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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Types of immunotherapy

Types of immunotherapy

Click on a chapter below to start learning

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

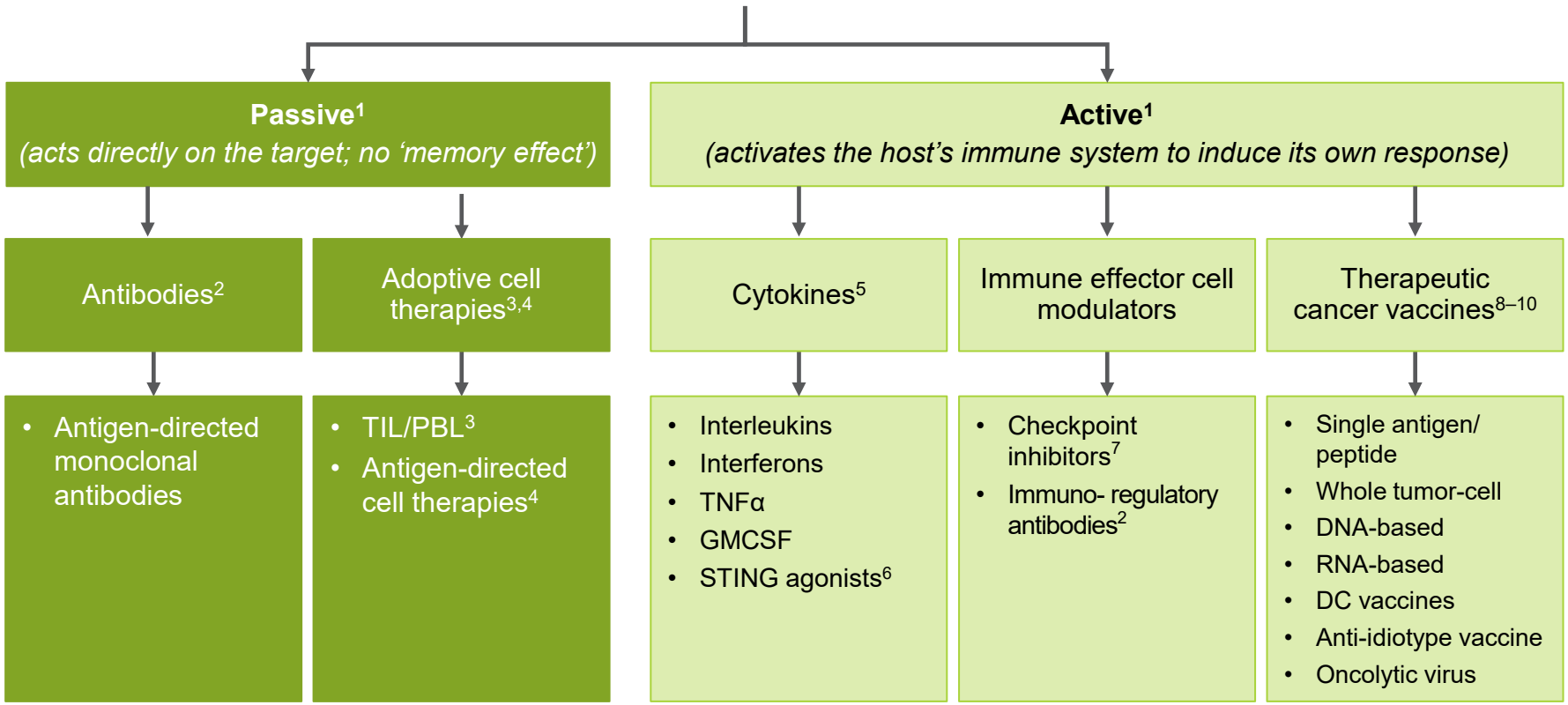
Introduction

Types of immunotherapy

What is immunotherapy?

Immunotherapy is a treatment that either **induces, enhances or suppresses** immune mechanisms

Immunotherapies encompass a wide variety of different classes

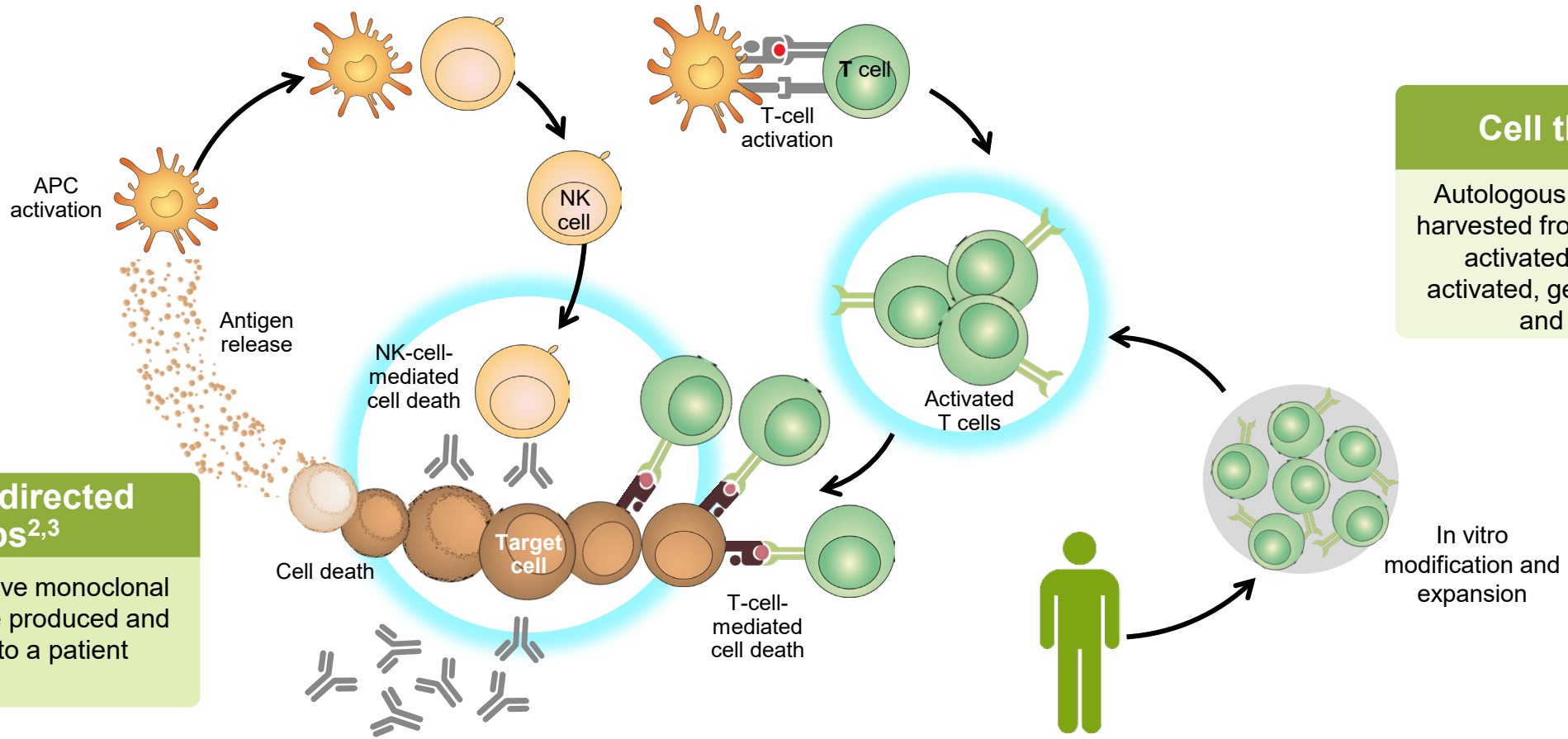


DC, dendritic cell; GMCSF, granulocyte-macrophage colony-stimulating factor; PBL, peripheral blood lymphocytes; STING, stimulator of interferon genes; TIL, tumor infiltrating T cells; TNF, tumor necrosis factor.

1. Finn. Ann Oncol 2012;23(suppl 8):viii6–9. 2. Redman et al. Mol Immunol 2015;67:28–45. 3. Dudley. J Cancer 2011;2:360–2. 4. Yu et al. J Hematol Oncol 2017;10:1–13. 5. List & Neri. Clin Pharmacol 2013;5:29–45. 6. Iurescia et al. Front Immunol 2018;9:711. 7. Pardoll. Nat Rev Cancer 2012;12:252–64. 8. Maithreye 2015. Available from https://www.slideshare.net/sunitamaithreye999/cancer-vaccine [Accessed October 2022]. 9. Guo et al. Adv Cancer Res 2013;119:421–475; 10. NCI. Cancer Treatment Vaccines. Available at: https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/cancer-treatment-vaccines [Accessed October 2022].

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

Passive immunotherapy does not require the patient's immune system to initiate the response[1–3,a]



Antigen-directed mAbs[2,3]

Antigen-reactive monoclonal antibodies are produced and injected into a patient

Cell therapies[4]

Autologous immune cells are harvested from the patient, then activated then selected, activated, genetically modified and expanded

[a]However, passive immunotherapies for cancer do depend on the patient's immune system for long-term tumor control or complete tumor elimination. Despite different classifications, some overlap between active and passive immunotherapies does exist.

APC, antigen-presenting cell; mAb, monoclonal antibody; NK, natural killer.

1. Finn. Ann Oncol 2012;23(suppl 8):viii6–9. 2. Rescigno et al. Biochim Biophys Acta 2007;1776:108–23. 3. Mellman et al. Nature 2011;480:480–9. 4. Rosenberg. Sci Transl Med 2012;4(127ps8):1–5.

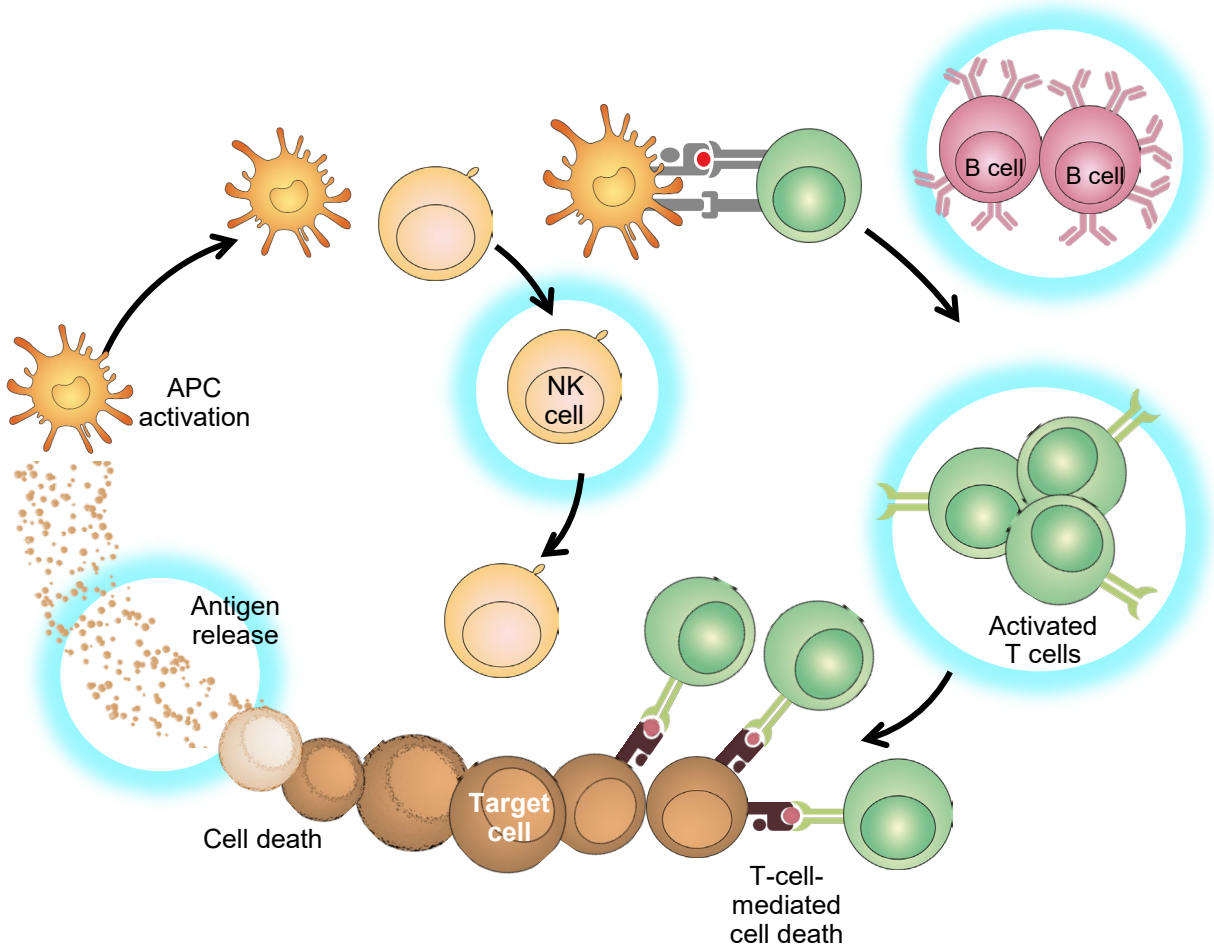
Active immunotherapy stimulates the immune system to elicit an immune response[1,2,a]

Therapeutic vaccines[2,3,5]

Therapeutic vaccines may prime the immune system to attack target cells in the body by introducing immune cells to one or more antigens

Cytokines[6]

Cytokines are small proteins that modulate the effector functions of immune cells, thereby influencing the immune response



Immunoregulatory antibodies[3,4]

Immunoregulatory monoclonal antibodies either act to enhance the immune response (in the treatment of cancer or infections) or suppress the immune response (in the treatment of autoimmunity or inflammatory diseases)

Checkpoint inhibitors[7,8]

Immune checkpoints refer to a set of 'control' pathways within the immune system. Overcoming checkpoint inhibition using antibodies or recombinant forms of the ligands or receptors enhances T-cell activity

[a]Despite different classifications, some overlap between active and passive immunotherapies does exist.

NK, natural killer.

1. Finn. Ann Oncol 2012;23(suppl 8):viii6–9. 2. Rescigno et al. Biochim Biophys Acta 2007;1776:108–23. 3. Mellman et al. Nature 2011;480:480–9. 4. Redman et al. Mol Immunol 2015;67:28–45. 5. Guo et al. Adv Cancer Res 2013;119:421–75. 6. List & Neri. Clin Pharmacol 2013;5(suppl):29–45. 7. Pardoll. Nat Rev Cancer 2012;12:252–64. 8. Thallinger et al. Wien Klin Wochenschr 2018;130:85–91.

Immunotherapy is either stimulatory or inhibitory

- Immunotherapy either activates or dampens the immune response; the choice of immunotherapy depends on the target disease

Tumors and infections

Autoimmunity and inflammatory diseases

‘Stimulatory’ immunotherapies

- Adoptive cell therapy[1]
- Antigen-directed monoclonal antibodies[2,3]
- Cytokines[4]
- Checkpoint inhibitors[5,6]
- Immunoregulatory monoclonal antibodies[3]

‘Suppressing’ immunotherapies[a]

- Immunoregulatory monoclonal antibodies[7,8]
- Allergen-specific immunotherapy[9]

[a]Other types of immunosuppressive therapy also exist (e.g. corticoids , immunoglobulins, tacrolimus) but are not covered in this module.

1. Rosenberg. Sci Transl Med. 2012;4:1–5. 2. Rescigno et al. Biochim Biophys Acta 2007;1776:108–23. 3. Mellman et al. Nature 2011;480:480–9. 4. List & Neri. Clin Pharmacol 2013;5(suppl):29–45. 5. Pardoll. Nat Rev Cancer 2012;12:252–64. 6. Thallinger et al. Wien Klin Wochenschr 2018;130:85–91. 7. Redman et al. Mol Immunol 2015;67:28–45. 8. Kalden. Rheumatol Ther 2016;3:31–42. 9. Viswanathan & Busse. Chest 2012;141:1303–14.

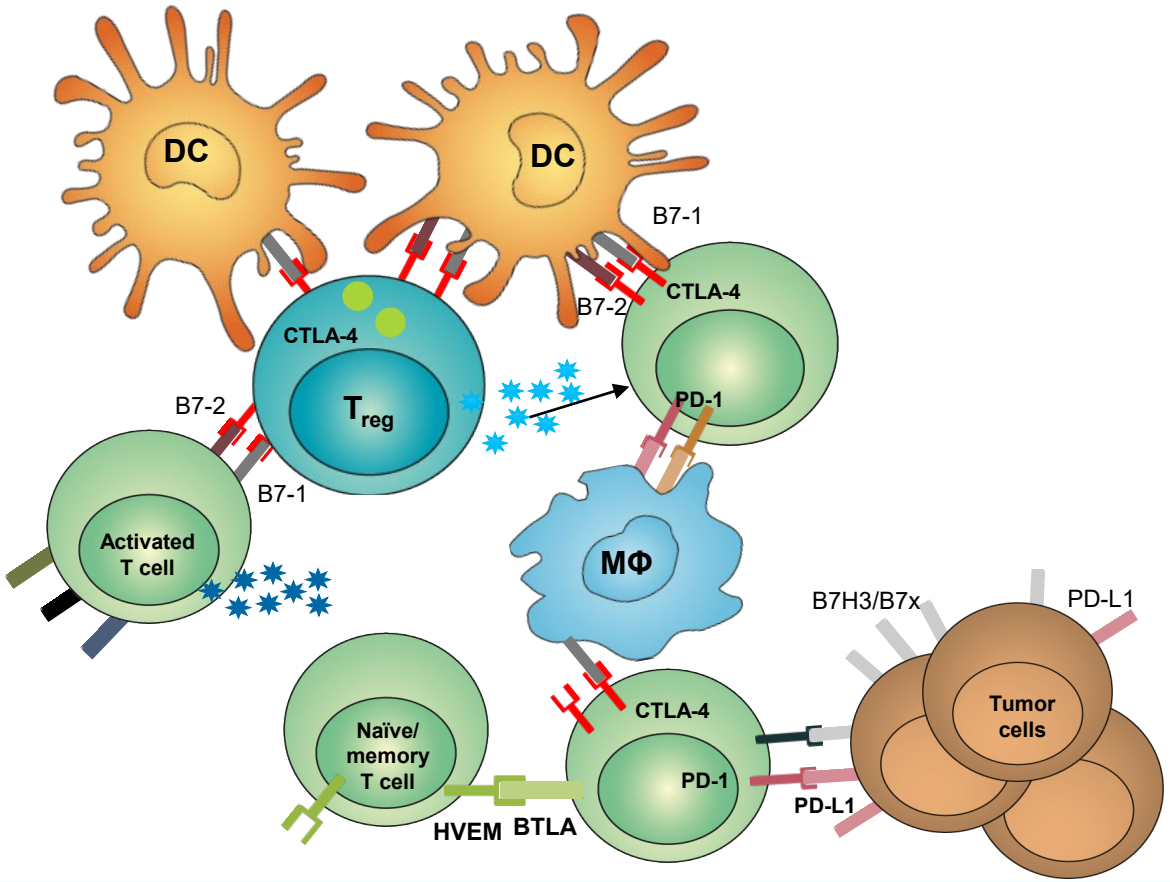
Checkpoint inhibitors

Types of immunotherapy

Inhibitory checkpoints of immune regulation

- Inhibitory signaling pathways, also termed immune checkpoints, are key to the immune response[1]
- They are vital to maintaining self-tolerance and limiting or modulating immune responses, and are initiated by ligand–receptor interactions[2]

Studies have shown that immune-checkpoint receptors are expressed during tolerance to self-antigens and chronic infection, and during inflammation[2,3]



Key players

CTLA-4 is expressed only on T cells and regulates the early stages of T-cell activation[2]

The main role of **PD-1** is to limit T-cell activity during an inflammatory response to infection and to limit autoimmunity[2,3]

PD-L1 is a ligand for PD-1. It is the major PD-1 ligand expressed on cells from solid tumors[2,3]

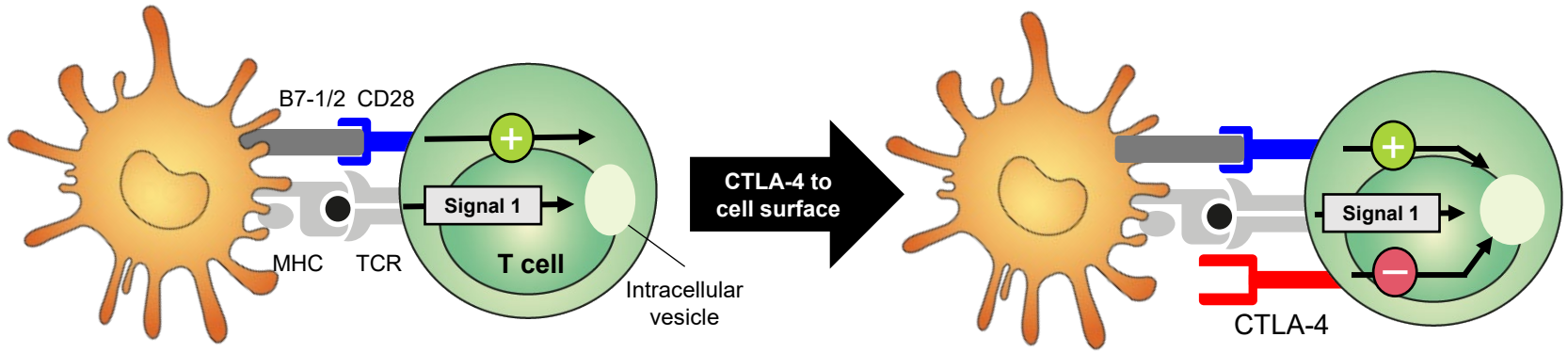
BTLA, B- and T-lymphocyte attenuator; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DC, dendritic cell; HVEM, herpesvirus entry mediator; MΦ, macrophage; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; Treg, regulatory T cell.

1. Wolchok & Saenger. Oncologist 2008;13:2–9. 2. Pardoll. Nat Rev Cancer 2012;12;252–64. 3. Thallinger et al. Wien Klin Wochenschr 2018;130:85–91.

Inhibitory checkpoints of immune regulation: potential targets for therapeutic intervention

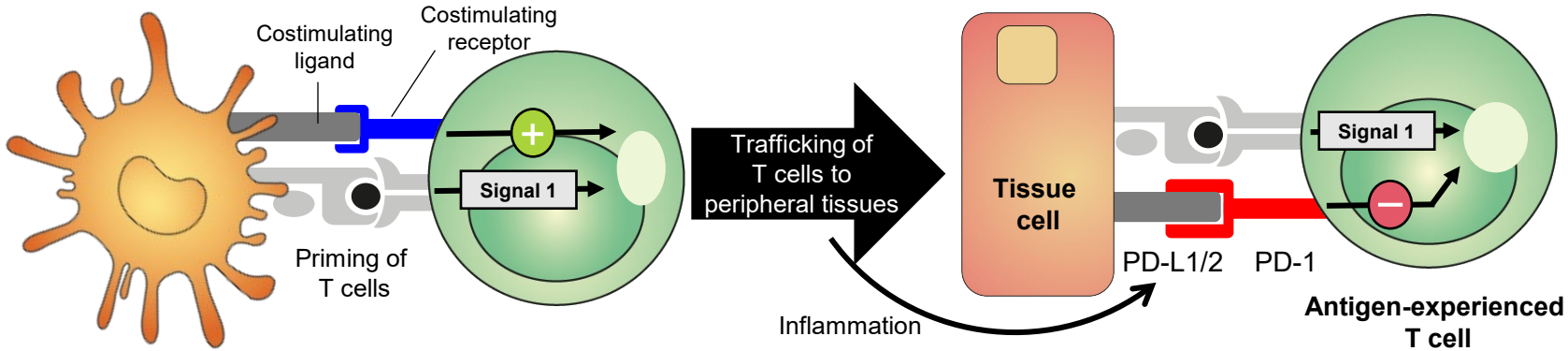
- Treatment with immune-checkpoint inhibitors currently involves the antibodies generated against CTLA-4, PD-1, or PD-L1[1]
- These checkpoint inhibitors are the targets of several therapies. Inhibitors of other immune checkpoints are also currently in development[2]

CTLA-4



CTLA-4 expression is induced in T cells upon initial response to the antigen

PD-1



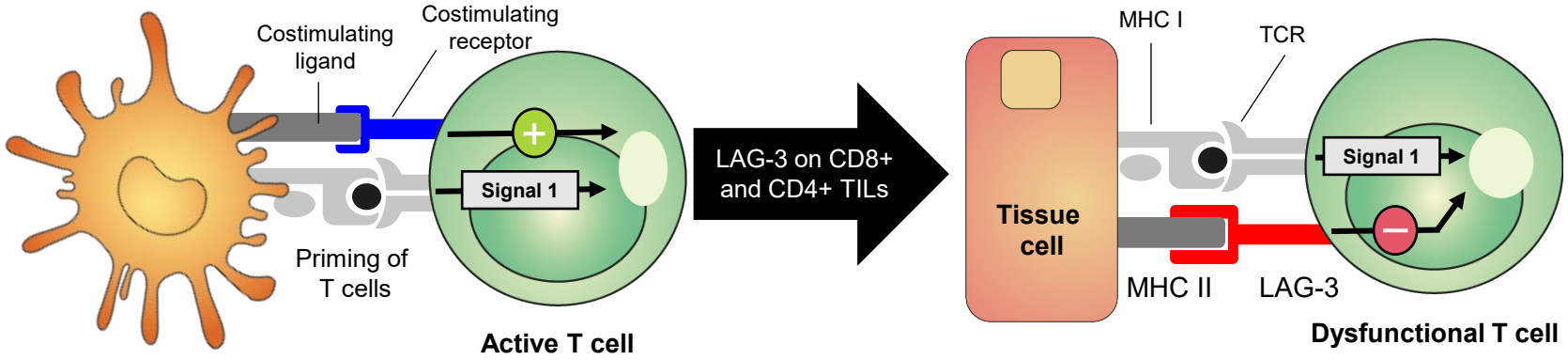
The PD-1 pathway regulates the inflammatory response by effector T cells

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DC, dendritic cell; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1/2, programmed cell death ligand 1/2; TCR, T-cell receptor.
1. Adapted from Pardoll. Nat Rev Cancer 2012;12;252–64; 2. Qin S, et al. *Mol Cancer* 2019;18:155.

Inhibitory checkpoints of immune regulation: potential targets for therapeutic intervention

- LAG-3 is a cell-surface molecule expressed on T cells and other immune cells that has diverse inhibitory biologic effects on the function of T cells[1,2]

LAG-3



Increased expression of LAG-3 on CD8+ and CD4+ TILs, especially in the context of PD-1 expression, inhibits effector T-cell function[1,3-5]

Interaction of LAG-3 with its ligands triggers inhibitory activity that reduces the function of effector T cells, leading to an impaired ability to fight tumor cells and an increased potential for tumor growth[1,5]

Ligands for LAG-3 are distinct from the ligands of other inhibitory immune checkpoints such as PD-1 or CTLA-4. Among its ligands, the most well established is MCH II; others are emerging, including FGL1[1,5–7]

APC, antigen-presenting cell; CTLA-4, cytotoxic T lymphocyte antigen 4; FGL1, fibrinogen-like protein 1; LAG-3, lymphocyte-activation gene 3; PD-1, programmed death-1; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte.

1. Long L, et al. Genes Cancer 2018;9:176-189; 2. Grosso JF, et al. J Clin Invest 2007;117:3383-3392; 3. Workman CJ, et al. J Immunol 2004;172:5450-5455; 4. Woo SR, et al. Cancer Res 2012;74:917-927; 5. Wang J, et al. Cell 2019;176:334-347.e12.; 6. Huang R-Y, et al. Oncoimmunology 2017;6:e1249561; 7. Maçon-lemaître L, Triebel F. Immunology 2005;115:170-178.

Checkpoint inhibitors 1: CTLA-4 inhibitors

Types of immunotherapy

CTLA-4 checkpoint inhibitors: the role of CTLA-4

CTLA-4 stops potentially autoreactive T cells during the first stage of naive T-cell activation and so can be considered the ‘frontrunner’ of the immune-checkpoint inhibitors[1]

What does CTLA-4 do?

- Inhibitory coreceptor expressed on activated T cells intended to prevent a physiological immune response (i.e. to an infection) getting out of control or continuing beyond the necessary time of response[1,2]
- It has a higher affinity than CD28 for ligands B7-1 (CD80) and B7-2 (CD86); however, unlike CD28, CTLA-4 binding to B7 ligands does not produce a stimulatory signal[1]
- Thus, CTLA-4 binding to B7 is a negative regulator of T-cell activation, preventing T-cell proliferation, survival, and differentiation[1]
- In the TME, CTLA-4 inhibits the proper immune response and promotes tumour cell survival[1,3]

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; TME, tumor microenvironment.

1. Buchbinder & Desai. Am J Clin Oncol 2016;39:98–106. 2. Parry et al. Mol Cell Biol 2005;25:9543–53. 3. Leach et al. Science 1996;271:1734–6.

Back to other mAbs

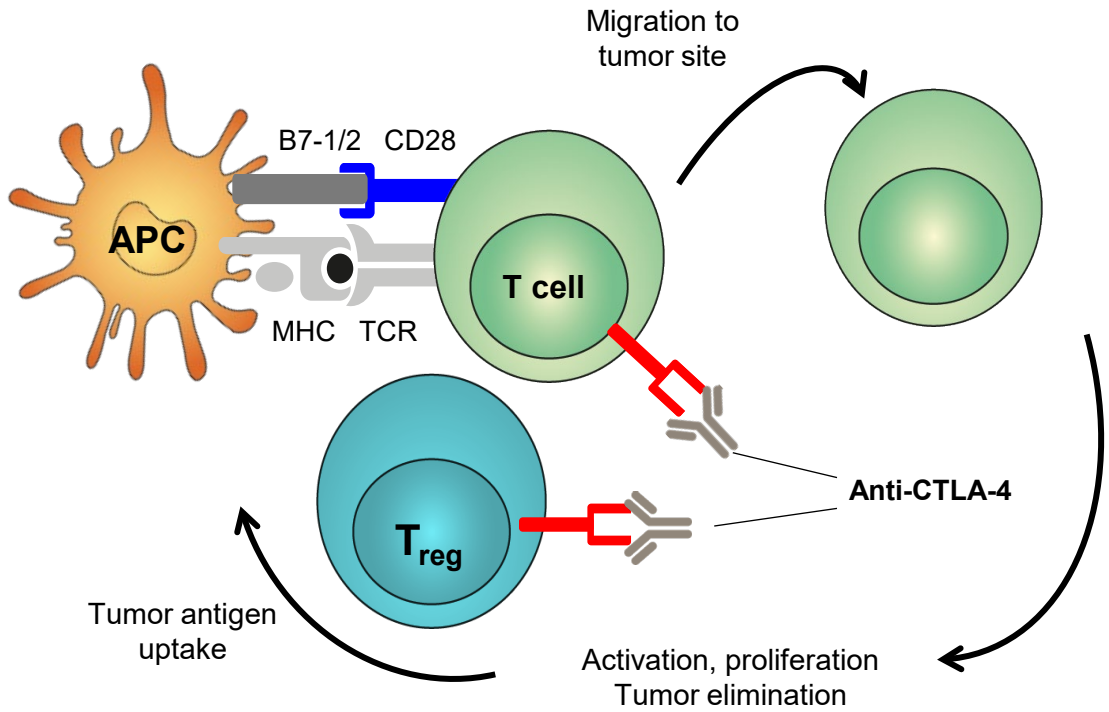
CTLA-4 checkpoint inhibitors: targeting CTLA-4

Targeting CTLA-4

- Preventing CTLA-4 from binding to its ligands can disrupt immune-checkpoint signaling, and this is the premise for immune-checkpoint inhibitors[1]
- CTLA-4 blockade can also reduce T_{reg} function, which may contribute to an antitumor immune response[1]
- Blockade of immune-checkpoint pathways can yield durable disease regression in a broad range of malignancies[2]

CTLA-4 inhibitors: mechanism of action[1]

- Inhibiting CTLA-4 allows more T-cell clones to activate and proliferate and reduces T_{reg}-mediated immunosuppression[1]
- Ipilimumab is a CTLA-4 immune-checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of reactive T-effector cells that mobilize to mount a direct T-cell immune attack against tumor cells[3]



APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; MHC, major histocompatibility complex; TCR, T-cell receptor; T_{reg}, regulatory T cell.

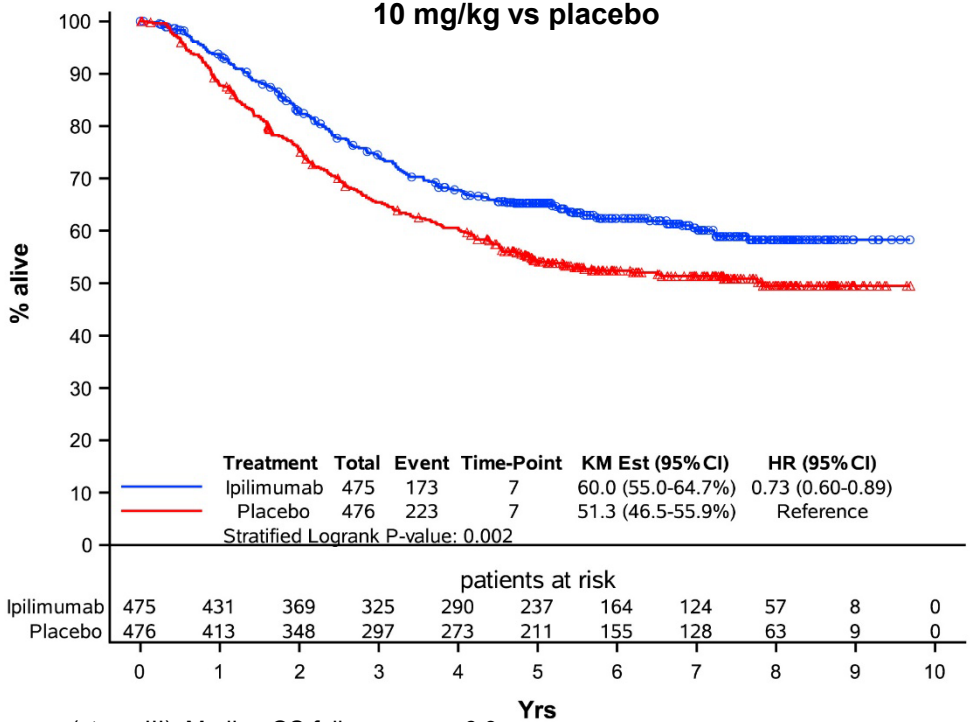
1. Buchbinder & Desai. Am J Clin Oncol 2016;39:98–106. 2. Callahan et al. Immunity 2016;44:1069–78. 3. Yervoy SmPC 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/yervoy-epar-product-information_en.pdf. Accessed October 2022.

CTLA-4 checkpoint inhibitors: clinical overview

- The CTLA-4 inhibitor ipilimumab improves OS in patients with advanced melanoma[1]

Significantly higher rates of RFS, OS, and distant metastasis–free survival[a] vs placebo[2]

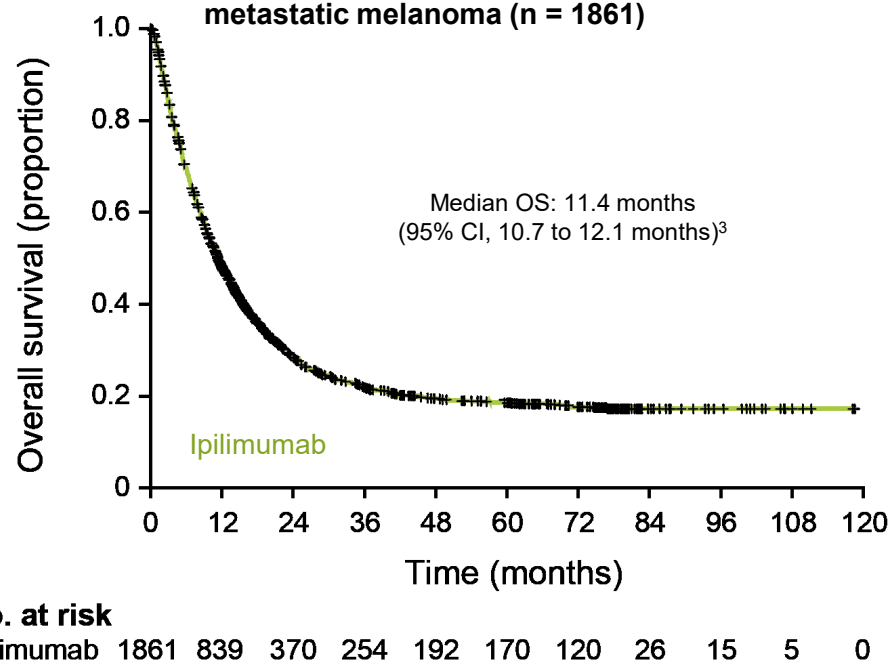
Kaplan–Meier estimate of OS in patients treated with ipilimumab 10 mg/kg vs placebo



[a]As adjuvant therapy (stage III). Median OS follow-up was 6.9 years.

Long-term survival for ipilimumab-treated patients with advanced melanoma[3]

Primary pooled analysis of OS data from 10 prospective trials and two retrospective, observational studies of ipilimumab in metastatic melanoma (n = 1861)



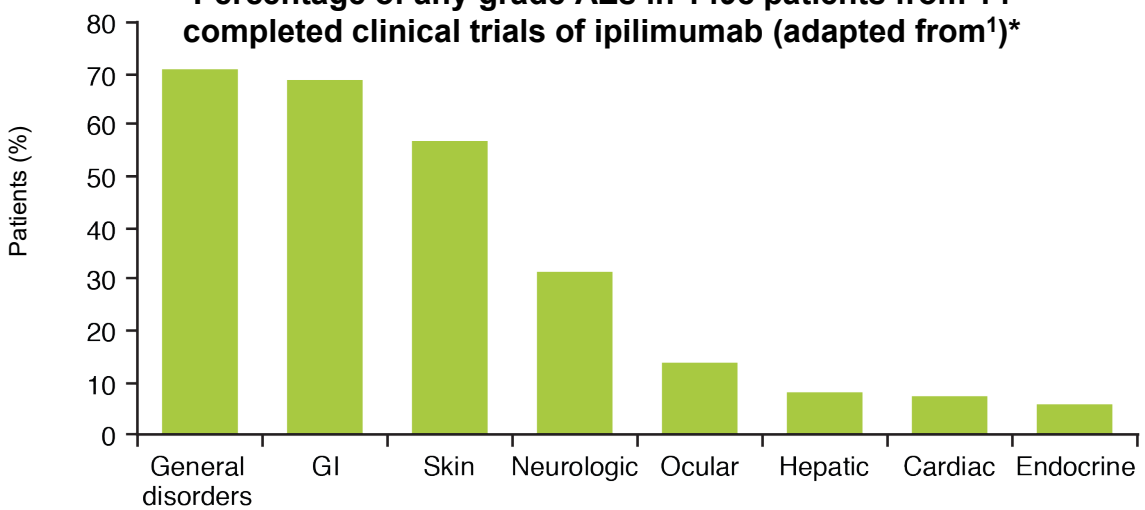
CI, confidence interval; OS, overall survival; RFS, recurrence-free survival.

1. Yervoy SmPC 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/yervoy-epar-product-information_en.pdf. Accessed October 2022. 2. Eggermont et al. Eur J Cancer 2019;119:1-10. 3. Schadendorf et al. J Clin Oncol 2015;33:1889–94.

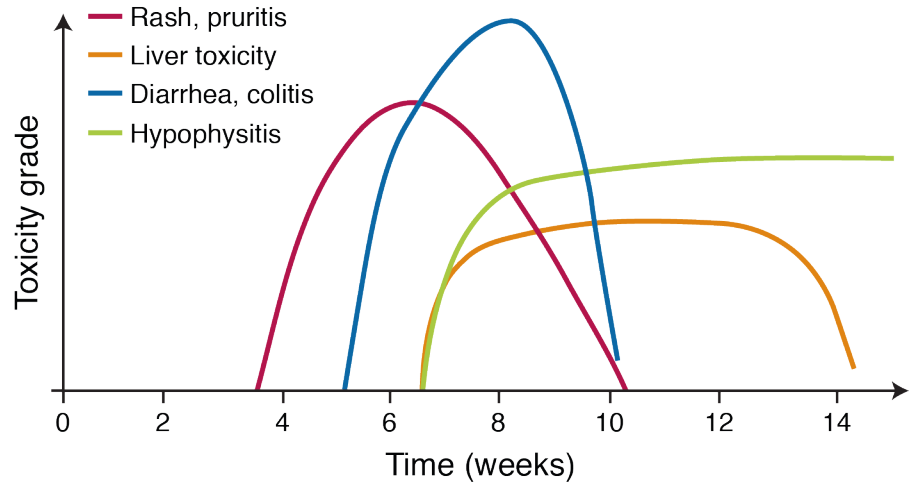
CTLA-4 checkpoint inhibitors: adverse events

- Owing to the immune-stimulatory action, CTLA-4 inhibitors, such as ipilimumab, are associated with a range of inflammatory- and immune-related AEs[1]
- These include dermatologic, gastrointestinal, endocrine, hepatic, immune system, infections, metabolic, musculoskeletal/connective tissue, nervous system, renal and respiratory toxicities[1,2]

Percentage of any-grade AEs in 1498 patients from 14 completed clinical trials of ipilimumab (adapted from[1])*



Timing of occurrence of irAEs following ipilimumab treatment[3]



Published guidance on the management of checkpoint-inhibitor toxicities is available[3–10]

*AEs were categorized by organ system. AEs were included regardless of causality.
Patients may have experienced more than one event.

AE, adverse event; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; GI, gastrointestinal; irAE, immune-related adverse event. 1. Camacho. Cancer Med 2015;4:661–72. 2. Almutairi A, et al. Front Oncol 2020;10:91. 3. Haanen et al. Ann Oncol 2017;28(suppl_4):iv119–iv42. 4. Puzanov et al. J Immunother Cancer 2017;5:95. 5. Davies & Duffield. Immunotargets Ther 2017:6:51–71. 6. Brahmer et al. J Clin Oncol 2018; 36:1714–68. 7. Aspeslagh et al. BMSO ImmunoManager. Available from https://www.bsmo.be/immunomanager/. Accessed October 2022. 8. NCCN Clinical Practice Guidelines. Management of Immunotherapy-Related Toxicities. Version 1.2022 — February 28, 2022. Accessed October 2022. To view the most recent and complete version of the guideline, go online to NCCN.org . 9. Castinetti F et al. French Endocrine Society Guidance on endocrine side effects of immunotherapy, Endocrine-Related Cancer (2019) 26, G1–G18. 10. Champiat S, et al. Ann Oncol 2016;27:559–74.

Checkpoint inhibitors 2: PD-1/PD-L1 inhibitors

Types of immunotherapy

PD-1/L1 checkpoint inhibitors: the role of PD-1 and PD-L1

PD-1 is a checkpoint protein on T cells. It normally acts as a type of “off switch” that helps keep the T cells from attacking other cells in the body. It does this when it attaches to PD-L1, a protein on some normal (and cancer) cells[1]

What do PD-1 and PD-L1 do?[2]

- PD-1 induces T-cell tolerance and inhibits the TCR signaling pathway through SHP-2
- When bound to its ligand (PD-L1 or PD-L2), PD-1 is able to suppress the function of T cells by recruiting SHP-2
- The key and instant outcome of stimulation via PD-1 is the inhibition of T-cell growth and cytokine secretion
- PD-1 serves an important role in tumor immune escape[3]

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; PD-1, programmed cell death protein 1; PD-L1/2, programmed cell death ligand 1/2; SHP-2, Src homology-2 domain containing phosphatase; TCR, T-cell receptor.

1. American Cancer Society. Available from: https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/immune-checkpoint-inhibitors.html. Accessed October 2022. 2. Okazaki et al. Nat Immunol 2013;14:1212–8. 3. Rosenblatt & Avigan. Blood 2017;129:275–9.

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

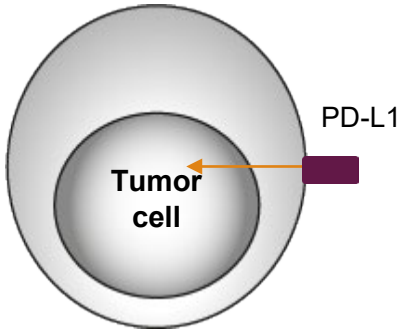
Targeting PD-1/PD-L1[1]

- In a pathologic setting, signaling via this pathway results in the emergence of an exhausted T-cell phenotype and the inability to mount protective immunologic responses
- In a malignant setting, upregulation of this pathway prevents the activation of tumor-reactive T cells, contributing to immune escape and growth of the tumor
- Therefore, blockade of this pathway is a viable therapeutic strategy

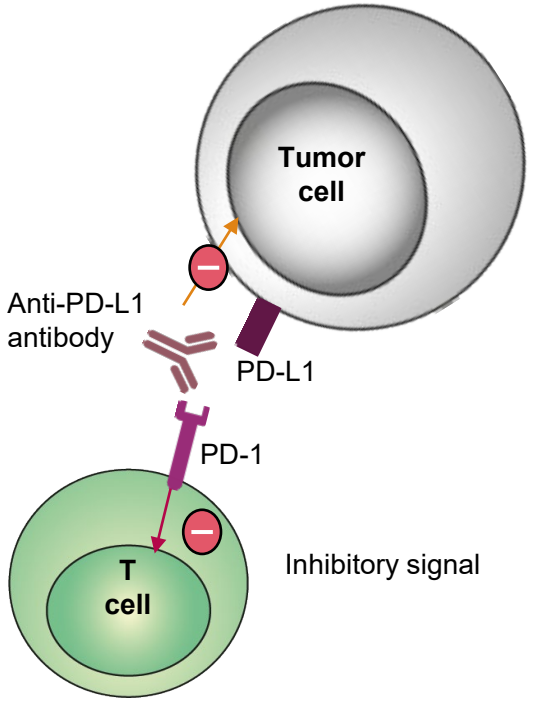
PD-1/L1 inhibitors: mechanism of action[2]

- Like anti-CTLA-4 antibodies, anti-PD-1 antibodies reverse the inhibitory signals sent to T cells to allow their metabolic reprogramming
- Thus, administration of anti-PD-1/PD-L1 antibodies results in activation of the immune system
- Only antibody isotypes activating FC receptors (on NK cells, and macrophages) can mediate ADCC

Reverse signaling via PD-L1 favors tumor growth and anti-apoptotic processes



Reinvigoration of T cells alter inhibition of the interaction of PD-1 with PD-L1



ADCC, antibody-dependent cell-mediated cytotoxicity; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; NK, natural killer; PD-1, programmed cell death protein 1; PD-L1/2, programmed cell death ligand 1/2; SHP-2, Src homology-2 domain containing phosphatase; TCR, T-cell receptor.

1. Rosenblatt & Avigan. Blood 2017;129:275–9. 2. Granier et al. ESMO Open 2017;2:e000213.

Back to other mAbs

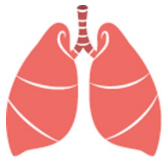
PD-1 and PD-L1 inhibitors

- PD-1 and PD-L1 inhibitors have been found to be efficacious in the treatment of several malignant diseases,[1–3] including advanced/refractory cancers[4]

Key

PD-1 inhibitor

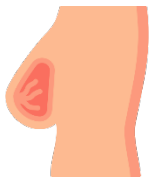
PD-L1 inhibitor



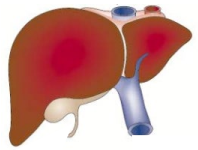
- Pembrolizumab
- Nivolumab
- Cemiplimab
- Atezolizumab
- Durvalumab

- Pembrolizumab
- Nivolumab

- Pembrolizumab
- Nivolumab
- Atezolizumab
- Avelumab



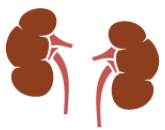
- Atezolizumab
- Pembrolizumab



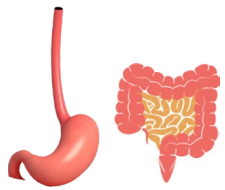
- Atezolizumab

- Pembrolizumab
- Nivolumab
- Avelumab
- Cemiplimab

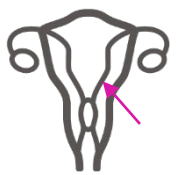
- Pembrolizumab
- Nivolumab



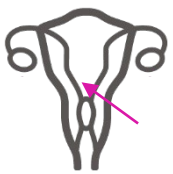
- Pembrolizumab
- Nivolumab
- Avelumab



- Pembrolizumab
- Nivolumab



- Pembrolizumab
- Dostarlimab



- Pembrolizumab

Licensed products for malignant indications only are shown. Non-malignant indications are not covered by this module

Images are not related to specific indications, but a broad category of disease types. PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1.

1. Shoushtari et al. Cancer 2016; 122:3354–62. 2. Jia et al. J Thorac Dis 2015;7:455–61. 3. Cancer Research Institute. Available at: https://www.cancerresearch.org/scientists/immuno-oncology-landscape/pd-1-pd-l1-landscape [Accessed October 2022]. 4. Zhang et al. Oncotarget. 2016;7:73068–79.

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

PD-1 inhibitors: clinical overview and selected key data (1)

Nivolumab: licensed indications[1]

Melanoma: monotherapy or in combination with ipilimumab; advanced (unresectable or metastatic)
Adjuvant melanoma: monotherapy; undergone complete resection
- Significant increase in RFS vs ipilimumab: HR 0.66, p < 0.0001; n = 906

NSCLC: monotherapy after prior chemotherapy; locally advanced or metastatic
- Increase in OS vs docetaxel (squamous; min follow-up 62.6 months): HR 0.62 (95% CI 0.48–0.79); n = 272
- Increase in OS vs docetaxel (non-squamous; min follow-up 62.7 months): HR 0.70 (95% CI 0.58–0.83); n = 582

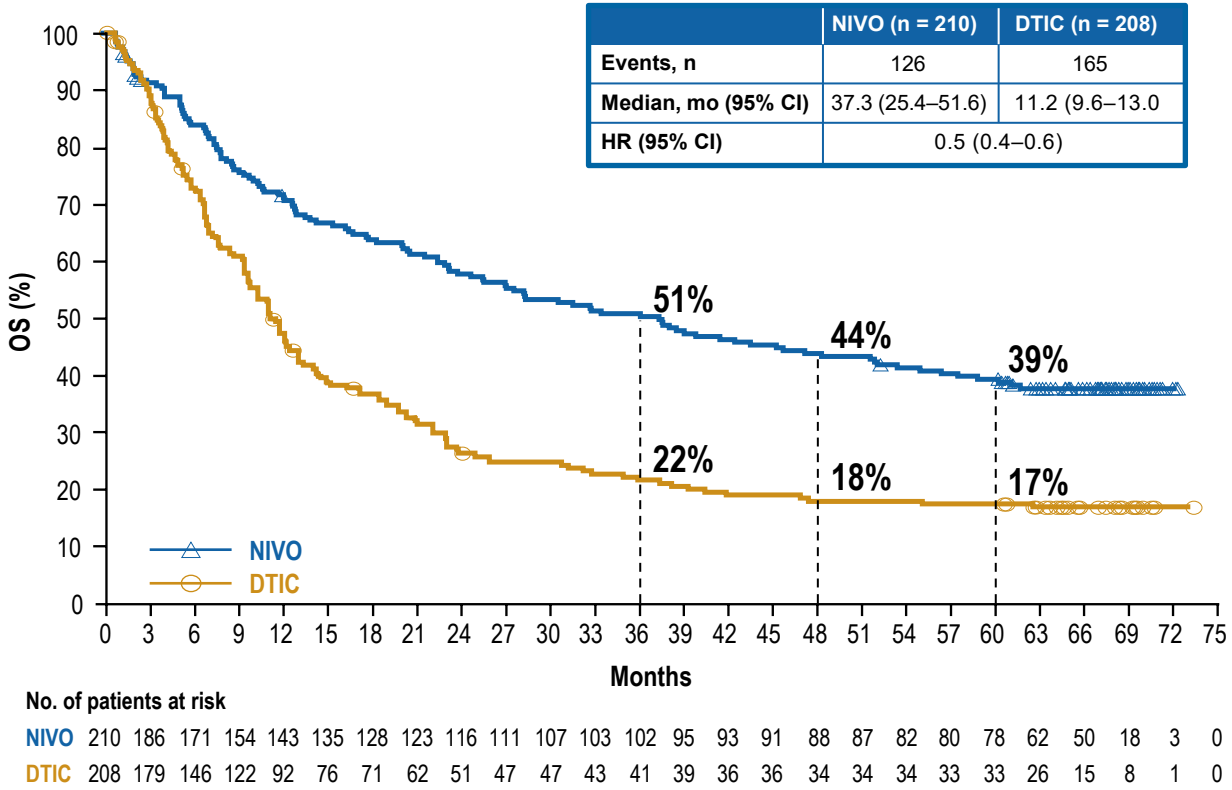
NSCLC: in combination with ipilimumab and 2 cycles of platinum-based chemotherapy first-line, tumors having no sensitizing EGFR mutation or ALK translocation.
MPM: in combination with ipilimumab; unresectable
RCC: monotherapy after prior chemotherapy, or first-line in combination with ipilimumab, or first-line in combination with cabozantinib; advanced
- Significant increase as monotherapy in OS vs everolimus: HR 0.73, p = 0.0018; n = 821
- Significant increase as combination in OS vs sunitinib: HR 0.63, p < 0.0001; n = 847

SCCHN: monotherapy after platinum-based therapy; recurrent or metastatic
- Significant increase in OS vs everolimus: HR 0.71, p = 0.0048; n = 361

cHL: monotherapy; relapsed or refractory
Urothelial carcinoma: monotherapy after failure of prior platinum-containing therapy; advanced unresectable or metastatic
Adjuvant urothelial carcinoma: monotherapy; MIUC with tumor PD-L1≥1%; high risk of recurrence
ESCC: monotherapy after prior fluoropyrimidine- and platinum-based combination chemotherapy, or in combination with ipilimumab first-line (with tumor PD-L1≥1%), or in combination with fluoropyrimidine- and platinum-based combination chemotherapy (with tumor PD-L1≥1%); unresectable advanced, recurrent or metastatic
Adjuvant EC or GEJC: monotherapy; residual pathologic disease following prior neoadjuvant chemoradiotherapy
Gastric, GEJ or esophageal adenocarcinoma: in combination with fluoropyrimidine- and platinum-based combination chemotherapy; HER2-negative advanced or metastatic; tumors express PD-L1 with a combined positive score (CPS) ≥ 5
dMMR/MSI-H CRC: in combination with ipilimumab after prior fluoropyrimidine-based combination chemotherapy

Survival outcomes in CheckMate 066 at 5 years[2a]

	NIVO (n = 210)	DTIC (n = 208)
Events, n	126	165
Median, mo (95% CI)	37.3 (25.4–51.6)	11.2 (9.6–13.0
HR (95% CI)	0.5 (0.4–0.6)	



No. of patients at risk

NIVO	210	186	171	154	143	135	128	123	116	111	107	103	102	95	93	91	88	87	82	80	78	62	50	18	3	0
DTIC	208	179	146	122	92	76	71	62	51	47	47	43	41	39	36	36	34	34	34	33	33	26	15	8	1	0

[a]minimum follow-up was 60 months from the last patient randomly assigned. With a median follow-up of 32.0 months for nivolumab and 10.9 months for dacarbazine (database lock April 9, 2019).

cHL, classical Hodgkin lymphoma; CRC, colorectal cancer; dMMR, mismatch repair deficient; DTIC, dacarbazine; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; GEJC, gastro-esophageal junction cancer; HR, hazard ratio; MIUC, muscle-invasive urothelial carcinoma; MPM, malignant pleural mesothelioma; MSI-H, microsatellite instability-high; NIVO, nivolumab; NSCLC, non-small-cell lung cancer; OS, overall survival; RCC, renal cell carcinoma; SCCHN, squamous cell cancer of the head and neck. 1. Opdivo SmPC 2022. Available fromhttps://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf [Accessed October 2022]. 2. Robert C, et al. J Clin Oncol 2020;38:3937–46.

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

PD-1 inhibitors: clinical overview and selected key data (2)

Pembrolizumab licensed indications[1]

Melanoma: monotherapy; advanced (unresectable or metastatic)
Adjuvant melanoma: monotherapy; undergone complete resection
- Higher RFS at 18 months vs placebo: 72% vs 54%

NSCLC:
Monotherapy; first-line metastatic and after prior chemotherapy
- First-line significant increase in OS vs chemotherapy: HR 0.63, p = 0.002; n = 305
- After prior chemotherapy significant increase for 2 mg/kg and 10 mg/kg vs chemotherapy (n = 1,033)
  - TPS ≥ 1% OS: HR 0.77, p = 0.00128 (n = 687); HR 0.61, p < 0.001 (n = 689), respectively
  - TPS ≥ 50% OS: HR 0.56, p < 0.001 (n = 291); HR 0.50, p < 0.001 (n = 303)

Combination; first-line metastatic
- Combination with pemetrexed and platinum chemotherapy significant increase in OS vs placebo with pemetrexed and platinum chemotherapy: HR 0.49, p < 0.00001 (n = 616)
- Combination with carboplatin and either paclitaxel or nab-paclitaxel significant increase in OS vs placebo with carboplatin and either paclitaxel or nab-paclitaxel: HR 0.64, P = 0.0008; n = 559

cHL: monotherapy; relapsed or refractory
- ORR = 69% (pembrolizumab 200 mg every 3 weeks (n = 210)

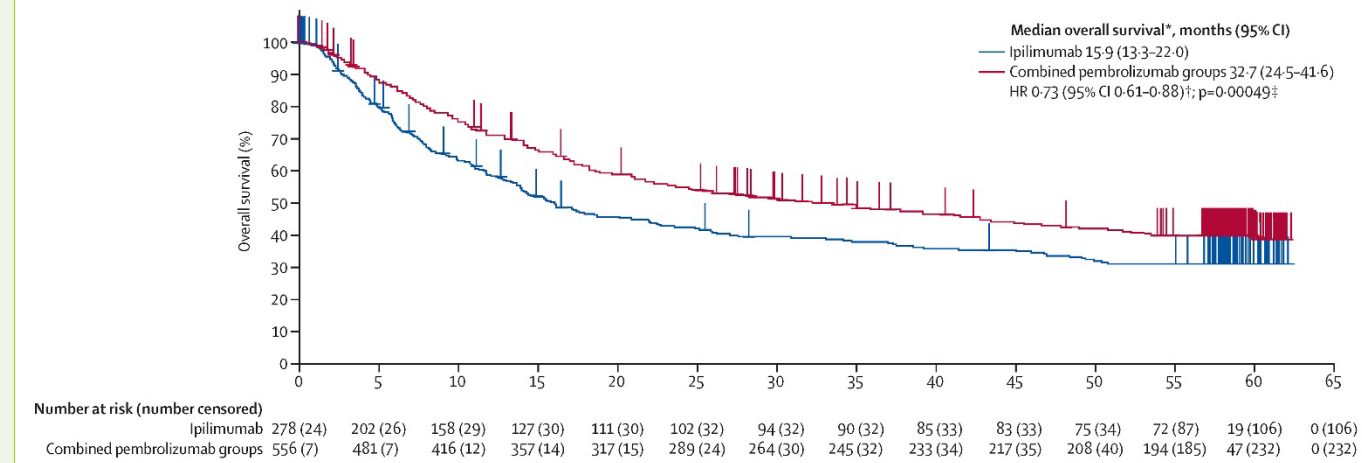
Urothelial carcinoma: monotherapy after prior chemotherapy and in patients who are not eligible for chemotherapy; locally advanced or metastatic
- After prior chemotherapy: significant increase in OS vs chemotherapy: HR 0.70, p < 0.001; n = 542
- Ineligible for chemotherapy: median OS (95% CI) 11.3 (9.7–13.1) months (n = 370)

HNSCC: monotherapy, or in combination with chemotherapy first-line; metastatic or unresectable. Monotherapy progressing on or after chemotherapy; recurrent or metastatic
- Significant increase in OS as monotherapy vs standard treatment: HR 0.74, p = 0.00133 (n = 512)
- Significant increase in OS as combination vs standard treatment: HR 0.65, p = 0.00002 (n = 477)
- Significant increase in OS as monotherapy after chemotherapy: HR 0.53, p = 0.001 (n = 129)

RCC: combination; first-line; advanced
- Significant increase in OS vs sunitinib: HR 0.53, p = 0.00005 (n = 861)

Adjuvant RCC: monotherapy; increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions
dMMR/MSI-H CRC: monotherapy, first-line (metastatic) or after previous fluoropyrimidine-based combination therapy (unresectable or metastatic)
dMMR/MSI-H non-CRC: monotherapy; following prior treatment with a platinum-containing therapy (advanced or recurrent) or following at least one prior therapy (unresectable or metastatic)
ESCC: combination; first-line; advanced unresectable or metastatic or HER-2 negative gastroesophageal junction adenocarcinoma, (PD-L1 CPS ≥ 10)
TNBC: combination as neoadjuvant followed by monotherapy as adjuvant (locally advanced, or early-stage), or combination (locally recurrent unresectable or metastatic)
EC: combination following prior treatment; advanced or recurrent
Cervical cancer: combination; persistent, recurrent, or metastatic

Overall survival in the total study population: post-hoc 5-year results[2]



cHL, classical Hodgkin lymphoma; CI, confidence interval; CRC, colorectal cancer; dMMR, mismatch repair deficient; EC, endometrial carcinoma; ESCC, esophageal squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer.

1. Keytruda SmPC 2021. Available from: https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf [accessed October 2022]. 2. Robert C, et al. Lancet Oncol 2019;20:1239-51.

PD-L1 inhibitors: clinical overview and selected key data

PD-L1 inhibitors: licensed indications

Avelumab[1]

- **Merkel cell carcinoma**: monotherapy; metastatic
- **Urothelial carcinoma**: monotherapy first-line; locally advanced. Monotherapy; metastatic & progression-free following platinum-based chemotherapy
- **RCC:** in combination with axitinib for the first-line treatment; advanced

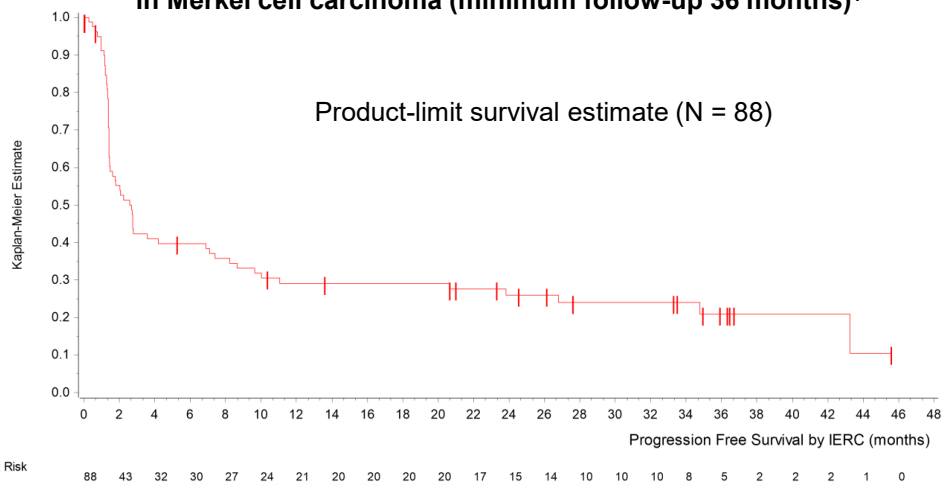
Atezolizumab[2]

- **Urothelial carcinoma**: monotherapy; locally advanced or metastatic; after prior platinum-containing chemotherapy, or who are considered cisplatin ineligible, and whose tumors have a PD-L1 expression ≥ 5%
- **Early-stage NSCLC:** monotherapy; adjuvant treatment following complete resection and platinum-based chemotherapy
- **NSCLC:** monotherapy; locally advanced or metastatic after prior chemotherapy. Monotherapy; first-line; in patients whose tumors have a PD-L1 expression ≥ 50% TC or ≥ 10% tumour-infiltrating immune cells and do not have EGFR mutant or ALK-positive. Combination with bevacizumab, paclitaxel and carboplatin as first-line in metastatic non-squamous, and following failure of targeted therapies in patients with EGFR-mutant or ALK-positive. Combination with nab-paclitaxel and carboplatin; first-line; metastatic non-squamous patients who do not have EGFR mutant or ALK-positive
- **SCLC:** first-line in combination with carboplatin and etoposide; extensive stage
- **TNBC:** combination with nab-paclitaxel
- **HCC:** first-line in combination with bevacizumab; advanced or unresectable

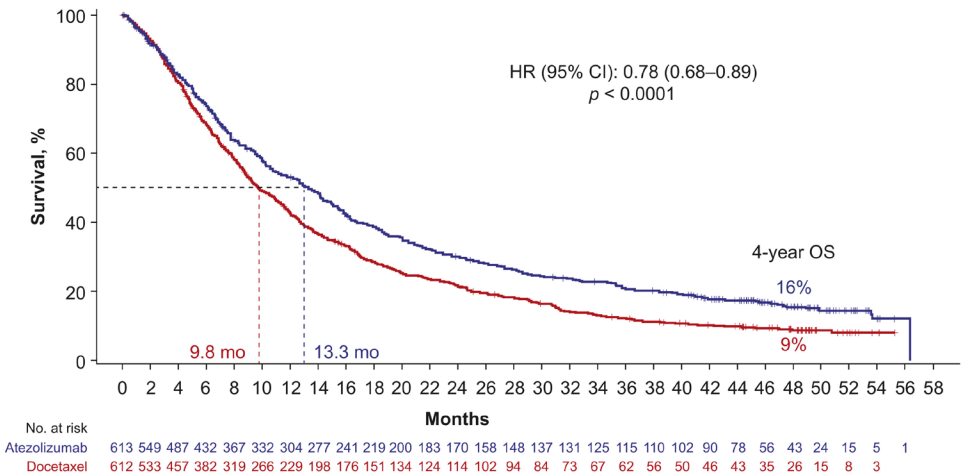
Durvalumab[3]

- **NSCLC:** monotherapy in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy; locally advanced, unresectable
- **ES-SCLC**: in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer

Kaplan-Meier estimates of PFS per RECIST v1.1, IERC for avelumab in Merkel cell carcinoma (minimum follow-up 36 months)[1]



4-year OS with atezolizumab vs docetaxel in NSCLC[4]



Data cutoff, January 9, 2019. Median follow-up: 47.7 months

CI, confidence interval; EMA, European Medicines Agency; HCC, hepatocellular carcinoma; IERC, Independent Endpoint Review Committee; MAA, Marketing Authorization Application; MCC, Merkel cell carcinoma; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; RCC, renal cell carcinoma; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer.

1. Bavencio SmPC 2022. 2. Tecentrc SmPC 2022. 3. Imfinzi SmPC 2022. All SmPCs available from: http://www.ema.europa.eu. 4. Mazieres J, et al. J Thorac Oncol 2021;16:140-50.

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

PD-1/PD-L1 checkpoint inhibitors: selected adverse events

- Owing to the immune-stimulatory action, PD-1/PD-L1 inhibitors are associated with a range of inflammatory- and immune-related AEs[1]
- These include dermatologic, gastrointestinal, endocrine, hepatic, immune system, infections, metabolic, musculoskeletal/connective tissue, nervous system, renal and respiratory toxicities[2–4]

Frequency of any-grade AEs reported with PD-1/PD-L1 inhibitors[5]

		PD-1 inhibitors (%)	PD-L1 inhibitors (%)
Dermatologic[4]	Rash and/or pruritus	~34	Not reported
Gastrointestinal[4]	Diarrhea, nausea or vomiting, colitis	Few data available	Few data available
Endocrine[4]	Hypophysitis	Very rare	Very rare
	Thyroid dysfunction	5–10	5–10
Hepatic[4]	Hepatitis	5–10 (single agent) Up to 30 (in combination with CTLA-4 blockade)	5–10 (single agent) Up to 30 (in combination with CTLA-4 blockade)
Other[4]	Fatigue	16–37	12–24
Pulmonary	Cough, dyspnea[4]	20–40	20–40
	Pneumonitis[5]	3.6	1.3
Other reported rare (≤ 1%) toxicities include neurologic, cardiac, hematologic, ocular, and renal toxicities[3]			

Published guidance on the management of checkpoint-inhibitor toxicities is available[5–12]

AE, adverse event; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

1. Pillai et al. Cancer 2018;271–7. 2. Gelao et al. Toxins 2014;6:914–33. 3. Villadolid Amin A. Transl Lung Cancer Res 2015;4:560–75. 4. Almutairi A, et al. Front Oncol 2020;10:91. 5.Haanen et al. Ann Oncol 2017;28(suppl_4):iv119–42. 6. Khunger et al. Chest 2017;152:271–81. 7. Puzanov et al. J Immunother Cancer 2017;5:95. 8. Davies & Duffield. Immunotargets Ther 2017;6:51–71. 9. Brahmer et al. J Clin Oncol 2018;JCO2017776385 (Epub ahead of print). 10. Aspeslagh et al. BMSO ImmunoManager. Available from: https://www.bsmo.be/immunomanager/. Accessed October 2022. 11. NCCN Clinical Practice Guidelines. Management of Immunotherapy-Related Toxicities. Version 1.2022 — February 28, 2022. Accessed Aug 2022. 12. Castinetti F et al. French Endocrine Society Guidance on endocrine side effects of immunotherapy, Endocrine-Related Cancer (2019) 26, G1–G18

Checkpoint inhibitors 2: LAG-3 inhibitors

Types of immunotherapy

LAG-3 checkpoint inhibitors: the role of LAG-3

LAG-3 is a cell-surface molecule expressed on T cells and other immune cells. It regulates an inhibitory immune checkpoint pathway that limits the activity of T cells[1,2]

What does LAG-3 do?

- Increased expression of LAG-3 on CD8+ and CD4+ TILs, especially in the context of PD-1 expression, inhibits effector T-cell function[1,3–5]
- LAG-3 activity results in reduced T-cell activation and proliferation, and attenuates proinflammatory cytokine responses, such as IFN-γ, IL-2, and TNF-α[1,6,7]
- Activation of the LAG-3 pathway, which occurs when LAG-3 interacts with its ligands, triggers inhibitory activity that reduces the function of effector T cells, leading to an impaired ability to attack tumor cells and an increased potential for tumor growth[1,5]

LAG-3, lymphocyte-activation gene 3; TILs, tumor–infiltrating lymphocytes.

1. Long L, et al. Genes Cancer 2018;9:176–89; 2. Grosso JF, et al. J Clin Invest 2007;117:3383–92; 3. Workman CJ, et al. J Immunol 2004;172:5450-55; 4. Woo SR, et al. Cancer Res 2012;72:917-27; 5. Andrews LP, et al. Sci Immunol 2020;5:eabc2728; 6. Huang RY, et al. Oncoimmunology 2017;6:e1249561; 7. Maçon-Lemaître L, Triebel F. Immunology 2005;115:170–8

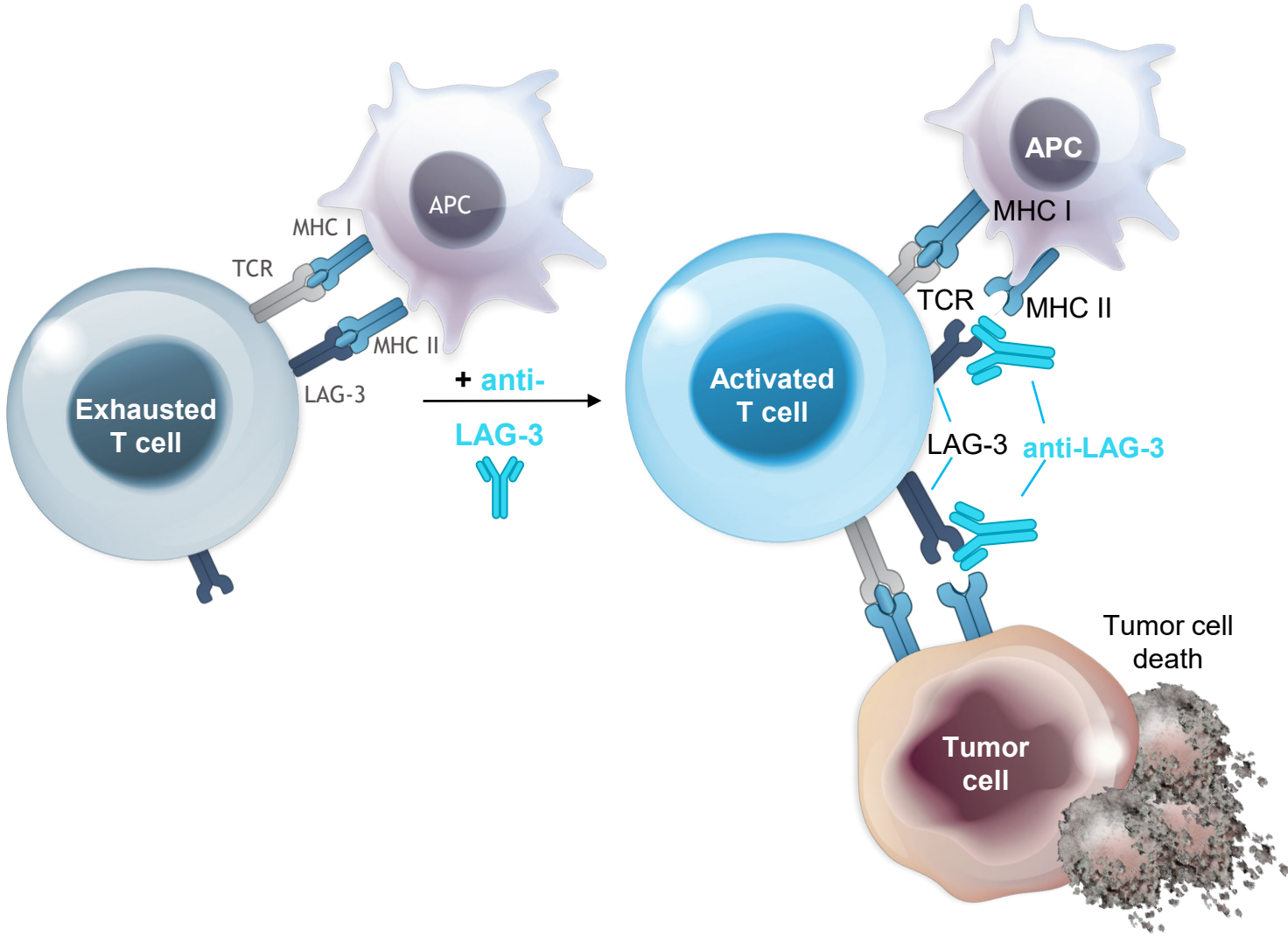
LAG-3 checkpoint inhibitors: targeting LAG-3

Targeting LAG-3[1–4]

- The interaction of LAG-3 with its ligands triggers inhibitory activity. Ligands for LAG-3 are distinct from the ligands of other inhibitory immune checkpoints such as PD-1 or CTLA-4. Among its ligands, the most well-established is MHC II; others are emerging, including FGL1

LAG-3 inhibitors: mechanism of action[1,5–9]

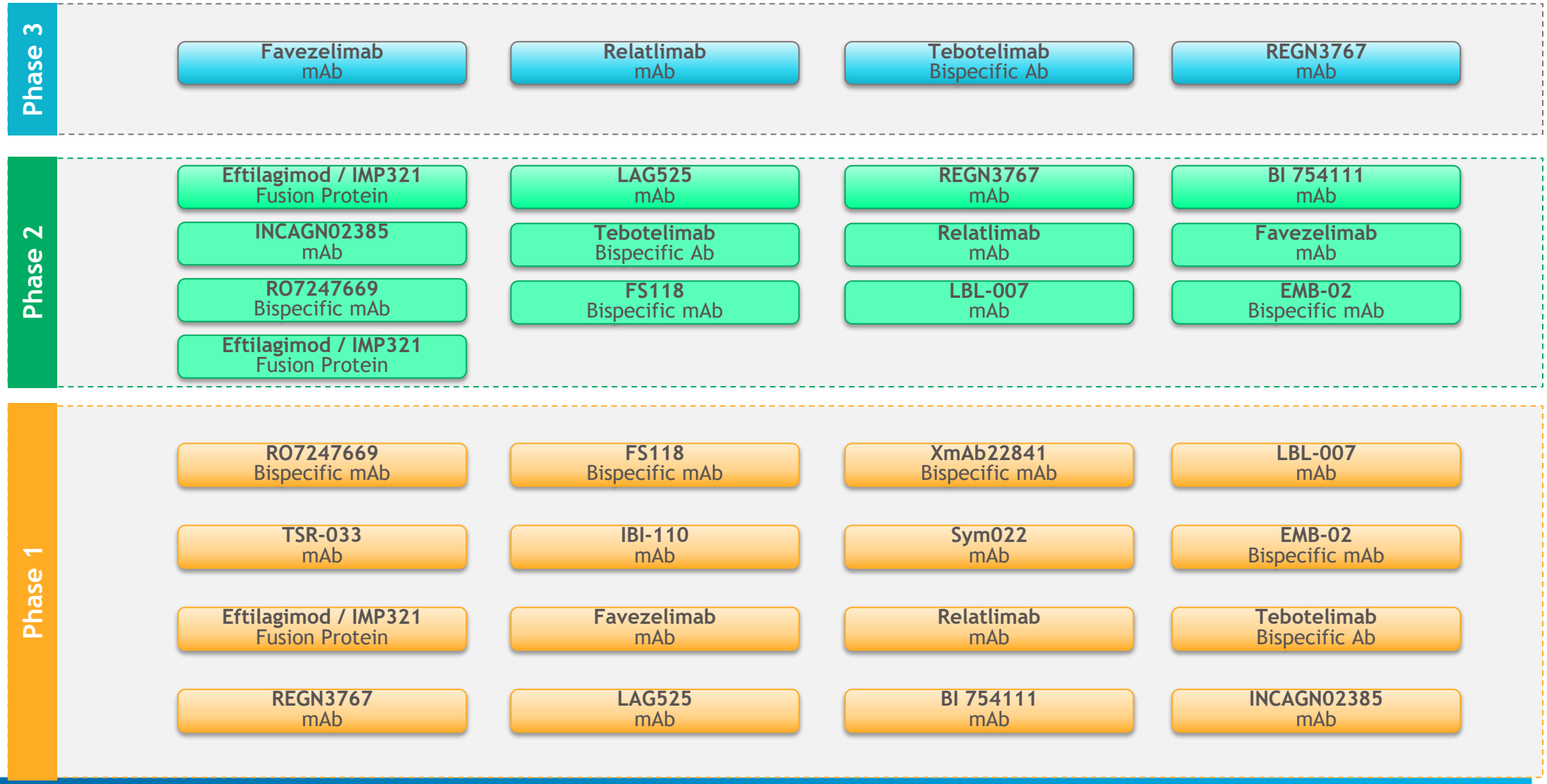
- LAG-3–blocking antibodies binds to LAG-3 on T cells, restoring effector function of exhausted T cells, and enhancing the immune response against cancer



FGL1, fibrinogen-like protein 1;

1. Long L, et al. Genes Cancer 2018;9:176–89; 2. Huang RY, et al. Oncoimmunology 2017;6:e1249561; 3. Wang J, et al. Cell 2019;176:334-47.e12; 4. Maçon-Lemaître L, Triebel F. Immunology 2005;115:170–8; 5. Ruffo E, et al. Semin Immunol 2019;42:101305; 6. Grosso JF, et al. J Clin Invest 2007;117:3383-92; 7. He Y, et al. Cancer Sci 2016;107:1193-7; 8. Nguyen LT, Ohashi PS. Nat Rev Immunol 2014;15:45-56; 9. Anderson AC, et al. Immunity 2016;44:989-1004

LAG-3 inhibitors: overview of agents in Phase I–III trials



ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/home. Accessed Aug 2022.

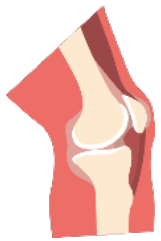
For full information of individual agents, always refer to the Summary of Product Characteristics

TNF-blocking agents

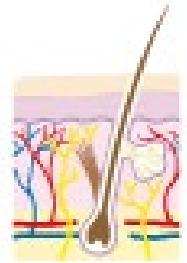
Types of immunotherapy

An overview of TNF-blocking agents

- The dysregulation of **cytokines**, such as TNFα, has been found to play a vital role in the pathogenesis of immune-mediated inflammatory diseases
- TNF-blocking agents are approved for the treatment of many non-malignant, inflammatory diseases, notably in **rheumatology**, **dermatology**, and **gastroenterology**, among others (not covered in this module)



- Infliximab
- Etanercept
- Adalimumab
- Certolizumab
- Golimumab



- Infliximab
- Etanercept
- Adalimumab

- Infliximab
- Adalimumab
- Certolizumab
- Golimumab

Images are not related to specific indications, but a broad category of disease types.
TNF, tumor necrosis factor.
1. Armuzzi et al. Int J Immunopathol Pharmacol 2014;27(1 Suppl.):11–32; 2. Zhang H, et al. Genes Dis 2020;8:38–47.
For full information of individual agents, always refer to the Summary of Product Characteristics

TNF-blocking agents and their mechanisms of action

- TNF-blocking agents can either be **whole antibodies** (such as infliximab, adalimumab, and golimumab) or pegylated **Fab fragments (**certolizumab)[1]
- TNFα has a key role in the pathogenesis of inflammatory diseases such as **rheumatoid arthritis** and **inflammatory bowel disease**[2]
- The **binding and neutralizing of sTNFα** is the key, common mechanism of action of TNF-blocking agents;[2] however, their **mechanisms of action may vary,** despite them occasionally having the same targets[2]

Etanercept[3]
Binds sTNF α, preventing its interaction with the receptor

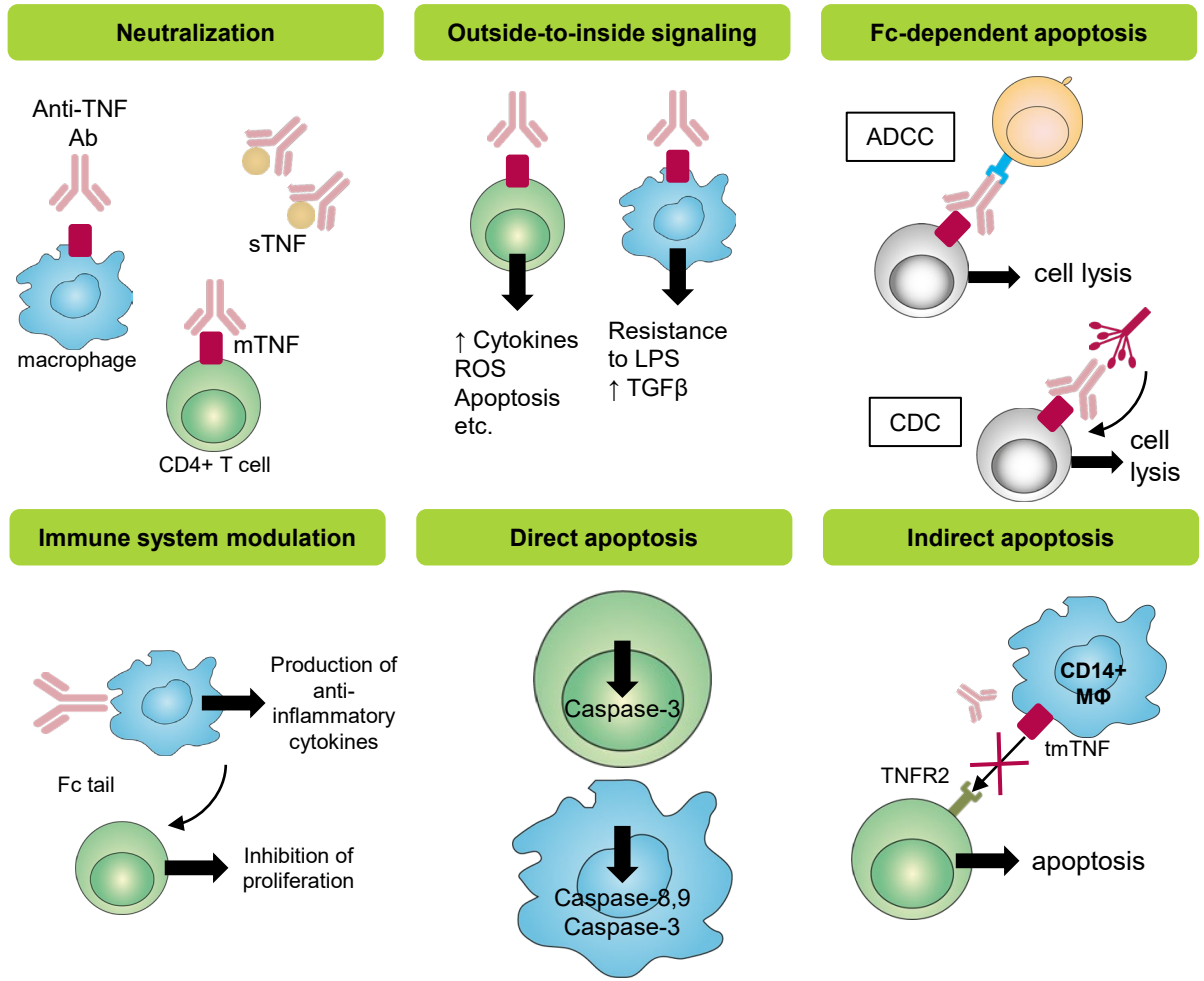
Infliximab[3]
Binds and neutralizes both sTNFα and tmTNF and can fix complement and cause cell apoptosis

Golimumab[4]
Binds sTNFα and tmTNF; neutralizes TNFα-induced E-selectin expression by endothelial cells

Certolizumab[3,5]
is unique in that it does not have the Fc portion of the antibody and has a pegylated Fab fragment. It binds and neutralizes sTNF and tmTNF

Adalimumab[3]
Binds to sTNFα and prevents its interaction with TNFR1 and TNFR2 receptors.

Mechanisms of action of anti-TNF antibodies[6]



Ab, antibody; ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity; LPS, lipopolysaccharide; MΦ, macrophage; ROS, reactive oxygen species; sTNF, soluble tumor necrosis factor; TGFβ, transforming growth factor beta; tmTNF, transmembrane tumor necrosis factor; TNFR1/2, tumor necrosis factor receptor 1/2.

1. Armuzzi et al. Int J Immunopathol Pharmacol 2014;27(1 Suppl.):11–32. 2. Mitoma et al. Cytokine 2018;101:56–63. 4.3. Sehgal et al. Indian J Dermatol 2014;59:425–41. 4. Shealy et al. MAbs 2010;2:428–9. 4. Goel & Stephens. MAbs 2010;2:137–47. 6. Billmeier et al. World J Gastroenterol 2016;22:9300–13.

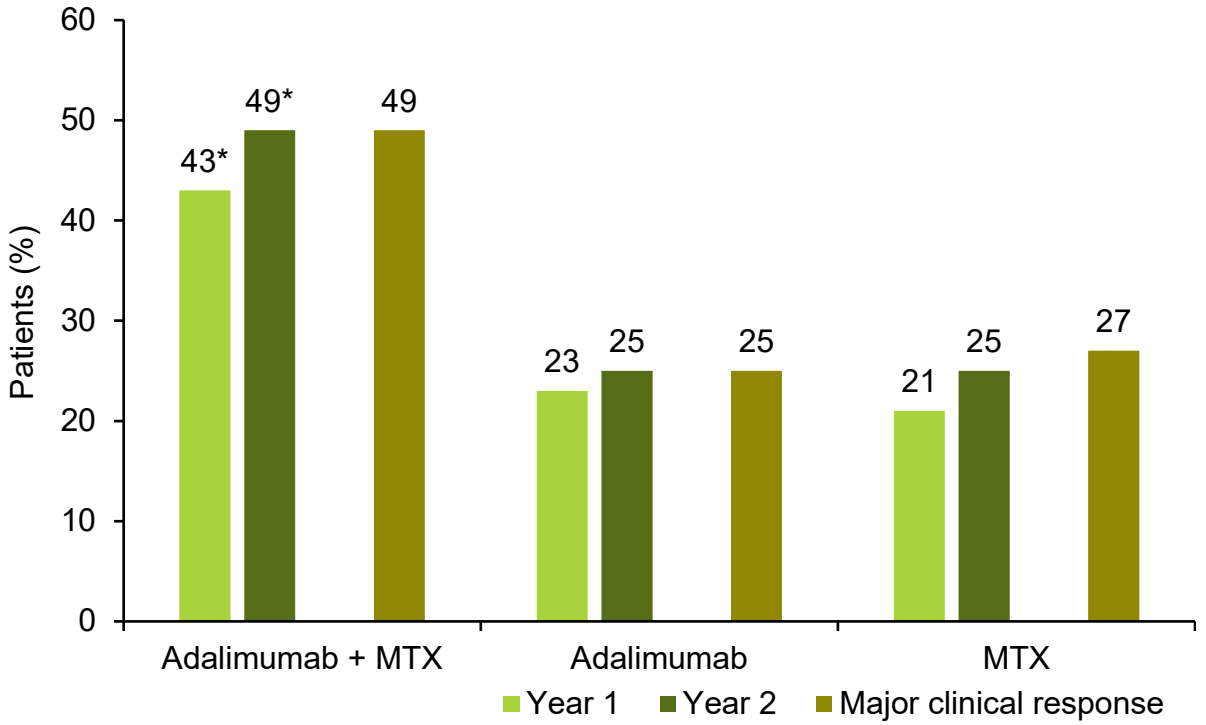
For full information of individual agents, always refer to the Summary of Product Characteristics

TNF-blocking agents: clinical overview and selected key data

- In many patients with rheumatic diseases (e.g. rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis) who are resistant to first-line therapies, TNF-blocking agents are used in combination with MTX, in view of the synergy between both categories of drugs

TNF-blocking agents: licensed indications	
Infliximab[1]	Rheumatoid arthritis, Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, psoriasis
Adalimumab[2]	Rheumatoid arthritis, psoriasis, hidradenitis suppurativa, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, pediatric plaque psoriasis, pediatric Crohn's disease, ulcerative colitis, uveitis, pediatric uveitis
Golimumab[3]	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis
Certolizumab[4]	Rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, plaque psoriasis
Etanercept[5]	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, axial spondyloarthritis, plaque psoriasis, pediatric plaque psoriasis

Clinical remission at Years 1 and 2 and major clinical response at Year 2 in adalimumab ± MTX in patients with early, aggressive rheumatoid arthritis[6]



*p < 0.001 versus adalimumab alone and versus MTX alone.

MTX, methotrexate; TNF, tumor necrosis factor.

1. Remicade SmPC 2022. 2. Humira SmPC 2022. 3. Simponi SmPC 2022 4. Cimzia SmPC 2022. 5. Enbrel SmPC 2022. All SmPCs available from: http://www.ema.europa.eu and accessed October 2022. 6. Breedveld et al. Arthritis Rheum 2006;54:26–37.

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

TNF-blocking agents: selected adverse events

AEs associated with TNF-blocking agents[1,2]

	Example
Infections	Tuberculosis, serious infections
Infusion reactions	Anaphylaxis, delayed-type hypersensitivity
Autoimmunity	Antinuclear antibodies, systemic lupus erythematosus
Malignancies	Non-melanoma skin cancer
Demyelinating disorders	Guillain-Barré syndrome, multiple sclerosis
Abnormal liver function tests	Hepatitis, cholestatic disease
Cardiac abnormalities	Heart failure
Skin eruptions	'Paradoxical' psoriasis

- **Neutralizing antibody formation**
  - Commonly reported with infliximab and adalimumab[1]
- **Tuberculosis**
  - Risk is lower with etanercept vs infliximab and adalimumab[3]
- **Life vaccines**
  - Administration of life vaccines is presently contraindicated in patients receiving TNF-blocking agents
- **Surgical site infections**
  - Increased risk in patients with RA who use or have recently used anti-TNFs at the time of orthopedic surgery[4]
- **Heart failure**
  - Administration of TNF-blocking agents is contraindicated in patients with impaired cardiac function
- **Non-melanoma skin cancer**
  - TNF-blocking agents are presently contraindicated in patients with past history of cancer

This list is not exhaustive. Specific adverse events depend on the target of individual agent used.

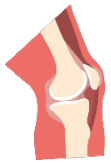
AE, adverse event; RA, rheumatoid arthritis; TNF, tumor necrosis factor.

1. Hoentjen & van Bodegraven. World J Gastroenterol 2009;15:2067–73. 2. Connor. Rheumatol Int 2011;31:327–37. 3. Dixon et al. Ann Rheum Dis 2010;69:522. 4. Goodman et al. Rheumatology (Oxford) 2016;55:573–82. 5. Mercer et al. Ann Rheum Dis 2012;71:869–74.

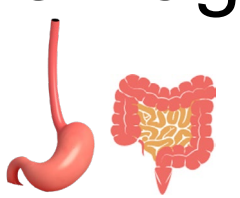
Other monoclonal antibodies

Types of immunotherapy

Monoclonal antibodies have become one of the largest classes of new agents approved in the past decade



Non-malignant diseases
- Eculizumab
- Infliximab
- Golimumab
- Certolizumab pegol
- Tocilizumab
- Etanercept
- Adalimumab
- Secukinumab



Malignancies
- Ramucirumab
- Golimumab
- Panitumumab
- Cetuximab
- Trastuzumab
- Pembrolizumab
- Nivolumab
- Bevacizumab

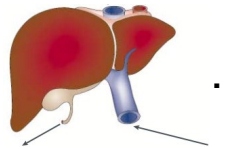
Non-malignant diseases
- Infliximab
- Ustekinumab
- Adalimumab

Malignancies
- Daratumumab
- Elotuzumab
- Obinutuzumab
- Rituximab
- Ibritumomab tiuxetan
- Pembrolizumab
- Nivolumab

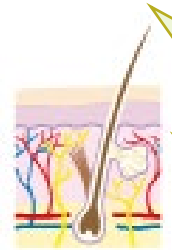
Non-malignant diseases
- Mepolizumab

Malignancies
- Bevacizumab
- Pembrolizumab
- Ramucirumab
- Nivolumab
- Cemiplimab
- Atezolizumab
- Durvalumab

Non-malignant diseases
- Reslizumab
- Mepolizumab
- Omalizumab



Malignancies
- Ramucirumab

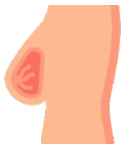


Learn more about anti-CTLA-4 Mabs

Learn more about anti-PD-1/L1 Mabs

Malignancies
- Bevacizumab
- Belimumab
- Pembrolizumab
- Nivolumab
- Avelumab
- Cemiplimab

Non-malignant diseases
- Secukinumab
- Infliximab
- Ustekinumab
- Etanercept
- Adalimumab
- Golimumab
- Certolizumab



Malignancies
- Trastuzumab
- Bevacizumab
- Trastuzumab emtansine
- Pertuzumab
- Atezolizumab

Malignancies
- Bevacizumab
- Pembrolizumab
- Nivolumab
- Avelumab

Non-malignant diseases
- Basiliximab

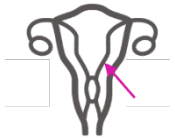
Malignancies
- Natalizumab
- Alemtuzumab

Non-malignant diseases
- Ofatumumab

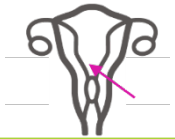
Malignancies
- Cetuximab
- Pembrolizumab
- Nivolumab

Non-malignant diseases
- Mepolizumab
- Omalizumab

Malignancies
- Pembrolizumab
- Nivolumab
- Atezolizumab
- Avelumab



Malignancies
- Pembrolizumab
- Dostarlimab
- Bevacizumab



Malignancies
- Pembrolizumab
- Bevacizumab

This list is not exhaustive. Images are not related to specific indications, but a broad category of disease types.

1. Falzone L, et al. Front Pharmacol 2018 ;9:1300. 2. Remicade SmPC 2022. 3. Humira SmPC 2022. 4. Simponi SmPC 2022. 5. Cimzia SmPC 2022. 6. Enbrel SmPC 2022.
All SmPCs available from: http://www.ema.europa.eu [accessed October 2022].

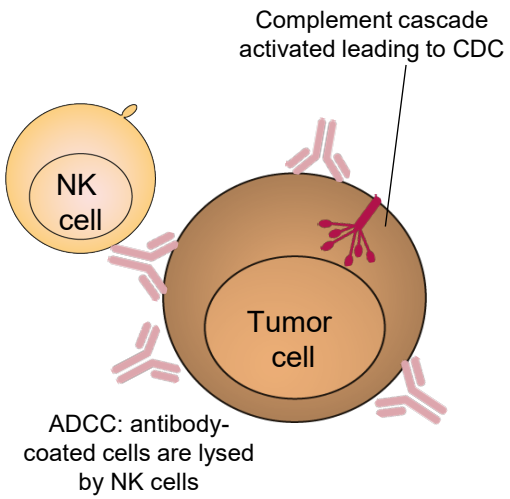
For full information of individual agents, always refer to the Summary of Product Characteristics

www.immunoscienceacademy.be

Monoclonal antibodies and their mechanism of action

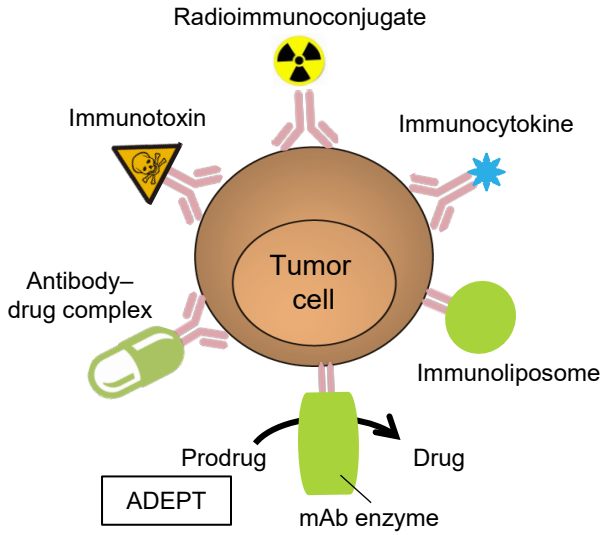
- The most commonly used class of therapeutic antibody is IgG, which is divided into subclasses based on unique properties such as ADCC and CDC[1]
- Monoclonal antibodies are used in a range of therapeutic areas and are particularly known for their multifactorial antitumor mechanisms.[1,2] Effector mechanisms of therapeutic monoclonal antibodies include:

Native IgG mechanisms[3]



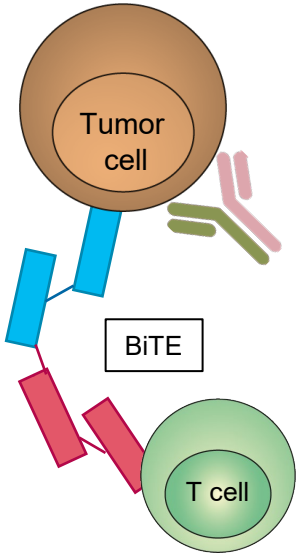
Fc region of mAb promotes cell death via ADCC and CDC[2]

Immunoconjugates[3]



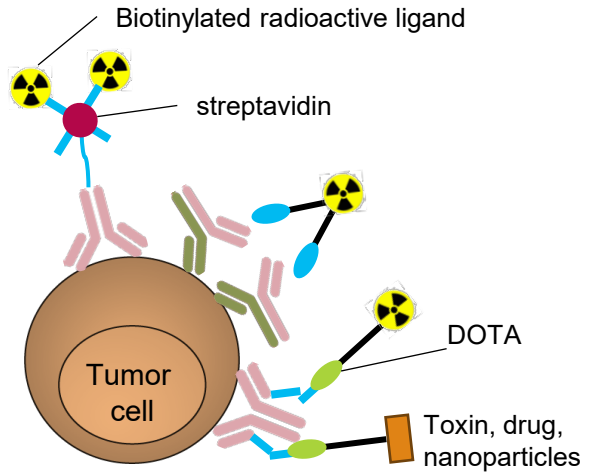
Target cell killing can be enhanced by using immunoconjugates[2]

Bispecific mAb[3]



A BiTE specifically binds two targets[1] and can enhance the antitumor effect of antibodies[2]

Multistep targeting[3]



A multistep targeted approach enhances antibody access to solid tumors to improved therapy delivery[4]

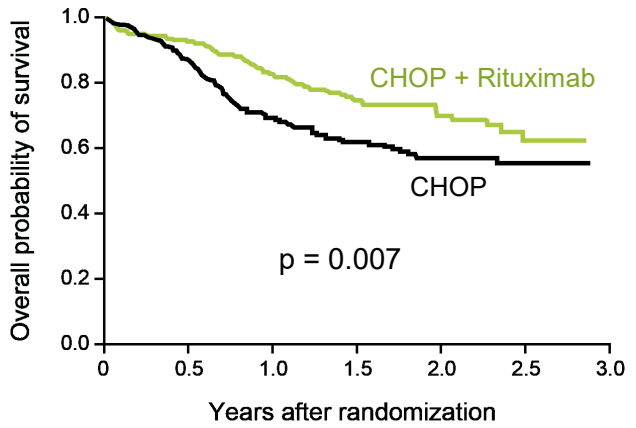
ADCC, antibody-dependent cellular cytotoxicity; ADEPT, antibody-directed enzyme prodrug therapy; BiTE, bispecific T-cell-engaging mAb; CDC, complement-dependent cytotoxicity; DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; mAb, monoclonal antibody; NK, natural killer. 1. Redman et al. Mol Immunol 2015;67:28–45. 2. Cheung. Available from: https://clinicalgate.com/therapeutic-antibodies-and-immunologic-conjugates-2/ [Accessed Aug 2022]. Images adapted from 3. Carter. Nat Rev Cancer 2001;1:118–29. 4. Nguyen et al. Cancer Biol Ther 2010;10:775–9.

Monoclonal antibodies: clinical overview and selected key data

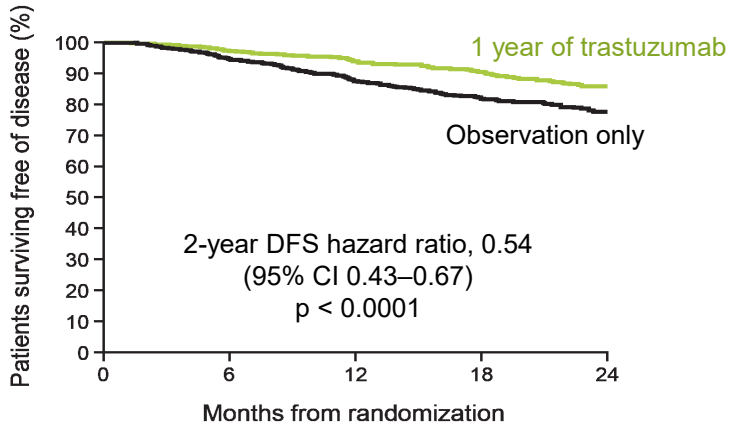
- A large number of monoclonal antibodies have been licensed or are in clinical trials, the majority of which are approved or intended for oncology indications[1]
- Two key approved monoclonal antibodies approved to treat malignancies are rituximab and trastuzumab

Selected monoclonal antibodies: licensed indications	
Rituximab[2]	• **Non-Hodgkin's lymphoma:** FL (first-line advanced; maintenance; relapsed/refractory) and DLBCL (with CHOP) • **Chronic lymphocytic leukemia:** with chemotherapy for previously untreated and relapsed/refractory • **Rheumatoid arthritis:** with MTX • **Granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis:** with glucocorticoids for induction of remission • **Pemphigus vulgaris**
Trastuzumab[3]	• **Breast cancer**: HER2+ metastatic and HER2+ early breast cancer • **Gastric cancer:** adenocarcinoma of the stomach or gastroesophageal junction in combination with chemotherapy for HER2+ metastatic disease

Significant increase in OS with rituximab + CHOP vs CHOP alone in DLBCL (n = 399)[4]



Significant increase in DFS with trastuzumab in metastatic HER2+ breast cancer (n = 1694)[5]



CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; DFS, disease-free survival; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HER, human epidermal growth factor receptor; MTX, methotrexate; OS, overall survival. 1. Redman et al. Mol Immunol 2015;67:28–45. 2. MabThera SmPC 2022. Available from: http://www.ema.europa.eu [Accessed October 2022]. 3. Herceptin SmPC 2021. Available from: http://www.ema.europa.eu [Accessed October 2022]. 4. Coiffier et al. N Engl J Med 2002;346:235–42. 5. Piccart et al. N Engl J Med 2005;353:1659–67.

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

Safety profiles of monoclonal antibodies

- Monoclonal antibodies have a wide range of indications, and their typically low mass and high specificity enable their precise action as a therapy[1]
- However, their use carries some risk of immune reactions

Infusion reactions[2,3]

Usually occur within ≤ 2 h

Affect any organ system

Range from injection-site reactions to potentially life-threatening anaphylaxis

Undesired effects related to the target antigen[2,3]

AEs may be directly related to the biology of the target antigen,

e.g. risk of cardiotoxicity with trastuzumab

Other irAEs[2,3]

Dermatologic, gastrointestinal, endocrine, and other inflammatory reactions

Infections and autoimmunity

Cytokine-release syndrome

AE, adverse event; irAE, immune-related adverse event.

1. Hansel et al. Nat Rev Drug Discov 2010;9:325–82. 2.Demlova et al. Physiol Res 2016;65:S455–62. 3. Perez & Rodeheffer. J Clin Oncol 2004;22:322–9.

Monoclonal antibodies: selected adverse events

- mAbs are established therapies for many conditions, including a range of different cancers[1,2]
- mAbs may be associated with a variety of AEs depending on their type (murine, chimeric, humanized or human, target and conjugate)[1]
- Hypersensitivity reactions (including infusion-related reactions) are the most common and among the most serious AEs associated with mAbs[1,2]
- Different mAbs have different toxicity profiles; associated AEs vary widely and can range from, for example, headache, mild gastrointestinal symptoms, transient rash and itching, to severe cytopenias, cardiac toxicity and anaphylaxis[1]
- For management recommendations see[2]

Selected AEs associated with mAbs[1]

Type of AE	Selected examples
Hematologic and vascular disorders	Thrombocytopenia, neutropenia, anemia, hemolytic anemia, vasculitis, hypertension
Infusion reactions	Anaphylaxis, delayed-type hypersensitivity
Pulmonary AEs	ARDS, bronchospasm, diffuse alveolar hemorrhage, hypersensitivity pneumonitis, interstitial pneumonitis
Neurologic toxicities	Peripheral neuropathies, encephalomyelitis
Hepatic toxicities	Hepatomegaly
Cardiac abnormalities	Cardiopulmonary arrest, arrhythmias, cardiomyopathy, LVD, pericarditis
Dermatologic events	Pruritus, eczema, rash, urticaria, morbilliform eruptions, erythema, petechiae, alopecia
Others	Serum sickness-like reaction, diarrhea, fatigue, infections

This list is not exhaustive. Specific adverse events depend on the target of individual mAb used.

AE, adverse event; ARDS, acute respiratory distress syndrome; ATE, arterial thromboembolic event; CD20/30, cluster of differentiation 20/30; EGFR, epidermal growth factor receptor; LVD, left ventricular dysfunction; mAb, monoclonal antibody; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; VTE, venous thromboembolic event.

1. Baldo. Oncoimmunology 2013;2:e26333. 2. Guan et al. BioMed Res Int 2015;2015:428169.

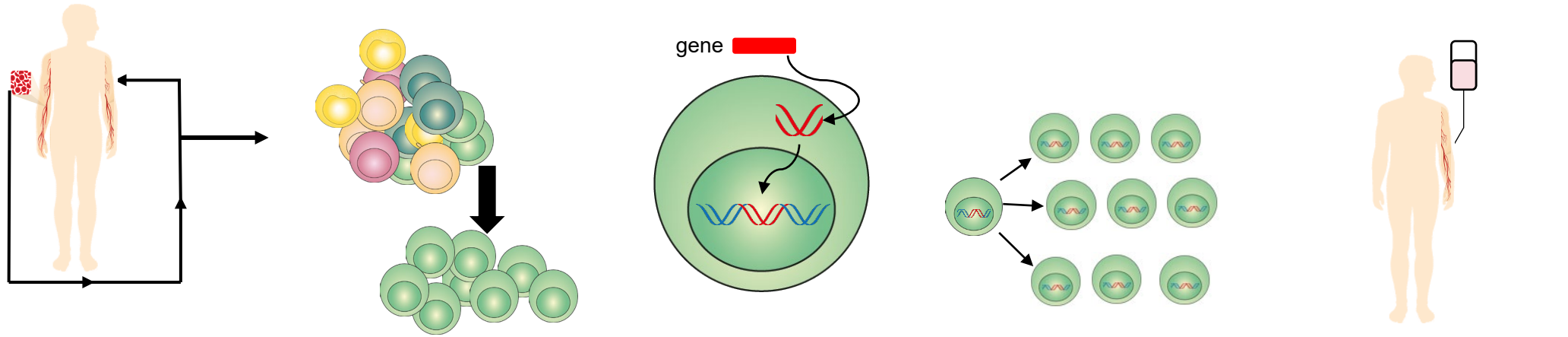
CAR T cells

Types of immunotherapy

An introduction to CAR T cells

- CAR T-cell immunotherapy is a more recently developed adoptive antitumor treatment, which involves harvesting, activating and then genetically modifying a patient's own T cells to recognize a particular TAA abundantly expressed on malignant cells[1]
- Once reinfused back into the patient, CAR T cells then recognize and kill TAA-expressing cells[1]
- CAR T-cell therapies are particularly effective in the treatment of relapsed/refractory B-cell malignancies[1,2]

An overview of the CAR T-cell immunotherapy clinical process[3]



CAR, chimeric antigen receptor; TAA, tumor-associated antigen.

1. Yu et al. J Hematol Oncol 2017;10:1–13. 2. Kerre. Belgian J Hematol 2017;8:94–101. 3. Davila et al. OncoImmunology 2012;1:1577–83. Figure based on information in Davila et al.[3]

Four generations of improved CAR T-cell construct design[1]

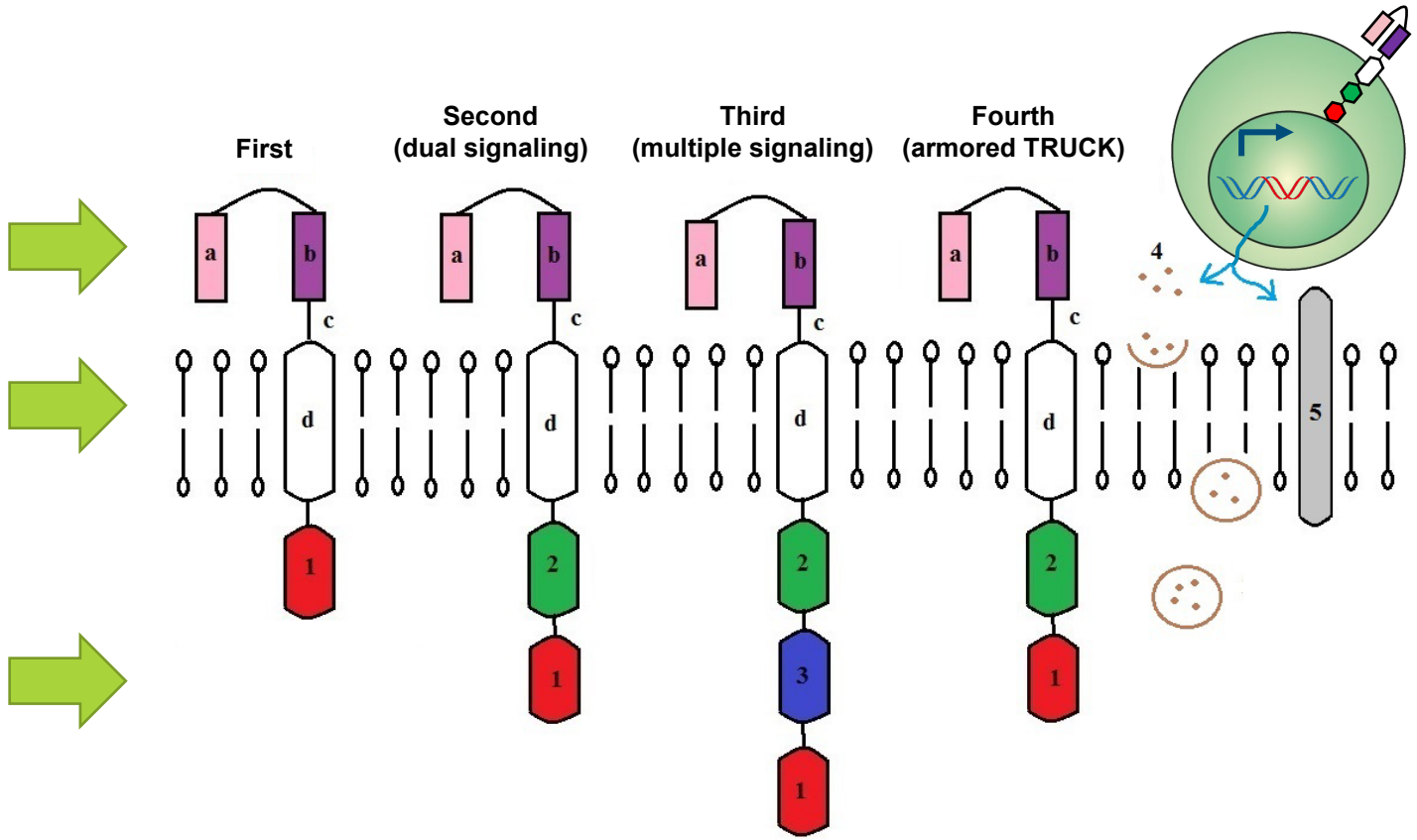
Components of the CAR construct

The extracellular, antigen-binding domain consists of an scFv [a, b]

The hinge [c] and a transmembrane domain [d] connect the extracellular and intracellular parts

The intracellular domain always contains a CD3ζ signaling domain **[1]** (first generation) and is combined with one (second generation) or two (third generation) costimulatory domains **[2, 3]**

The fourth-generation CARs contain an additional inducible cytokine cassette (inducing production of cytokines **[4]**, such as IL-12, upon recognition of the CAR ligand) **[5]**



CAR, chimeric antigen receptor; IL-12, interleukin 12; scFv, single-chain variable fragment; TRUCK, T cell redirected for universal cytokine mediated killing.

1. Kerre. Belgian J Hematol 2017;8:94–101. Figure adapted, with permission, from original artwork kindly provided by Steven Van Schandevyl.

CAR T-cell therapy antigen targets in clinical trials

CAR T cells have been engineered to target many different antigens to treat various cancers

Hematologic malignancies[1]

Antigen	Cancer
BCMA	MM
CD123	AML, leukemia, lymphoma
CD138	MM
CD16V	DLBCL, MCL, PMBCL, FL
CD19	CLL, NHL, ALL, DLBCL, PMBCL, MCL, DLBCL transf. FL, lymphoma, FL, PLL, DMBCL, leukemia, SLL, BAL, HL, MLBCL, MM
CD19/CD20	DLBCL
CD19/CD22	Leukemia, lymphoma
CD20	ALL, CLL, PLL, DLBCL, FL, MCL, leukemia, Lymphoma, SLL, MZL, NHL
CD22	FL, ALL, NHL, DLBCL, MCL, leukemia, lymphoma
CD30	NHL, HL, lymphoma, CD30+ cancer
CD33	AML
CD38[2]	B cell malignancies
CD70	CD70+ cancer
CD123[2]	B cell malignancies
Ig k	CLL, NHL, MM
IL-1RAP	CLL
Lewis Y	MM, AML, MDS
NKG2D ligand	AML, MDS, MM
ROR1	CLL, SLL, MCL, ALL

Solid malignancies[1]

Antigen	Cancer
CAIX	Renal cell carcinoma
CEA	Liver metastases, liver, adenocarcinoma, gastric, colorectal, breast
C-MET	Breast
EGFR	EGFR+ solid tumors, GBM, glioma
EGFRvIII	Glioma, GBM, glioblastoma
EpCam	Liver, stomach, breast
EphA2	Malignant glioma
ErbB2/Her2	HER2+ malignancy, sarcoma, GBM, head and neck, breast, glioblastoma,
FAP	Metastatic mesothelioma
FR-a	Ovarian
GD2	Neuroblastoma, sarcomas
GPC3	Hepatocellular carcinoma, LSCC, GPC3+ solid tumor
IL-13Ra2	Malignant glioma, brain and CNS
L1-CAM	Neuroblastoma
Mesothelin	MPM, MPDAC, malignant pleural disease, pancreatic, breast, mesothelin+ tumors
MUC1	Hepatocellular carcinoma, NSCLC, TNBC, PC, malignant glioma, CC, GC
MUC16ecto	Ovarian
PD-L1	GBM
PSCA	Pancreatic
PSMA	Prostate
ROR1	NSCLC, breast cancer (TNBC)
VEGFR-2	various

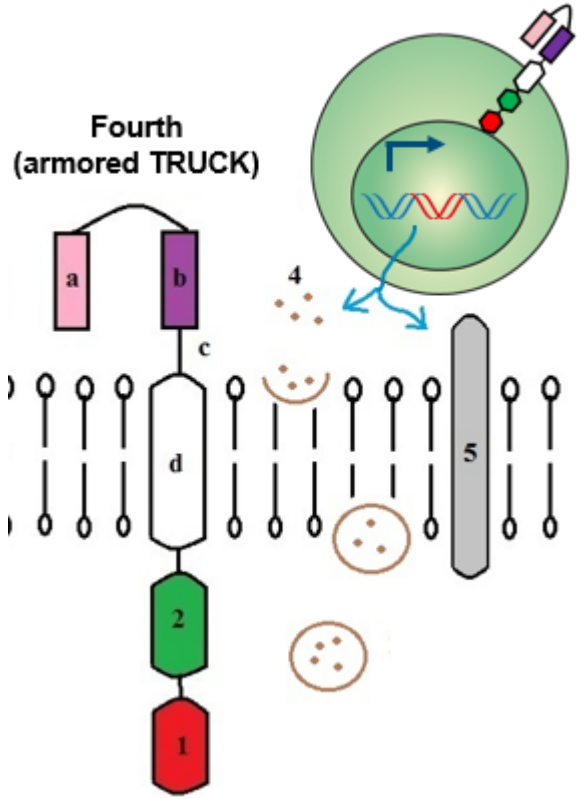
Expanded abbreviations in notes section.

1. Hartmann et al. EMBO Mol Med 2017;9:1183–97. 2. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT03125577 [Accessed Aug 2022].

Efficacy of CAR T-cell therapies[1]

- The biggest successes so far have been achieved with CAR T cells directed toward CD19+ B-cell malignancies
- However, although theoretically feasible, it is not fully clear yet whether this success can be repeated for other hematologic and solid tumors
- In solid tumors, additional challenges exist for CAR T-cell therapy:
  - The anatomical location (challenging for the T cell to traffic towards the heart of the tumor)
  - The heterogeneity of the tumor cells
  - The immune-suppressing microenvironment
- Fourth-generation CARs or 'TRUCKs' could be more effective in solid tumors, as they, by inducing cytokine production in the heart of the tumor, also stimulate the other tumor-infiltrating T cells to kill tumor cells

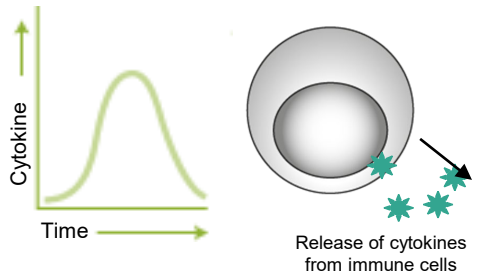
Fourth-generation CARs may be more effective against solid tumors than earlier versions



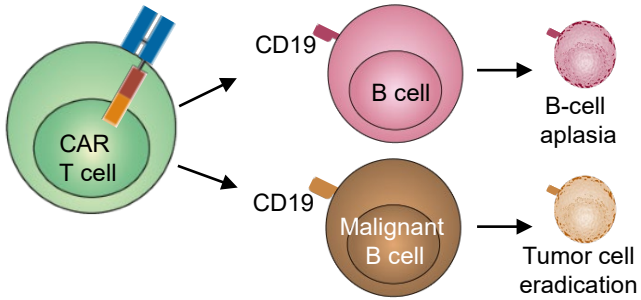
CAR, chimeric antigen receptor; TRUCK, T cell redirected for universal cytokine mediated killing.
1. Kerre. Belgian J Hematol 2017;8:94–101. Figure adapted, with permission, from original artwork kindly provided by Steven Van Schandevyl.

CAR T cells: selected adverse events

Reported/potential toxicities following the use of CAR T cells[1]



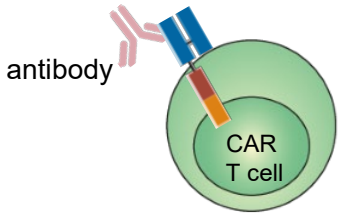
To date, the most prevalent adverse effect following infusion of CAR T cells is the onset of immune activation, known as CRS[1] (5.6–90% in clinical trials)[2]



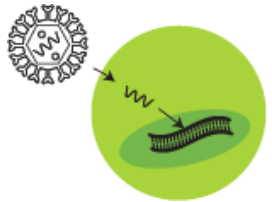
The severity of reported events for 'on-target, off-tumor' toxicity has ranged from manageable lineage depletion (B-cell aplasia) to severe toxicity (death), depending on the target[1]

The development of neurologic toxicities, including confusion, delirium, expressive aphasia, obtundation, myoclonus, and seizure, has been reported in patients who received CD19-specific CAR T cells[1] (12–48% in clinical trials)[2]

Several dermatologic complications have also been described, including secondary cutaneous malignancies[3]



Both cellular and humoral rejection of CAR T cells have been demonstrated due to the immunogenicity of foreign protein. Host reaction can manifest as anaphylaxis or allergy[1]



The risk of insertional oncogenesis following gene transfer into T cells is seemingly low; however, investigators must remain vigilant and adhere to strict monitoring[1]

CAR, chimeric antigen receptor; CD, cluster of differentiation; CRS, cytokine-release syndrome.

1. Bonifant et al. Mol Ther Oncolytics 2016;3:16011. 2. Kerre. Belgian J Hematol 2017;8:94–101. 3. Rubin et al. J Am Acad Dermatol 2016;75:1054–7. 4. Adkins S. J Adv Pract Oncol. 2019;10(Suppl 3):21–28. 5. Sievers S. Front Oncol. 2020 Jun 24;10:885.

Tumor vaccines

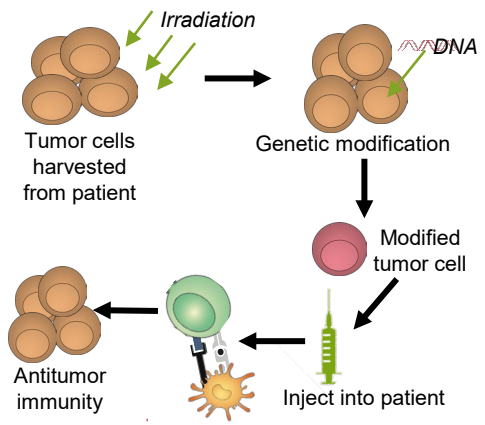
Types of immunotherapy

An overview of tumor vaccines

(see also www.ncbi.nlm.nih.gov/pmc/articles/PMC8185206/)

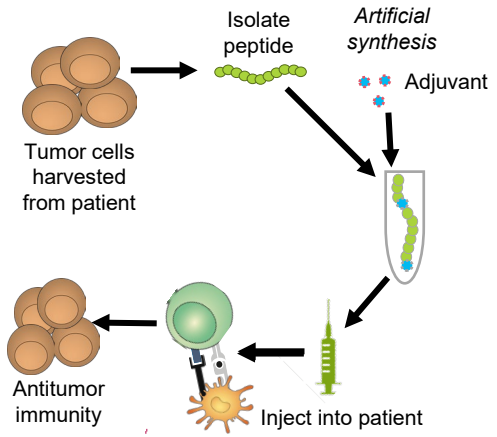
- Targeting cancer with vaccines has been investigated since the 1950s, but challenges have been encountered in the process;[1] consequently, very few are currently licensed in Europe
- They do, however, have the potential to become effective immunotherapies, and some of the key concepts underlying their activity are shown below:

Tumor cell vaccines[2]



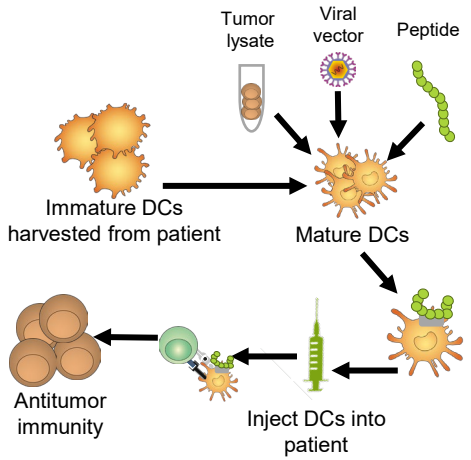
- Autologous tumor cell vaccines (colon cancer)
- Autologous renal cell tumor vaccine (RCC)
- Allogeneic irradiated pancreatic tumour cell lines (pancreatic cancer)

Antigen vaccines[3]



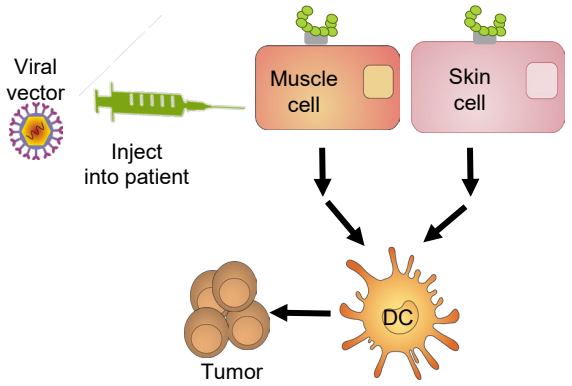
- Oncophage (renal cancer, melanoma and glioma)
- Tecemotide (lung, breast, prostate and colorectal cancers)

Dendritic cell vaccines[4]



- Sipuleucel-T (prostate cancer)

Vector-based vaccines[5]



- Ad-sig-hMUC-1/ecdCD40L (breast cancer)
- α-Fetoprotein adenoviral vector (hepatocellular cancer)

CTL, cytotoxic T lymphocyte; DC, dendritic cell; RCC, renal cell carcinoma.

1. Vergati et al. J Biomed Biotechnol 2010;2010:pii: 596432. 2. Srivastan et al. Hum Vaccin Immunother 2014;10:52–63. 3. Chiang et al. Vaccines 2015;3:344–72. 4. Tacken et al. Nat Rev Immunol 2007;7:790–802. 5. Larocca & Schlom. Cancer J 2011;17:359–71. Images adapted from Health Hearty. Available from: https://healthhearty.com/strategies-for-cancer-vaccine-development [Accessed October 2022].

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

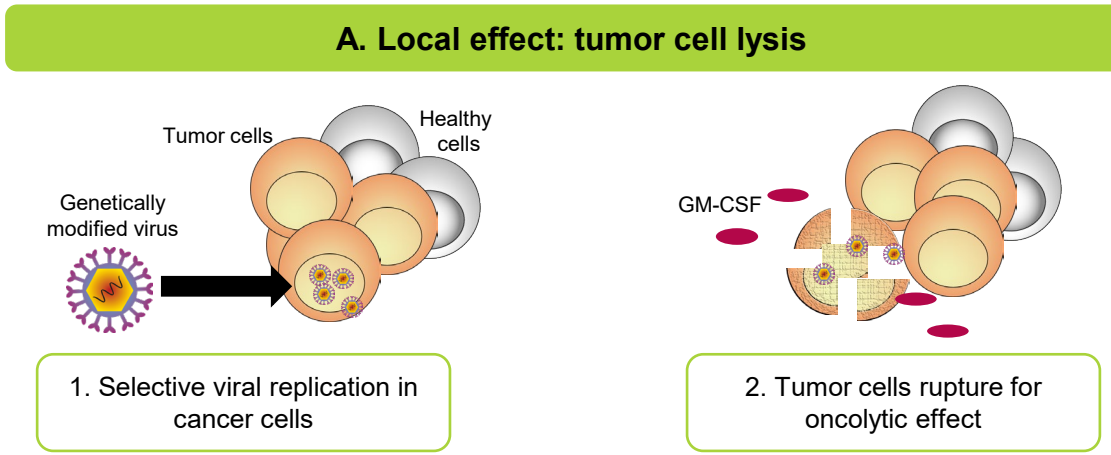
Licensed tumor vaccines in Europe[a]

- Talimogene laherparepvec is an oncolytic immunotherapy that has demonstrated therapeutic benefit against melanoma in a phase III clinical trial[1]
- Talimogene laherparepvec is designed to produce both local and systemic effects resulting in tumor lysis and death[2]
- It is currently licensed to treat adults with unresectable melanoma (regionally or distantly metastatic)[3]

- Efficacy

	T-VEC (n = 295)	GM-CSF (n = 141)	p
DRR	16.3%	2.1%	< 0.001
ORR	26.4%	5.7%	< 0.001

Mechanism of action of talimogene laherparepvec[2]



[a]Allogeneic irradiated pancreatic tumour cell lines and autologous renal cell tumor vaccine have been granted orphan designation by the EMA in Germany[4,5]

DC, dendritic cell; DRR, durable response rate; GM-CSF, granulocyte-macrophage colony-stimulating factor; ORR, overall response rate; T-VEC, talimogene laherparepvec.

1. Andtbacka et al. J Clin Oncol 2015;33:2780–8. 2. Doepker & Zager. Am J Hematol Oncol 2016;12:17–20. 3. Imlygic SmPC 2022. Available from: http://www.ema.europa.eu [Accessed Aug 2022]. 4. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2016/02/WC500201232.pdf [Accessed Aug 2022]. 5. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2009/10/WC500005835.pdf [Accessed Aug 2022].

Summary and key takeaways

- Immunotherapy is any treatment aimed at boosting or restoring the ability of the immune system to fight cancer, infections, and other diseases
- Several different classes of immune-modulating therapies are now in use and transforming patient outcomes
  - Checkpoint inhibitors, including agents that target CTLA-4, PD-1, and PD-L1, have been some of the most successful new therapeutic strategies in recent years
  - Checkpoint inhibitor, LAG-3 has garnered recent interest as a potential cancer treatment and there are several molecules being investigated in phase I–III trials
  - Monoclonal antibodies have become one of the largest classes of new agents approved for cancer treatment in the past decade
  - CAR T-cell immunotherapy is a more recently developed adoptive antitumor treatment, which involves collecting and then modifying a patient's own T cells, and is now available to treat B-cell malignancies
  - Tumor vaccines remain a significant area of research, with one product currently licensed in Europe for the treatment of unresectable melanoma

CAR, chimeric antigen receptor; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1.

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