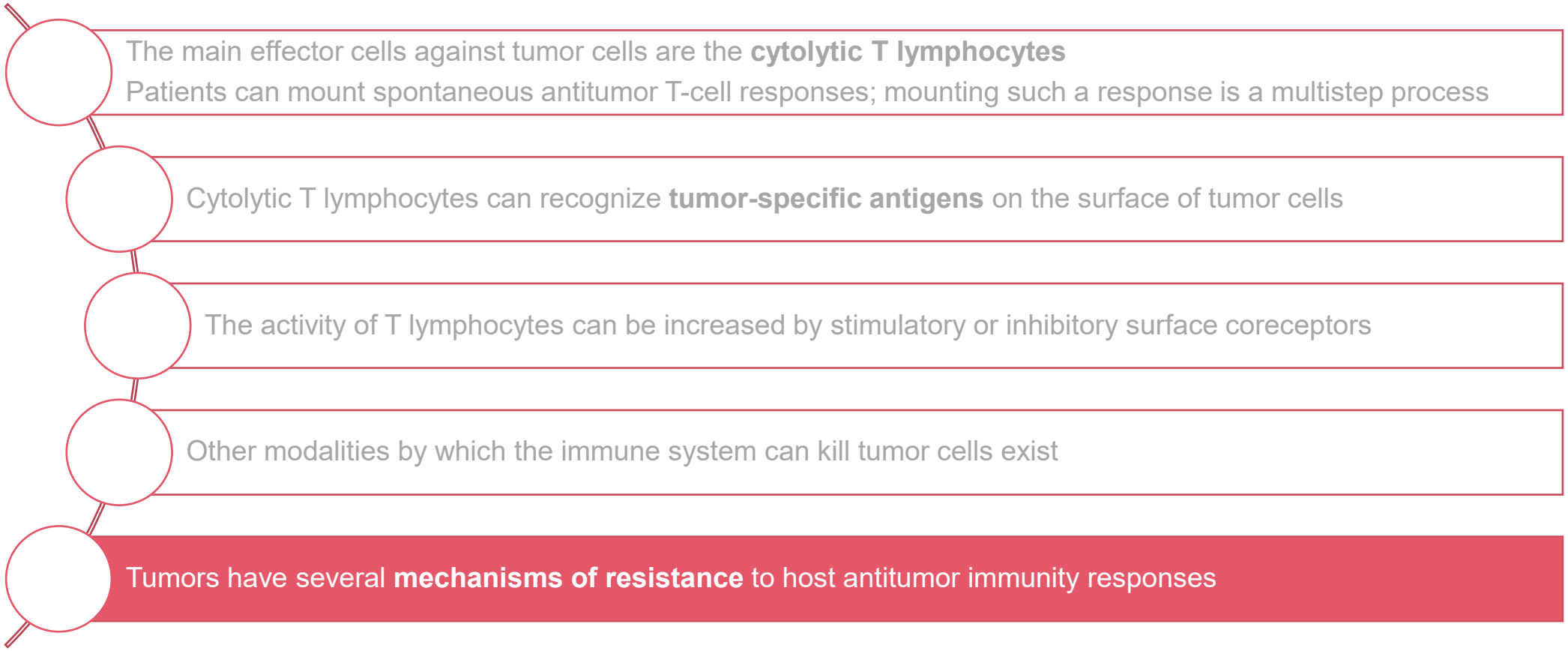


Recognition of **intracellular** tumor antigens by CTLs



CTL, cytolytic T lymphocyte; CD, cluster of differentiation; HLA, human leukocyte antigen; Ig, immunoglobulin; NK, natural killer; TCR, T-cell receptor.
Professor P Coulie, personal communication.

Key scientific concepts that underpin current immunotherapy for cancer



Professor P. Coulie, personal communication

Tumor resistance to immune attack

- The genetic instability of tumors and the selection by the immune system that destroys tumor cells create a 'darwinian machine', i.e. rounds of variation, selection and inheritance
- For all treatments that eliminate tumor cells, the residual cells resist the treatment
- If one admits that all incipent tumors are recognized by the host's immune system, clinically apparent tumors must have developed, prior to immunotherapy, mechanisms to avoid immune elimination[2]
- There are three main mechanisms of tumor resistance[2]

Loss/decrease of antigenicity[2]

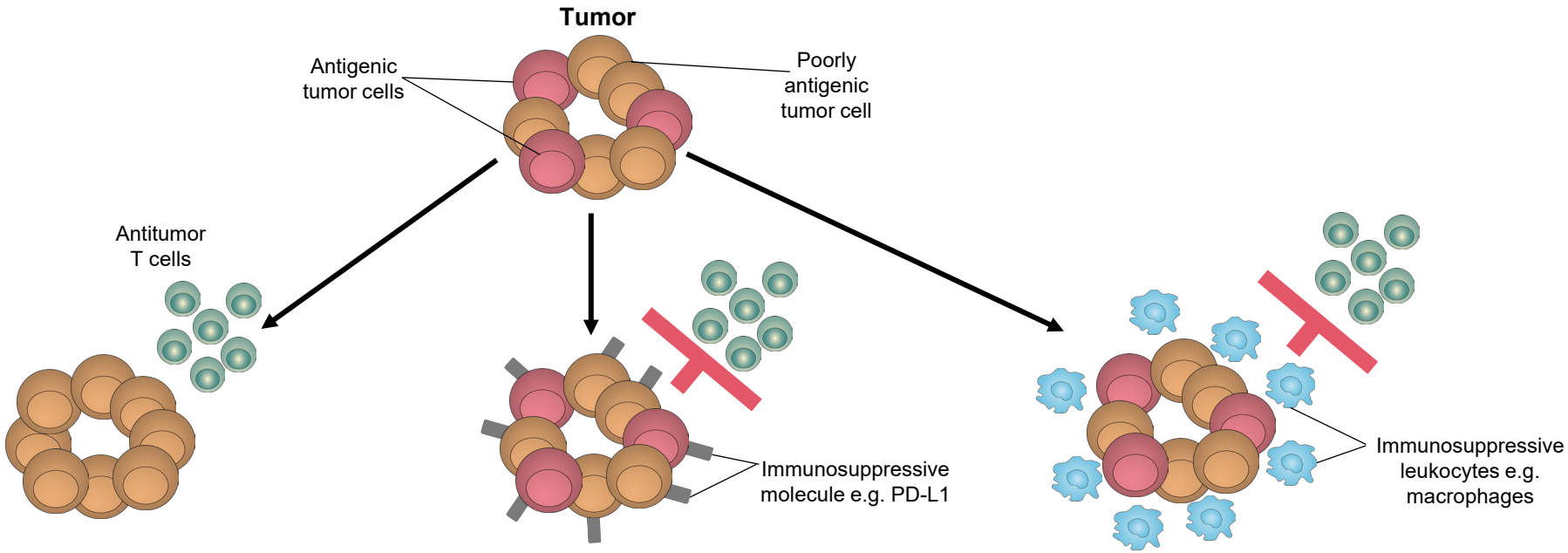
Loss/decrease of immunogenicity[2]

Tumor-driven immunosuppression[2]

TME, tumor microenvironment

1. Mittal et al. Curr Opin Immunol 2014;27:16–25. 2. Beatty & Gladney. Clin Cancer Res 2015;21:687–92. 3. Professor P. Coulie, personal communication.

Mechanisms of tumor resistance to immune attack



Loss/decrease of antigenicity[1,2]

- Can be achieved by downregulation or loss of expression of the antigenic peptide or antigen processing machinery (e.g. loss of HLA, ß2m, TAP)
- Can be irreversible (e.g. mutations, gene deletions) or reversible (mostly through IFNγ)[2]

Loss/decrease of immunogenicity[1]

- Tumors with adequate antigenicity for immune recognition can decrease their immunogenicity through modulation of checkpoint molecules
- e.g. IFN-γ produced by TILs can induce upregulation of PD-L1 on tumor cells (an example of adaptive resistance)

Immunosuppressive environment[1]

- Alterations in oncogenes and tumor suppressor genes can result in an immune reaction that suppresses or inhibits antitumor immunity within the TME

Learn more about the TME and immunosuppression

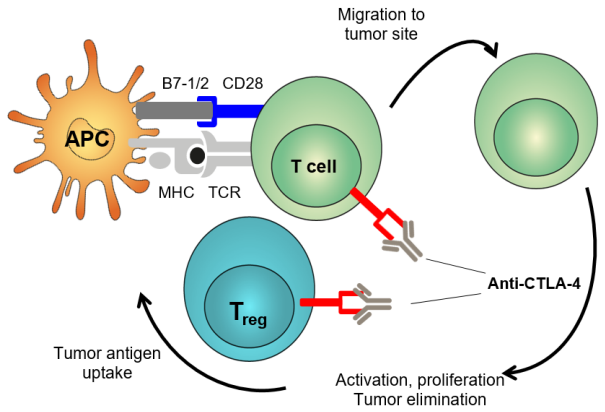
ß2m, beta$_2$ macroglobulin; HLA, human leukocyte antigen; IFN, interferon; PD-L1, programmed-death ligand 1; TAP, transporter associated with antigen presentation; TIL, tumor-infiltrating lymphocyte; TME, tumor microenvironment.

Adapted from Beatty & Gladney. Clin Cancer Res 2015;21:687–92. 2. Professor P. Coulie, personal communication.

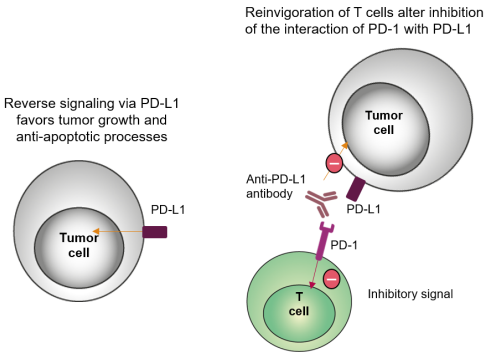
Clinical relevance

Immunoregulatory, or 'immune checkpoint' molecules in cancer treatment

CTLA-4 'checkpoint' inhibitors: targeting CTLA-4



PD-1/L1 'checkpoint' inhibitors: targeting PD-1 and PD-L1



- Immune checkpoints such as **CTLA-4** and **PD-1** serve vital roles in regulating T-cell responses[1]
- In cancer, T-cells undergo chronic exposure to continuous antigen stimulation, which can lead to deteriorated T-cell function and constitutive action of immune checkpoints, termed '**exhaustion**'[1]
- This state is commonly associated with poor tumor control[1]
- Immune checkpoints have been assessed as **potential targets in the treatment of cancer**, and have been found to be effective in reinvigorating exhausted T cells by restoring immunity to eliminate cancer[2]

Newly defined immune checkpoints:
LAG-3 , TIM-3 and TIGIT[3]

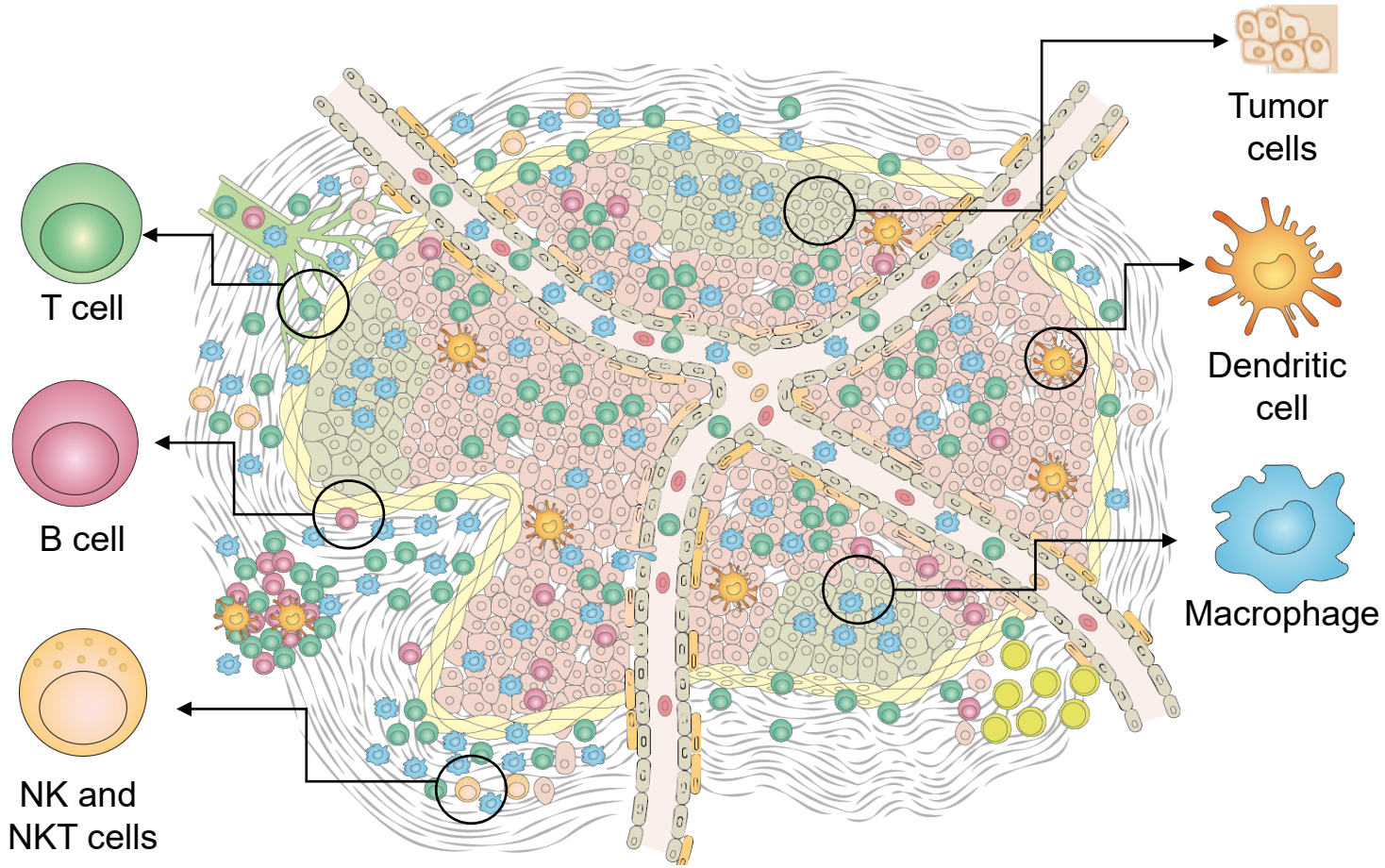
APC, antigen-presenting cell; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte associated protein 4; LAG3, lymphocyte activation gene 3; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TCR, T-cell receptor; TIGIT, T-cell immunoreceptor; TIM-3, T cell immunoglobulin and mucin domain 3; T_{reg}, regulatory T-cell.

1. Beatty & Gladney. Clin Cancer Res 2015;21:687–92. 2. Buchbinder & Desai. Am J Clin Oncol 2016;39:98–106. 3. Tsai & Hsu. J Biomed Sci 2017;24:35–43.

Back to antitumor responses
Back to tumor resistance

The tumor microenvironment

- Interactions between tumor and normal cells, particularly immune cells, create the TME
- The TME plays a pivotal role in tumor growth and metastasis[1,2]
- There are numerous tumor-driven immunosuppressive mechanisms at work within in the TME, including:[3]
  - A shortage of nutrients e.g. tryptophan (downgraded by IDO-1), arginine, oxygen
  - Immunosuppressive soluble factors e.g. TGF-ß, IL-10, galectins, PGE2, extracellular adenosine
  - Immunosuppressive cells e.g. T_{regs}, myeloid-derived suppressor cells
  - Inhibitory cofactors e.g. constitutive expression of PD-L1 on tumor cells

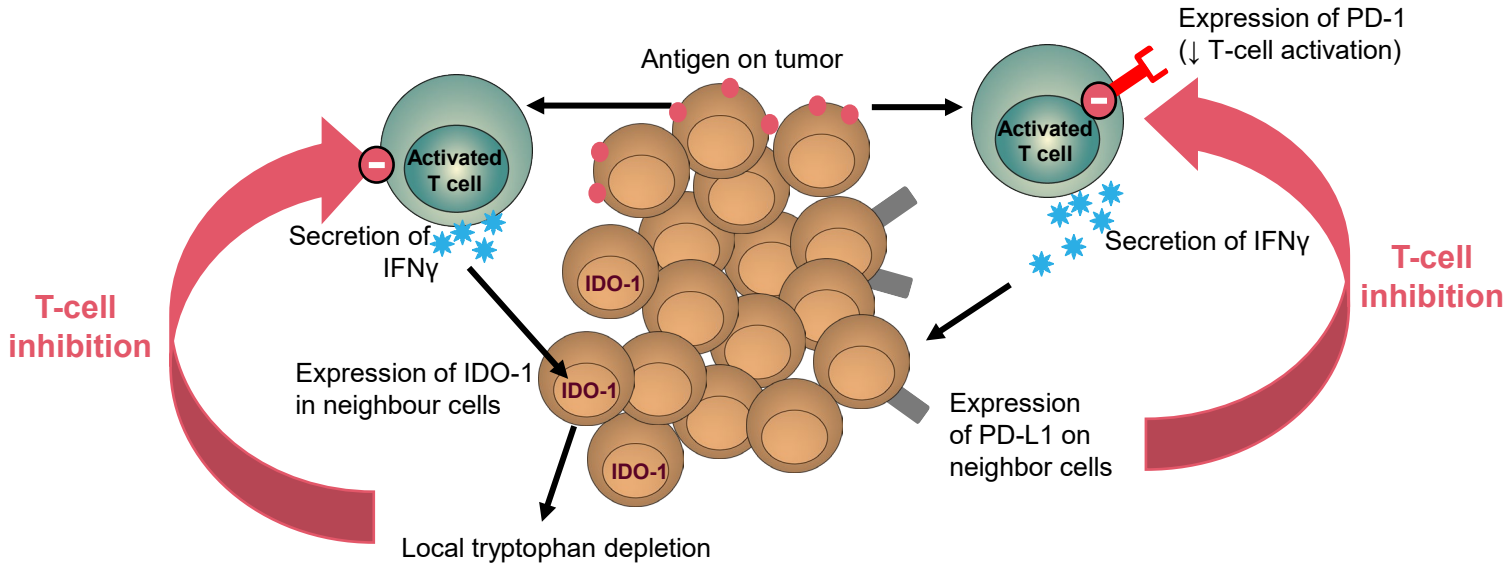


IDO-1, Indoleamine-pyrrole 2,3-dioxygenase-1; IL, interleukin; NK, natural killer; NKT, natural killer T; PD-L1, programmed death-ligand 1; PGE-2. prostaglandin E2; TGF-ß, transforming growth factor beta; TME, tumor microenvironment; T_{reg}, regulatory T cell.

1. Balkwill et al. J Cell Sci 2012;125:5591–6. 2. Chen et al. BMC Medicine 2015;13:45. 3. Professor P. Coulie, personal communication.

TILs: the numbers game

- Insufficient recruitment of immune cells into the tumor can also promote tumor resistance to the immune response[1]
- Antitumor T cells are inhibited though inhibitory coreceptors such as PD-1[1]
- Adaptive resistance describes the induction of immune suppressive pathways in the tumor (such as PD-1) following active immune attack on the tumor[2]
- It is a scalable process where the magnitude of immune suppression matches the magnitude of the immune attack; the net balance between suppression and attack determines the durability of the anti-tumor response and tumor outcome[2]
- Adaptive resistance is mediated via physiologic negative feedback systems[1]



- PD-1 and PD-L1 inhibit the function of TILs, causing tumor cells to evade immune response[3]

IDO, Indoleamine-pyrrole 2,3-dioxygenase-1; IFNγ, interferon gamma; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; TIL, tumor-infiltrating lymphocyte; T_{reg}, regulatory T.

1. Professor P. Coulie, personal communication. 2. McGray & Bramson. Adv Exp Med Biol 2017;1036:213–27. 3. Beatty & Gladney. Clin Cancer Res 2015;21:687–92. Figure adapted from 1.

Mounting antitumor T-cell responses: the prognostic value of TILs

There is a demonstrable correlation between the level of immune cell infiltration and prognosis in a number of cancers

Tumor type	Immune cell infiltrate	Clinical outcome
Melanoma	CD4 T cell	Improved survival and spontaneous tumor regression
Breast cancer	Intratumoral T cells, including CD8 T cells and Th1 CD4 T cells	Improved survival and earlier stage disease
Ovarian cancer	T cells, including CD8 T cells	Improved survival and reduction in VEGF
NSCLC	CD4 and CD8 T cells	Improved prognosis in early stage and advanced stage disease
Breast cancer	High T_{reg} cells	Poor prognosis disease (high-tumor grade, ER-negative negative lymph node positive); reduced disease-free and overall survival
Melanoma	High T_{reg} cells	Increased recurrence rate
Ovarian cancer	High T_{reg} cells	Poor prognosis
NSCLC	High T_{reg} cells	Increased risk of recurrence in resected early stage disease

High CD4 and CD8 T cell infiltration usually indicates a clinically relevant antitumor immune response, and is associated with a positive prognosis

T_{reg} cells are immunosuppressive; tumors with high T_{reg} infiltration are associated with a poorer prognosis

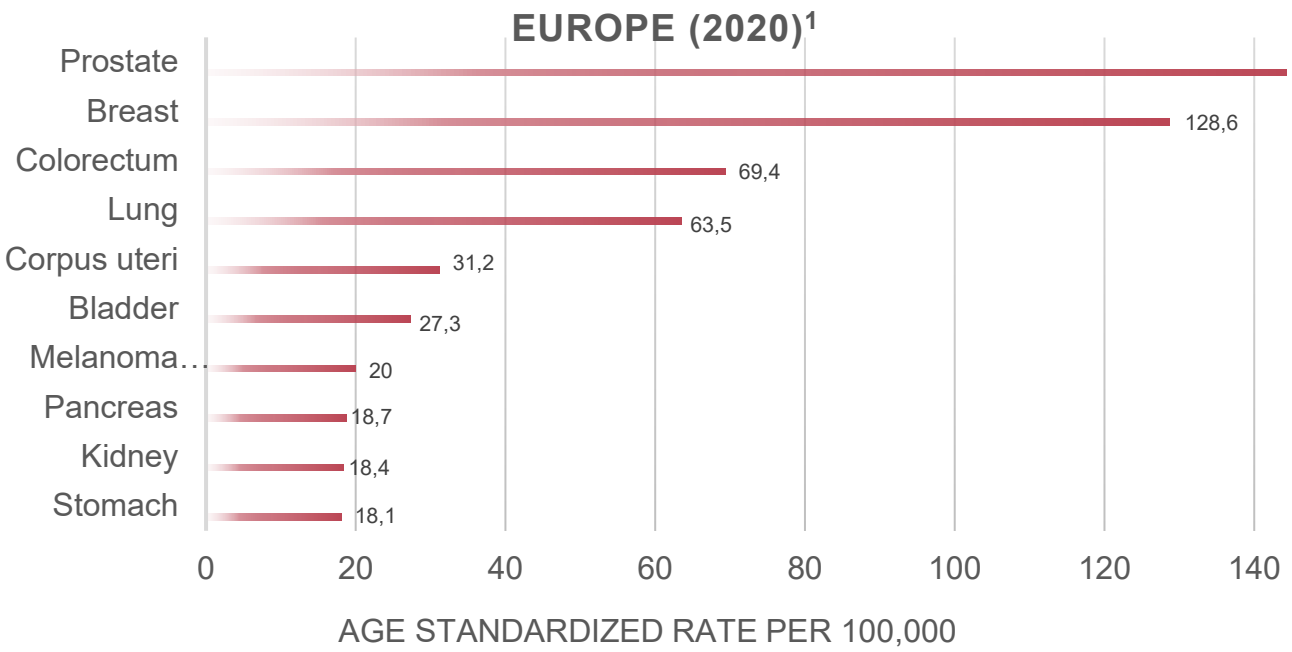
CD, cluster of differentiation; ER, estrogen receptor; NSCLC, non-small-cell lung carcinoma; Th, helper T; T_{reg}, regulatory T; TIL, tumor infiltrating lymphocyte; VEGF, vascular endothelial growth factor.
Spurrell and Lockley. Ecancermedicalscience 2014;8:441.

Immunotherapy for solid tumors

Immunotherapy for malignancies

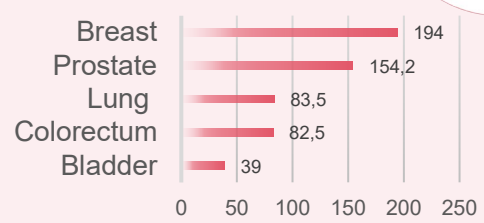
Most frequent solid tumor cancers in Europe

ESTIMATED INCIDENCE FOR BOTH SEXES

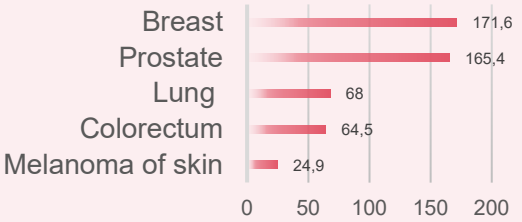


COUNTRY-SPECIFIC (2020)

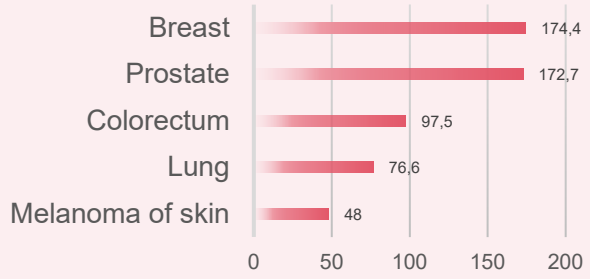
- Belgium[2]



- Luxembourg[3]



- The Netherlands[4]



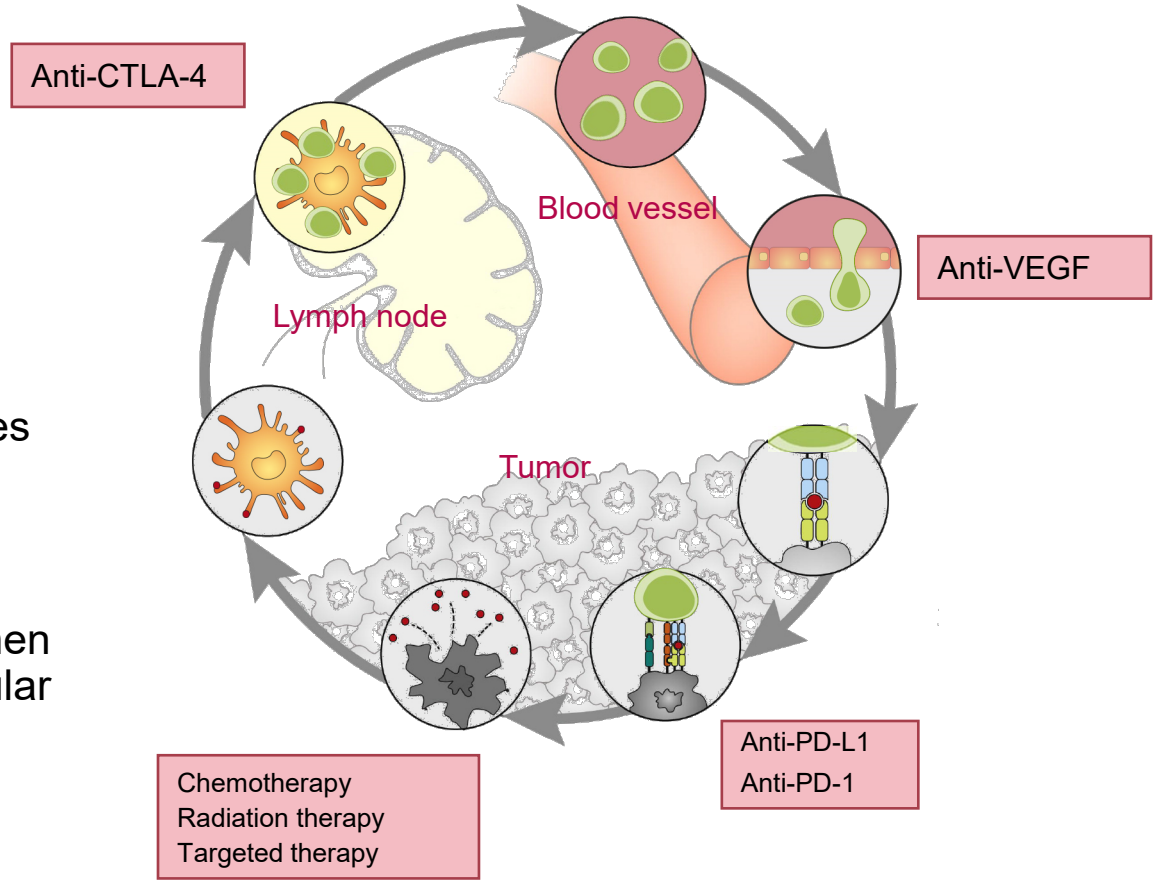
1. EUCAN. Available from http://eco.iarc.fr/EUCAN/Country.aspx?ISOCountryCd=968. 2. EUCAN. Belgium. Available from http://eco.iarc.fr/EUCAN/Country.aspx?ISOCountryCd=56.. 3. EUCAN. Luxembourg. Available from http://eco.iarc.fr/EUCAN/Country.aspx?ISOCountryCd=442. 4. EUCAN. Netherlands. Available from http://eco.iarc.fr/EUCAN/Country.aspx?ISOCountryCd=528. All URLs accessed July 26, 2022.

Immunotherapeutic agents that target the TME

- The TME is an integral part of cancer and, therefore, offers many effective treatment targets[1]

For example:

- Bevacizumab is a monoclonal antibody that blocks **angiogenesis** by inhibiting VEGF-A
- Pembrolizumab and nivolumab are monoclonal antibodies that target the **PD-1 receptor** of lymphocytes
- Ipilimumab is a **CTLA-4 blocker** that increases activation of $CD4^+$ and $CD8^+$ effector cells
- **CAR T-cell immunotherapy** involves collecting and then modifying a patient's own T cells to recognize a particular TAA, selectively expressed on malignant cells[2]



CAR, chimeric antigen receptor; CTLA-4, cytotoxic T-lymphocyte associated protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TAA, tumor-associated antigen; TME, tumor microenvironment; VEGF-A, vascular endothelial growth factor A.

1. Chen et al. BMC Medicine 2015;13:1–13. 2. Yu et al. Journal of Hematology & Oncology 2017;10:1–13.

Selected examples[a] of immunotherapies for solid tumor malignancies

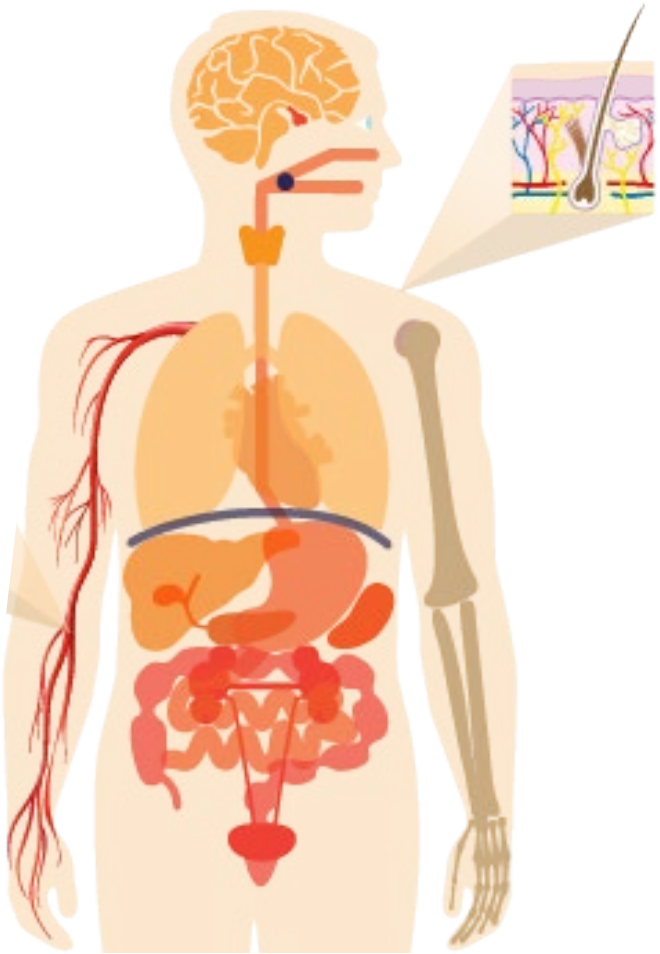
Gastric cancer
- Trastuzumab[4]
- Nivolumab[1]
- Pembrolizumab[2]

HNSCC
- Nivolumab[1]
- Pembrolizumab[2]

RCC
- Nivolumab[1]
- Pembrolizumab[2]
- Ipilimumab[6]
- Avelumab[7]

Mesothelioma
- Nivolumab[1]
- Ipilimumab[6]

NSCLC
- Nivolumab[1]
- Pembrolizumab[2]
- Atezolizumab[3]
- Ipilimumab[6]
- Durvalumab[8]
- Cemiplimab[9]



CRC
- Pembrolizumab[2]
  Nivolumab[1]
- Ipilimumab[6]

Breast cancer
- Trastuzumab[4]
- Pertuzumab[5]
- Atezolizumab[3]

Melanoma
- Nivolumab[1]
- Pembrolizumab[2]
- Ipilimumab[6]
- Avelumab[7]
- Cemiplimab[9]

Urothelial carcinoma
- Nivolumab[1]
- Pembrolizumab[2]
- Atezolizumab[3]

Esophageal cancer
- Nivolumab[1]
- Pembrolizumab[2]
- Durvalumab[8]

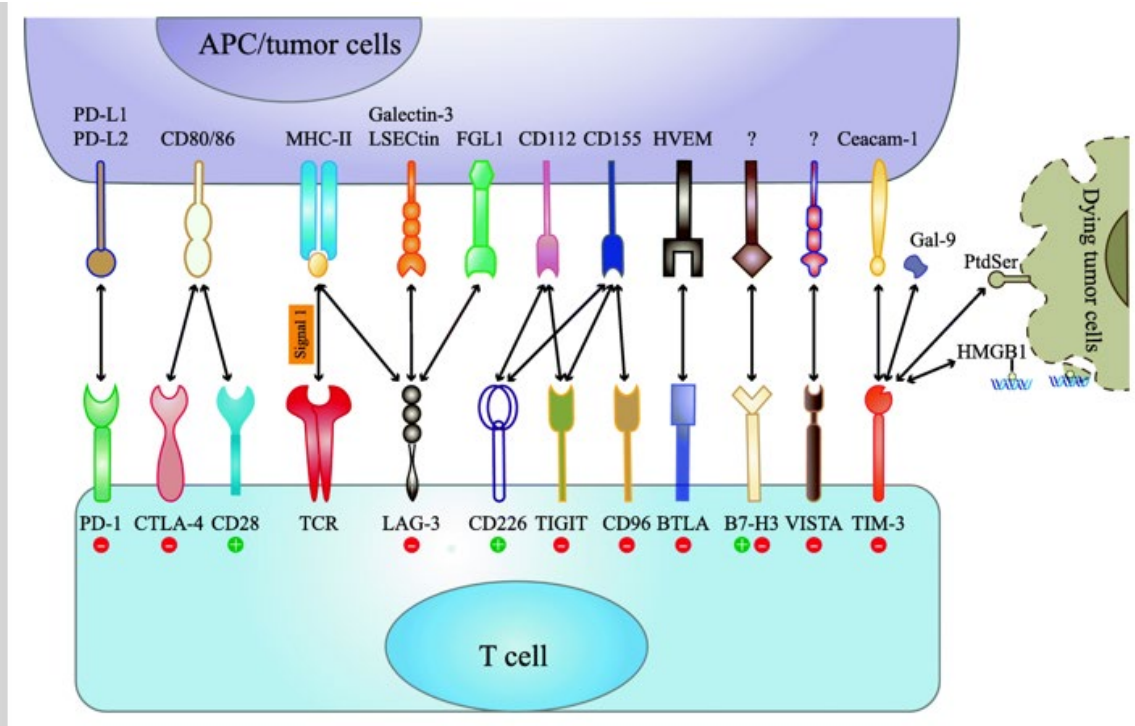
[a]These lists contain only selected examples of EMA licensed immunotherapies and are not exhaustive. For details of other monoclonal antibodies licensed to treat solid tumors, see Module 2: Types of immunotherapy.

EMA, European Medicines Agency; HCC, hepatocellular carcinoma; CRC, colorectal cancer; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung carcinoma; RCC, renal cell carcinoma;
1. Opdivo SmPC. 2. Keytruda SmPC. 3. Tecentriq SmPC. 4. Herceptin SmPC. 5. Perjeta SmPC. 6. Yervoy SmpC. 7. Avelumab SmPC. 8. Durvalumab SmPC. 9. Cemiplimab SmPC. All SmPCs available from: http://www.ema.europa.eu/. All URLs accessed July 27, 2022.

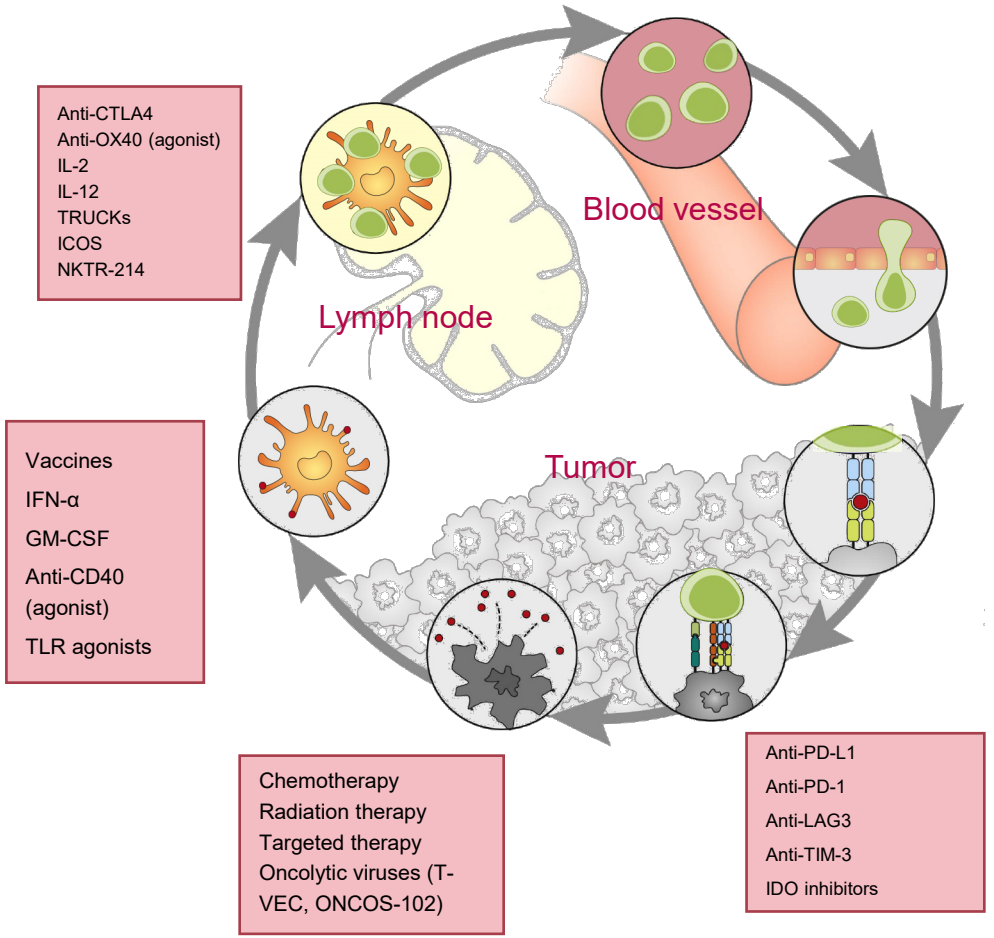
For full information of individual agents, always refer to the Summary of Product Characteristics

Future prospects for immunotherapy in solid tumors

Current and emerging immune checkpoint receptors and their respective ligands[1]



Immunotherapeutic targets investigated in cancer[2-4]



Ab, antibody; BTLA, B- and T-cell lymphocyte attenuator; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte associated protein 4; GITR, glucocorticoid-induced tumor necrosis factor-like receptor; GM-CSF, granulocyte macrophage colony-stimulating factor; HVEM, herpes virus entry mediator; ICOS, inducible T-cell costimulatory; IDO, indoleamine 2,3-dioxygenase; IFN-α, interferon alpha; IL, interleukin; LAG-3, lymphocyte activation gene 3; PD-1, programmed cell death protein 1; TIM-3, T-cell immunoglobulin and mucin-domain 3; TLR, toll-like receptor; TRUCK, T cell redirected for universal cytokine mediated killing; T-VEC, talimogene laherparepvec; VISTA, V-domain Ig suppressor of T-cell activation.

1. Quin et al. Molecular Cancer 2019;18:155. 2. Chen & Mellman. Immunity 2013;39:1–10. 3. Kerre. Belgian J Hematol 2017;8:94–101; 4. Murciano-Goroff et al. Cell Research 2020;30:507–519

Immunotherapy in hematology

Immunotherapy for malignancies

An overview of selected hematologic malignancies relevant to immunotherapy

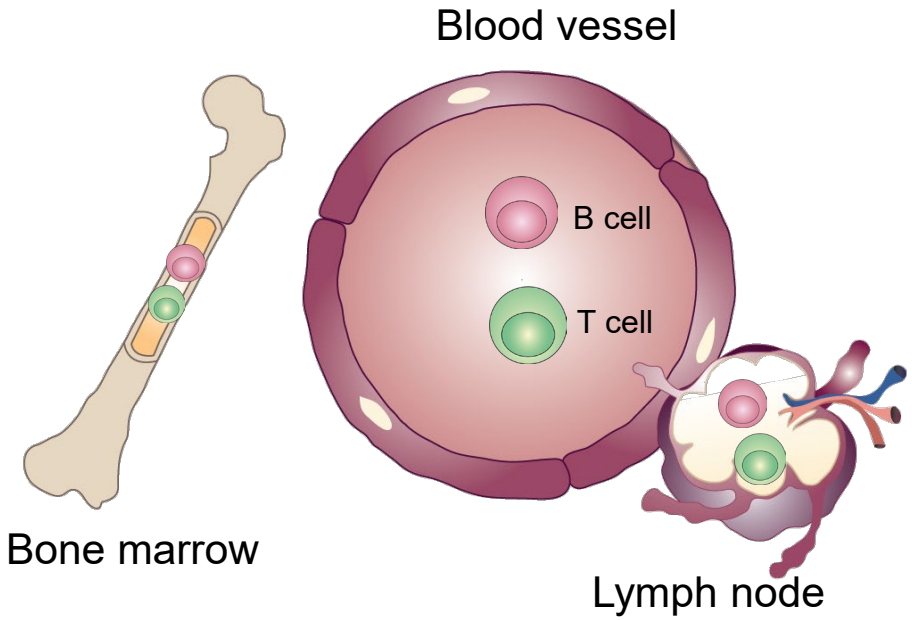
- Various types of hematologic malignancies affect the bone marrow, lymph nodes and blood – all of which are immune organs

Myeloproliferative disorders

Bone marrow disorders that lead to an excess of one or more types of myeloid cell
e.g. **CML**

Myelodysplastic syndromes

Bone marrow disorders that result in clonal production of dysplastic myeloid cells. Owing to failing to sufficiently mature, blast cells arise
e.g. **AML** (develops in ~1/3 patients)



Leukemia

A number of diseases that result in a clonal proliferation of white blood cells
e.g. **ALL, CLL, Hairy cell leukemia**

Lymphoma

Involve the clonal proliferation of lymphoid cells
e.g. **classical HL, nHL**

Myeloma

Involve the clonal proliferation of plasma cells
e.g. **Light chain/Bence Jones and non-secretory myeloma**

ALL, acute lymphoblastic leukemia; AML, acute myeloid (myelogenous) leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid (myelogenous) leukemia; HL, Hodgkin's lymphoma; nHL, non-Hodgkin lymphoma.

1. Sant et al. Blood 2010;116:3724–34. Image adapted from Di Rosa & Pabst. Trends Immunol 2005;26:360–6.

Licensed immunotherapies for hematologic malignancies

- Hematologic malignancies have unique features compared with solid tumors, such as a number of targetable surface antigens, which make them strong targets for immunotherapy[1,2]

Monoclonal antibodies	Antibody-drug conjugates	BiTE monoclonal antibodies	Immune checkpoint blockade	CAR T cell therapy
Rituximab (CLL, NHL) **Obinutuzumab** (CLL, FL) **Alemtuzumab**[a] (CLL) **Daratumumab** (MM) **Elotuzumab** (MM) **Isatuximab** (MM) **Mogamulizumab**[a] (NHL) **Tafasitamab** (DLBCL)	**Brentuximab** (HL, systemic anaplastic large cell lymphoma) **Ibritumomab tiuxetan** (NHL) **Inotuzumab ozogamicin** (ALL) **Polatuzumab vedotin** (NHL) **Gemtuzumab ozogamicin** (AML) **Tragaxofusp** (BPDCN) **Belantamab mafodotin** (MM)	**Blinatumomab** (ALL)	**Nivolumab** (cHL) **Pembroluzimab** (cHL)	**Axicabtagene ciloleucel** (NHL) **Tisagenlecleucel** (ALL, DLBCL) **Brexucabtagene autoleucel** (MCL) **Idecabtagene vicleucel** (MM) **Lisocabtagene maraleucel (**DLBCL, PMBCL, FL3B) **Ciltacabtagene autoleucel** (MM)

[a]Alemtuzumab and Mogamulizumab, approved by FDA but not EMA to date.

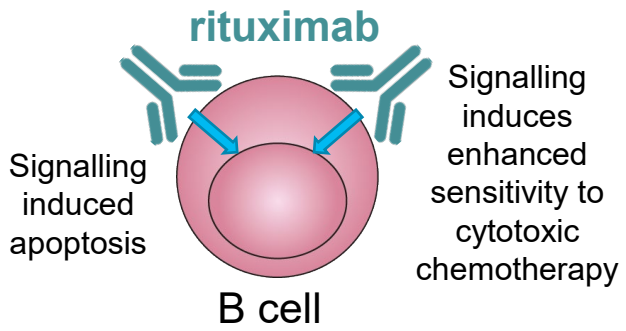
ALL, acute lymphoblastic leukemia; BPDCN: blastic plasmacytoid dendritic cell neoplasm; CAR, chimeric antigen receptor; cHL, classical Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; FL3B, follicular lymphoma grade 3B; HCL, hair cell leukemia; HL, Hodgkin lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; PMBCL, primary mediastinal large B-cell lymphoma. 1. Im & Pavletic. J Hematol Oncol 2017;10:94. 2. i-Yoon Noh et al. Int. J. Mol. Sci. 2020, 21, 8000;. Prescribing information available from: http://www.ema.europa.eu/ema/, https://www.fda.gov/ and https://www.cancerresearch.org/immunotherapy/cancer-types/leukemia . All URLs accessed Aug 22, 2022.

For full information of individual agents, always refer to the Summary of Product Characteristics

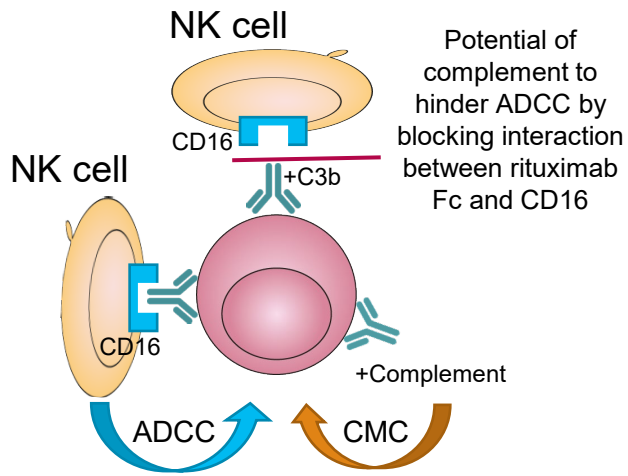
Monoclonal antibodies for hematologic malignancies: a key example

- Rituximab – an anti-CD20 antibody – was the first monoclonal antibody to be approved for a hematological malignancy by the EMA in 1998[1]
- Rituximab-mediated signaling, CMC and ADCC are mechanisms by which rituximab likely exerts its anti-tumor action[2]

Rituximab mechanisms of action[2]



Direct rituximab/CD20-induced signalling



Rituximab-induced CMC and ADCC

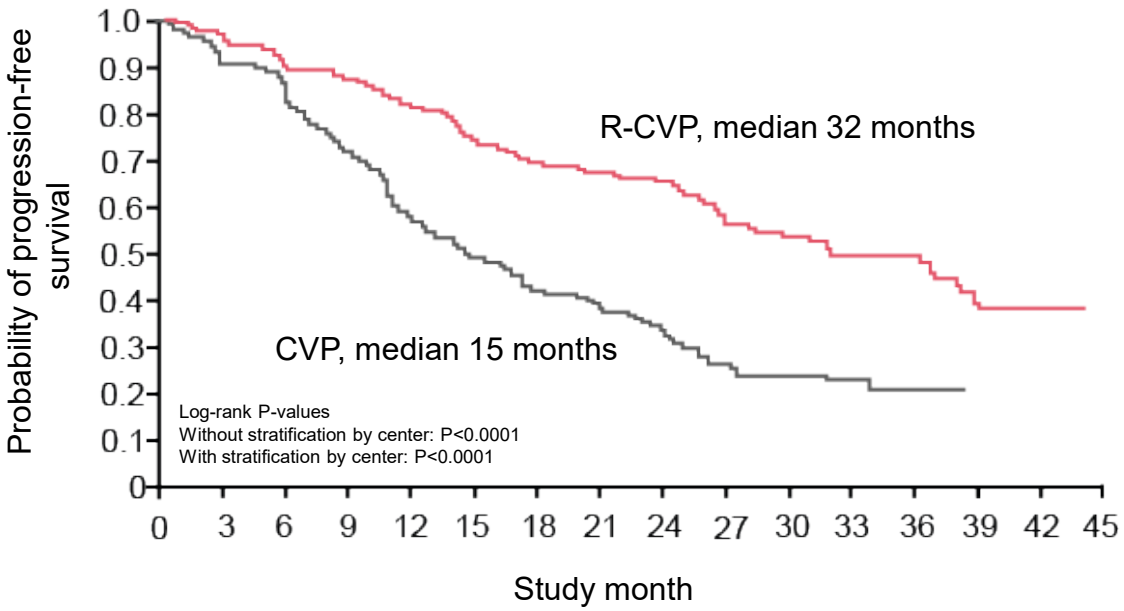
Selected monoclonal antibodies: licensed indications

Rituximab[3]	• Non-Hodgkin lymphoma: FL (first-line advanced; maintenance; relapsed/refractory) DLBCL (with CHOP); BL; BAL or BLL. • Chronic lymphocytic leukemia: previously untreated and relapsed/refractory • Rheumatoid arthritis: with MTX • Granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis: with glucocorticoids • Pemphigus vulgaris: moderate to severe

ADCC: antibody-dependent cellular cytotoxicity; BAL, Burkitt leukaemia (mature B-cell acute leukaemia); BL, Burkitt lymphoma; BLL, Burkitt-like lymphoma. CD, cluster of differentiation; CDC: complement mediated cytotoxicity; CHOP, cyclosphamide, hydroxydaunorubicin, oncovin and prednisone; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicines Agency; FL, follicular lymphoma; MTX, methotrexate; NK, natural killer; SmPC, Summary of Product Characteristics. 1. ACTIP. Available from: http://www.actip.org/products/monoclonal-antibodies-approved-by-the-ema-and-fda-for-therapeutic-use/. Accessed: Aug 22, 2022. 2. Weiner. Semin Hematol 2010;47:115–23. 3. Rituximab. SmPC available from: http://www.ema.europa.eu. Accessed Jul 26, 2022.

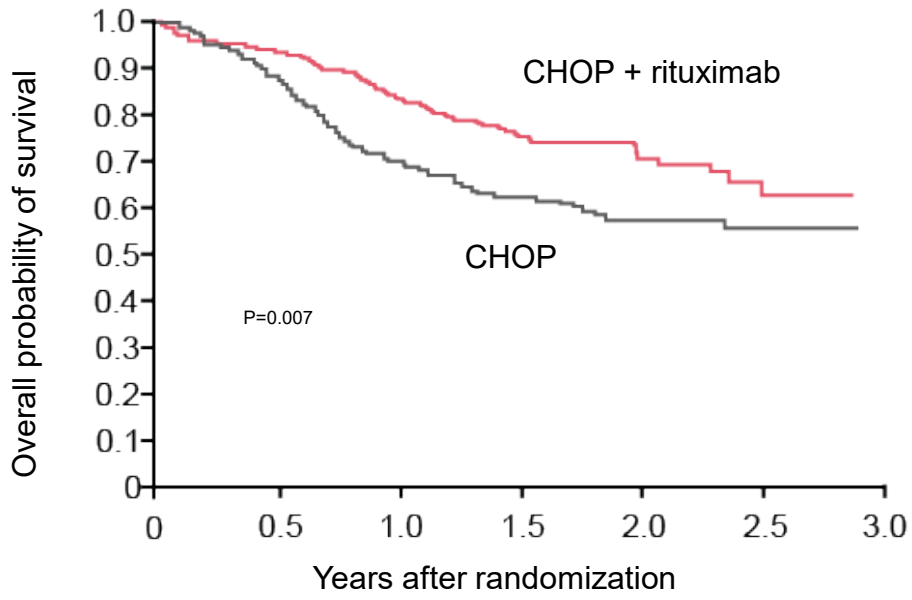
Monoclonal antibodies for hematologic malignancies: clinical overview and selected key data

Rituximab + CVP significantly prolonged time to progression vs CVP[1]



Time to disease progression, relapse or death[1]. R-CVP vs CVP as first-line treatment for advanced follicular lymphoma (n = 321). At a median follow-up of 30 months, patients treated with R-CVP had a significantly prolonged time to progression (median 32 months versus 15 months for CVP; p < 0.0001). Adapted from Marcus et al.[1]

Rituximab + CHOP significantly improved OS vs CHOP[2]



Overall survival in previously untreated patients with previously untreated diffuse large B-cell lymphoma (n = 399). Survival was significantly longer for patients treated with CHOP plus rituximab vs those treated with CHOP alone (p = 0.007): at 2 years, 70% patients treated with CHOP + rituximab were alive vs 57% of those treated with CHOP alone. Adapted from Coiffier et al.[2]

CHOP, cyclosphamide, hydroxydaunorubicin, oncovin and prednisone; CVP, cyclophosphamide, vincristine and prednisione; OS, overall survival; R, rituximab.

1. Marcus et al. Blood 2005;105:417–23. 2. Coiffier et al. N Engl J Med 2002;346:235–42.

Monoclonal antibodies for hematologic malignancies[a]

AML	CLL	B-cell precursor ALL	HL	NHL		Multiple myeloma
Gemtuzumab ozogamicin + daunorubicin and cytarabine	**Rituximab** + chemotherapy (previously untreated; relapsed/refractory)	**Inotuzumab ozogamicin** (relapsed/refractory)	**Brentuximab** (relapsed/refractory CD30+ HL)	**Rituximab** + chemotherapy (previously untreated stage III-IV FL); **Rituximab** maintenance (FL responding to induction therapy) **Rituximab** monotherapy (relapsed/refractory stage III-IV FL) **Rituximab** + CHOP (CD20 positive DLBCL)	**Brentuximab** + CHP (previously untreated sALCL)	**Elotuzumab** + lenalidomide + dexamethasone (≥ 1 prior therapy)
	Obinutuzumab + chlorambucil (previously untreated)	**Blinatumomab** (Philadelphia chromosome negative relapse/refractory)	**Pembrolizumab** (relapsed/refractory cHL) **Nivolumab** (relapsed/refractory cHL)		**Ibritumomab tiuxetan + rituximab** (relapsed or refractory CD20+ FB-NHL)	**Daratumumab** monotherapy (relapsed/refractory multiple myeloma) **Daratumumab +** lenalidomide + dexamethasone, or bortezomib + dexamethasone (≥ 1 prior therapy)
					Polatuzumab vedotin + bendamustine and rituximab (relapsed/refractory DLBCL)	**Isatuximab +** pomalidomide + dexamethasone (≥ 2 prior therapy), or carfilzomib + dexamethasone (≥ 1 prior therapy)
					Tafasitamab + lenalidomide (DLBCL)	
					Obinutuzumab + chemotherapy (previously untreated advanced FL) **Obinutuzumab** + bendamustine (relapsed/refractory FL)	**Belantamab mafodotin** (≥ 4 prior therapy)

[a]This is not an exhaustive list. Please refer to individual SmPCs for a full list of licensed indications

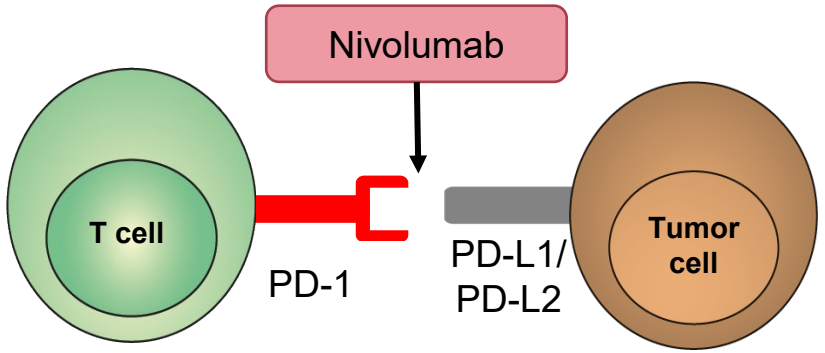
ALL, acute lymphoblastic leukemia; CD, cluster of differentiation; cHL, classical Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; CHOP, cyclosphamide, hydroxydaunorubicin, oncovin and prednisone; DLBCL, diffuse large B-cell lymphoma; FB-NHL, follicular B-cell non-Hodgkin's lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; SmPC, Summary of Product Characteristics; sALCL, systemic anaplastic large cell lymphoma; Cut-off date: Aug 2022, SmPC available from: http://www.ema.europa.eu/ema/. Accessed Jul 26, 2022. 2. i-Yoon Noh et al.Int. J. Mol. Sci. 2020, 21, 8000

For full information of individual agents, always refer to the Summary of Product Characteristics

Checkpoint inhibitors for hematologic malignancies: key examples

- PD-1 ligands are overexpressed on Reed-Sternberg cells in cHL[1]
- Two PD-1 inhibitors are currently licensed for classical HL, nivolumab and pembrolizumab[2,3]

Nivolumab mechanism of action



Nivolumab prevents the binding of PD-1 to its ligands (PD-L1 and PD-L2), which releases T cell responses against tumor cells

	Indication
Nivolumab[2]	Adult patients with relapsed or refractory cHL after ASCT and treatment with BV
Pembrolizumab[3]	Adult patients with relapsed or refractory cHL who have failed ASCT and BV, or who are transplant-ineligible and have failed BV

ASCT, autologous stem cell transplant; BV, brentuximab vedotin; HL, Hodgkin lymphoma; PD-1, programmed cell death protein 1; PD-L1/2, programmed death-ligand 1/2.

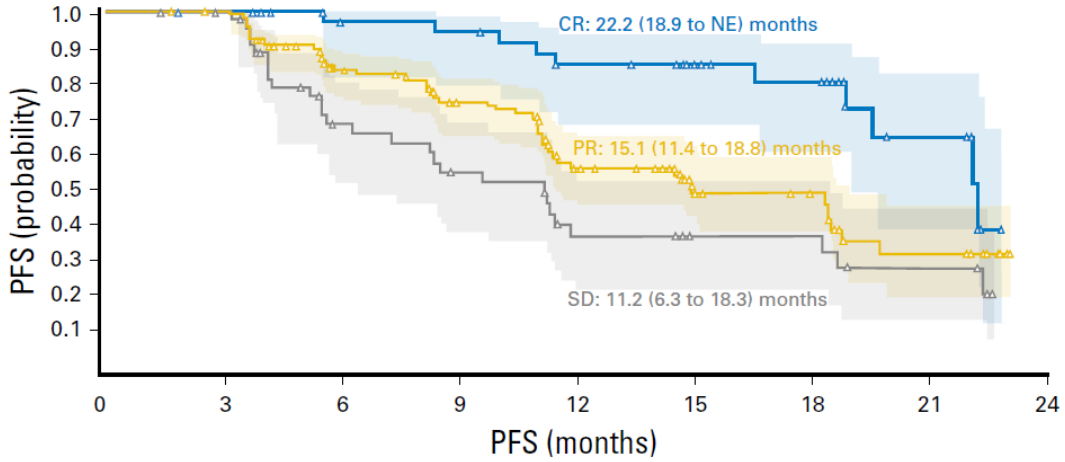
1. Younes et al. Lancet Oncol 2016;17:1283–94. 2. Nivolumab. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003985/WC500189765.pdf. 3. Pembrolizumab. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003820/WC500190990.pdf. Accessed Jul 27, 2022.

For full information of individual agents, always refer to the Summary of Product Characteristics

Checkpoint inhibitors for hematologic malignancies: clinical overview and selected key data

- Checkpoint inhibitors for the treatment of hematologic malignancies is a rapidly evolving field, and selected results from some key studies are shown below

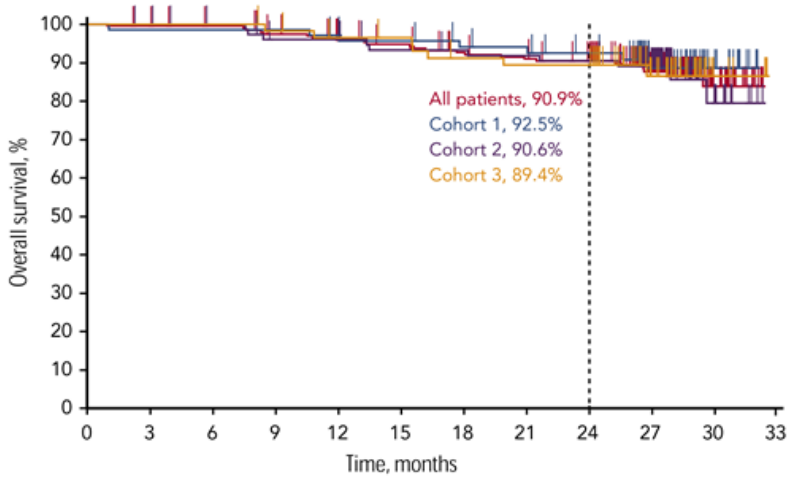
PFS in adult patients with cHL treated with nivolumab



No. at risk:									
CR	40	40	33	32	27	20	16	7	0
PR	128	126	89	71	46	25	21	8	0
SD	47	44	25	19	11	8	8	5	0

Armand et al. [1]

OS in patients with relapsed or refractory cHL treated with pembrolizumab



No. at risk												
	210	207	205	198	190	186	178	175	170	115	26	0
	69	68	68	68	64	64	61	60	56	40	11	0
	81	79	77	72	71	68	67	66	65	47	10	0
	60	60	60	58	55	54	50	49	49	28	5	0

Chen et al.[2]

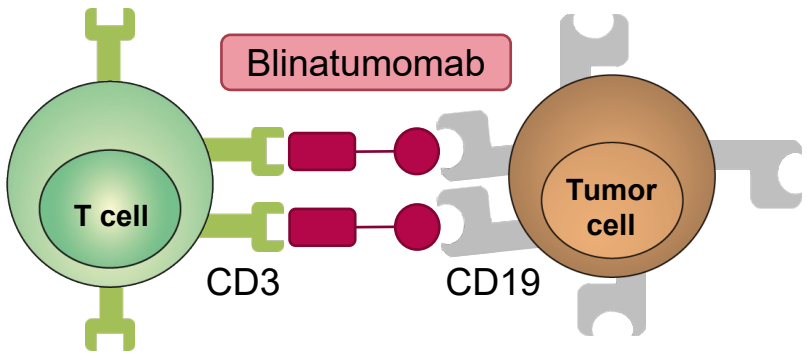
cHL, classical Hodgkin lymphoma; CI, confidence interval; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival.

1. Armand et al. J Clin Oncol 2018 36:1428-1439.. 2. Chen et al. Blood 2019 Oct 3;134(14):1144-1153.

Bispecific T-cell engagers for hematologic diseases

- BiTEs are a class of antibody that has multiple binding sites and specificities[1]
- Blinatumomab is the only BiTE currently approved to treat Philadelphia chromosome negative relapsed or refractory B-precursor ALL[2]
- It binds to CD19 on B cells and to CD3 on T cells
- B cells and T cells are brought together by blinatumomab molecules and T cells are activated by CD3 cross-linking
- Blinatumomab facilitates the formation of a cytolytic synapse between T cells and tumor cells, which kills proliferating and resting target cells by releasing proteolytic enzymes[3]

Blinatumomab mechanisms of action[4]



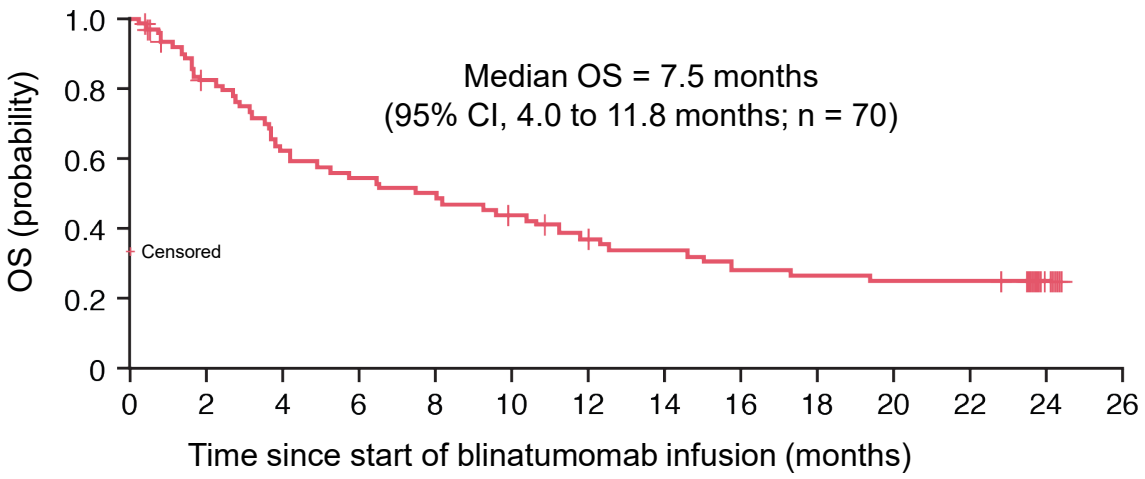
One arm of blinatumomab binds to CD19, and the other binds to CD3, thereby activating T cells, which destroy the CD19+ cells

ALL, acute lymphoblastic leukemia; BiTE, bispecific T-cell engager; CD, cluster of differentiation.

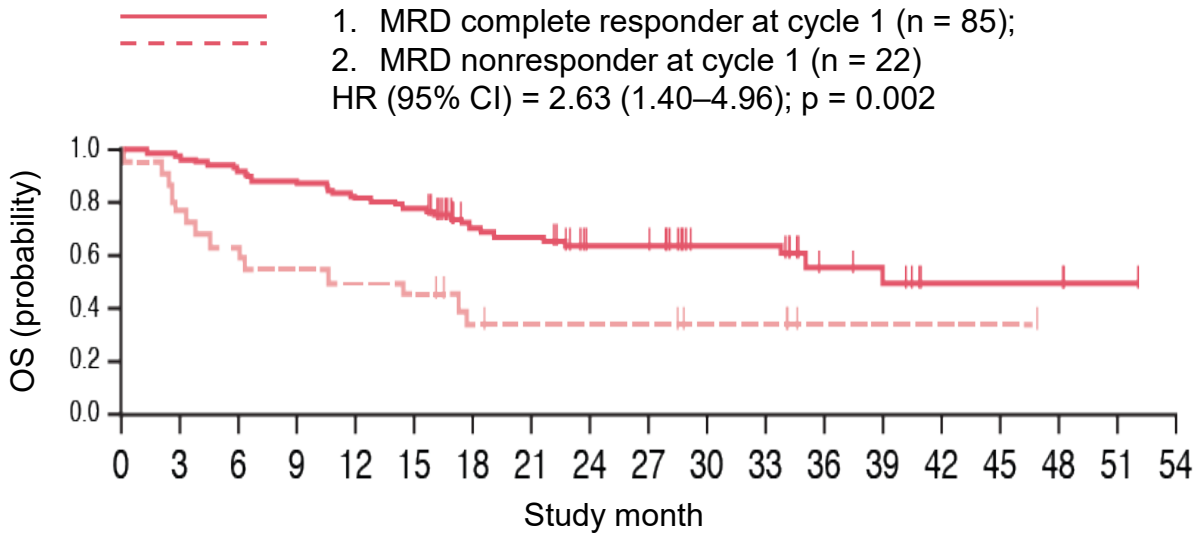
1. Huehls et al. Immunol Cell Biol 2015;93:290–6. 2. Blinatumomab SmPC. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003731/WC500198228.pdf. Accessed Jul 27, 2022. 3. Von Stackelberg et al. J Clin Oncol 34:4381–9. 4. Wu et al. Journal of Hematology & Oncology 2015;8:104.

BiTEs for hematologic malignancies: clinical overview and selected key data

Overall survival in all patients who received the recommended dosage of blinatumomab[1]



Median overall survival was 38.9 vs 12.5 months (p = 0.002) in patients with and without a complete MRD response (cycle 1)[2a]



[a]Overall survival by MRD response during cycle 1, without censoring at allogeneic SCT and post-blinatumomab chemotherapy

BiTE, bispecific T-cell engager; CI, confidence interval; HR, hazard ratio; MRD, minimal residual disease; OS, overall survival; SCT, stem cell transplantation.

1. Von Stackelberg et al. J Clin Oncol 2016;34:4381–9. 2. Gökbuget et al. Blood 2018;131:1522–31.

Summary and key takeaways

- Immunotherapy is a therapeutic modality that harnesses the body's own immune system to fight cancer[1–3]
- The immune response to tumors can vary between continuous activation and suppression, with tumor progression favored when the immune response is suppressed[4,5]
- The TME plays a pivotal role in tumor growth and metastasis by suppressing infiltrating immune cells[6,7]
- Tumors may target activating and inhibitory mechanisms of immune pathways, resulting in tumor evasion of the immune system and tumor survival/growth[8,9]
- A number of therapeutic approaches have been developed or are being studied to harness the immune system and control malignancy[4]. These approaches include:
  - Cytokines
  - Checkpoint inhibitors
  - Agonism of costimulatory receptors
  - Manipulation of T cells
  - Oncolytic viruses
  - Therapies directed at non immune cell types in the TME
  - Vaccines

BiTE, bispecific T-cell engager; CAR, chimeric antigen receptor; CTLA-4, cytotoxic T-lymphocyte antigen protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TME, tumor microenvironment.

1. Murphy. Oncology 2010;4:67–80. 2. Kirkwood et al. CA Cancer J Clin 2012;62:309–35. 3. Borghaei et al. Eur J Pharmacol 2009;625:41–54. 4. Chen & Mellman. Immunity 2013;39:1–10. 4. Dunn et al. Annu Rev Immunol 2004;22:329–60. 5. Mittal et al. Curr Opin Immunol 2014;27:16–25. 6. Balkwill et al. J Cell Sci 2012;125:5591–6. 7. Chen et al. BMC Medicine 2015;13:45. 8. Mittal et al. Curr Opin Immunol 2014;27:16–25. 9. Beatty & Gladney. Clin Cancer Res 2015;21:687–92.

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