ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

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Understanding immunoscience

A guide for specialists working with immunotherapies

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Immunotherapy adverse events and their management

Immunotherapy adverse events and their management

Click on a chapter below to start learning

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

A large part of this slide deck focuses on checkpoint inhibitor-related adverse events in oncology. The type, onset and severity of immunotherapy-related adverse events varies. **Healthcare providers are advised to remain vigilant for any symptoms at all times and always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies**

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

Introduction

Immunotherapy adverse events and their management

The type, onset and severity of immunotherapy-related adverse events varies.
Healthcare providers are advised to remain vigilant for any symptoms at all times and always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Immunotherapy adverse events

The type, onset and severity of immunotherapy-related adverse events varies. Healthcare providers are advised to remain vigilant for any symptoms at all times and refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

- ► The toxicities of immunotherapy are as diverse as the type of treatments that have been devised

○ Rare
● Common
– Not reported

Immunotherapy class[a]	Selected example	Immunotherapy-related side effects[a]						
		Flu-like symptoms[b]	Skin toxicity	GI toxicity	Hepato-toxicity	Endocrine toxicity	Infections	Other
Cytokines[1]	IFN, IL-2, etc	●	●	●	●	●	○	Congestive heart failure, anemia, pulmonary edema, hypotension
T-cell therapies[1,6-7]	TILs	●	●	○	○	●	○	Prolonged lymphopenia
	CAR	●	●	○	●	–	●	● Cytokine release Syndrome (characterized by high fevers, sinus tachycardia, hypotension, hypoxia, depressed cardiac function) , Neurotoxicity [6,7]
	TCR	●	●	●	○	–	○	Encephalopathy, myocarditis with MAGE-3 TCR
Checkpoint inhibitors[1]	CTLA-4 inhibitor	●	●	●	●	●	–	Neuropathy, nephritis
	PD-1/L1 inhibitors	●	●	○	○	●	–	Pneumonitis
TNF-blocking agents[2]	anti-TNFα antibodies	–	○	-	○	–	●	Neutralizing antibody formation, autoimmunity, malignancies, neurological disorders
Other monoclonal antibodies[3,4]	anti-IL-1, anti-CD20, etc.	●	●	●	○	●	●	CRS, infusion reactions, pulmonary adverse events, inflammatory reactions, hypersensitivity reactions, autoimmunity[3,4]
Vaccines[1,5]	Oncolytic viral vaccine	●	●	○	○	–	○	Allergic reactions (local to anaphylaxis), hypotension

[a]Individual immunotherapies may be immune-stimulating or immune-dampening and will therefore have different toxicity profiles. [b]Fever, chills, lethargy, fatigue and myalgia.

CAR, chimeric antigen receptor; CRS, cytokine release syndrome; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; GI, gastrointestinal; IFN, interferon; IL-2, interleukin-2; PD-1, programmed cell death receptor 1; PD-L1, programmed death-ligand 1; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte; TNF, tumor necrosis factor.
1. Weber et al. J Clin Oncol 2015;33:2092–99. 2. Hoentjen and van Bodegraven. World J Gastroenterol 2009;15:2067–73. 3. Demlova et al. Physiol Res 2016;65:S455–S462. 4. Baldo. Oncoimmunology 2013;2:e26333. 5. Andtbacka et al. J Clin Oncol 2015;33:2780–8. 6. Yanez Let al. HemaSphere. 2019;3:e186. 7. Brudno JN.et al. Blood Rev. 2019;34:45-55.

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

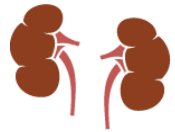
Immune-related adverse events (focus on checkpoint inhibitors)

- Increasing the activity of the immune system through immunotherapy, especially checkpoint inhibitors,[1] is associated with a unique spectrum of inflammatory side effects, so-called irAEs[1–3]
- Although any organ can be affected, irAEs most commonly involve the gastrointestinal tract, skin, endocrine glands, liver and lung[1–3]
- Less commonly, irAEs affect the nervous system and hematologic systems[1–3]
- Physicians must be ready to detect and manage this wide range of new types of adverse events[1–3]
- A collaborative, multidisciplinary approach to the management of irAEs is highly recommended[1–3]

Learn more about management of irAEs

irAEs affect many organ systems


Anemia, thrombocytopenia, neutropenia, hemophilia

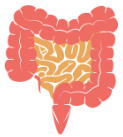

Nephritis


Rash, pruritus, psoriasis, vitiligo DRESS, Stevens-Johnson syndrome


Uveitis, conjunctivitis, scleritis, episcleritis, blepharitis, retinitis


Myocarditis, pericarditis, vasculitis


Hepatitis


Colitis, ileitis, pancreatitis, gastritis


Hyper- or hypothyroidism, hypophysitis, adrenal insufficiency, diabetes


Pneumonitis, pleuritis, sarcoid-like granulomatosis


Neuropathy, Guillain-Barré syndrome, myelopathy, meningitis, encephalitis, myasthenia


Arthritis, dermatomyositis

DRESS, drug reaction with eosinophilia and systemic symptoms; irAEs, immune-related adverse events.

1. Postow et al. N Engl J Med 2018;378:158–68. 2. Champiat et al. Ann Oncol 2016;27:559–74. 3. Haanen et al. Ann Oncol. 2017;28:iv119-iv142.

Immune-related adverse events occur due to increased activity of the Immune System

Mechanisms that result in irAEs are still being elucidated.

Potential mechanisms are:

- Cross-reactivity between T cells directed against a tumor and T cells directed against a related antigen in normal tissue
- Increasing levels of pre-existing autoantibodies (e.g. in the thyroid gland)
- Increase in the level of inflammatory cytokines (e.g. in the GI tract)
- Enhanced complement-related inflammation due to direct binding of an antibody against CTLA-4 expressed on normal tissue

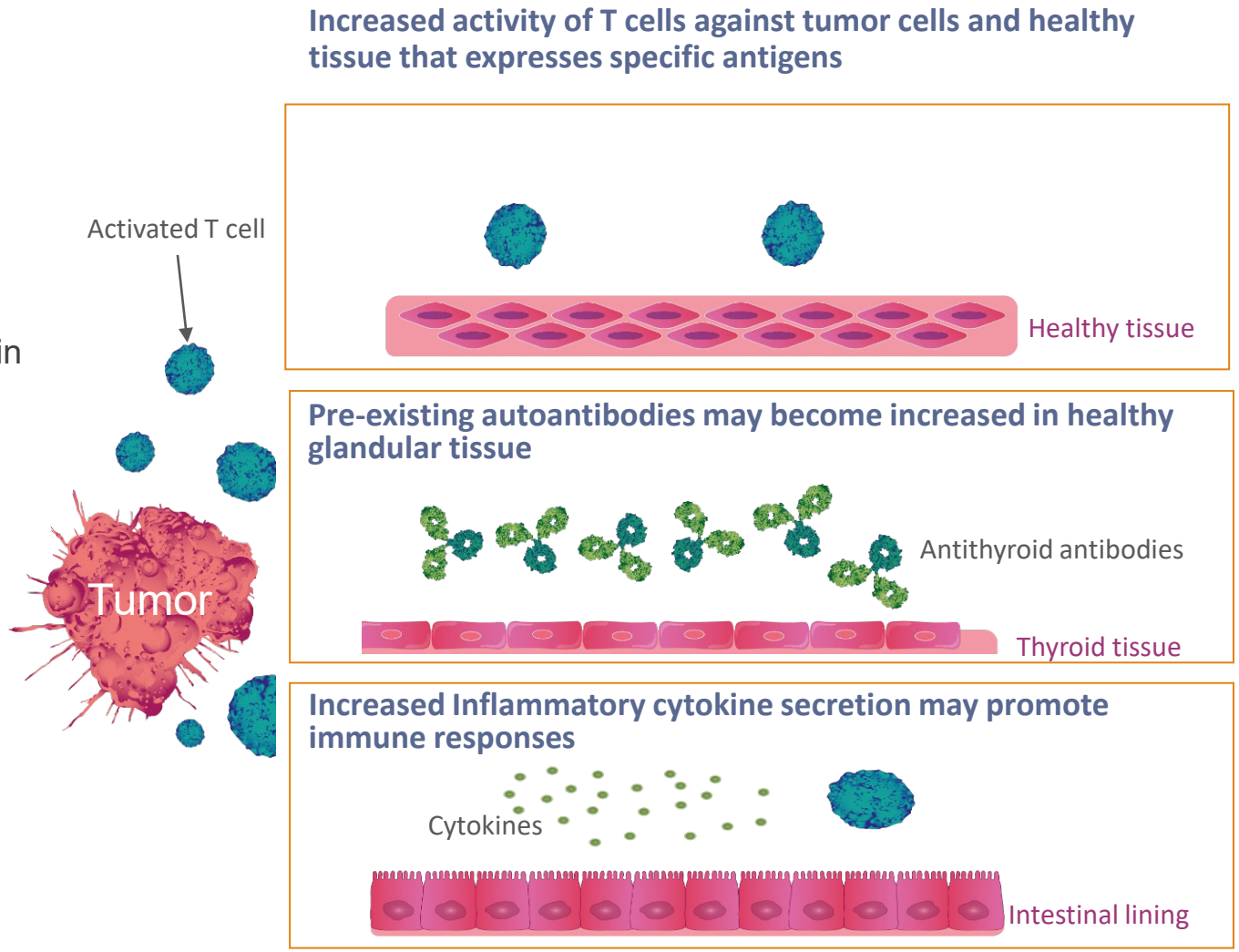


Figure adapted from Postow et al, 2018, *N Engl J Med*[1]

CTLA-4, Cytotoxic T-lymphocyte-associated antigen; GI, gastrointestinal; irAEs, immune-related adverse events.

1. Postow et al. N Engl J Med 2018;378:158–68.

Adverse events according to type of immunotherapy

Immunotherapy adverse events and their management

The type, onset and severity of immunotherapy-related adverse events varies.
Healthcare providers are advised to remain vigilant for any symptoms at all times and always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

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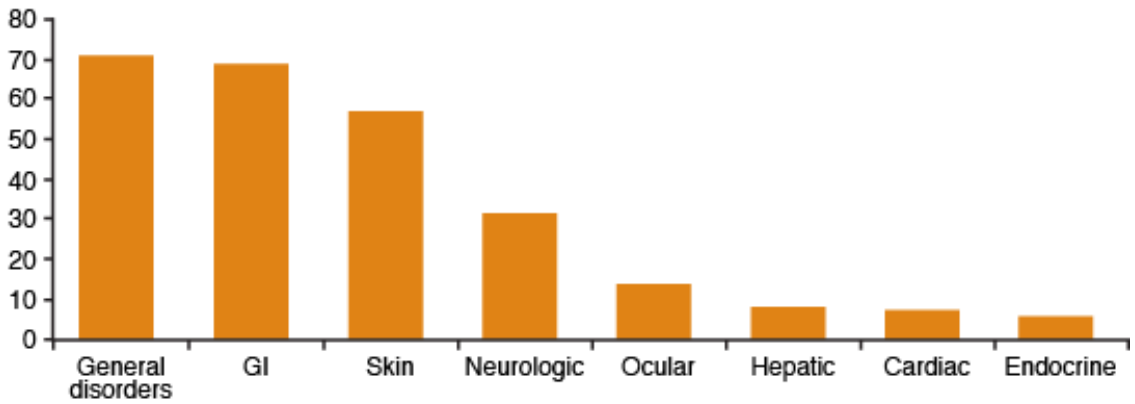
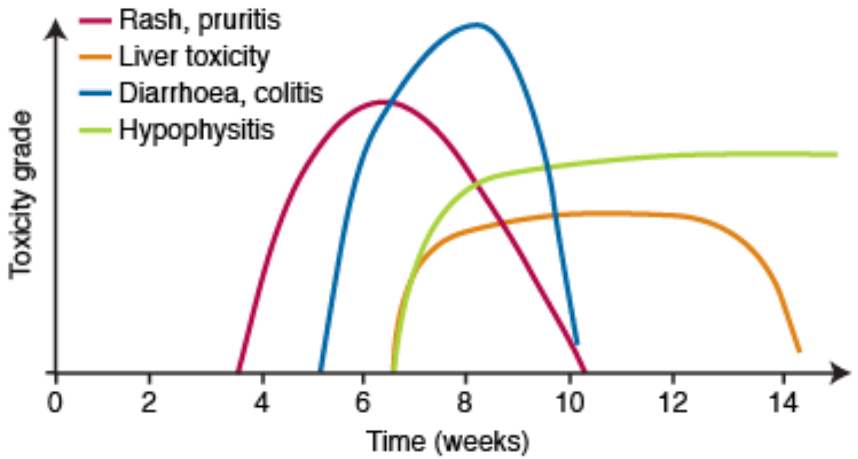
CTLA-4 checkpoint inhibitors: selected adverse events

- Owing to their 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 and hepatic toxicities[1,2]

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



Timing of occurrence of irAEs following ipilimumab treatment[3]



Published guidance on the management of checkpoint inhibitor toxicities is available[3–7]

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

AE, adverse event; irAE, immune-related adverse event; CTLA-4, cytotoxic T-lymphocyte-associated antigen; GI, gastrointestinal.

1. Camacho. Cancer Med 2015;4:661–72. 2. Linardou & Gogas. Ann Transl Med 2016;4:272. 3. Haanen et al. Ann Oncol 2017;28(suppl_4):iv119–iv142. 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; JCO2017776385 (Epub ahead of print). 7. Aspeslagh et al. BMSO ImmunoManager. Available from https://www.bsmo.be/immunomanager/. Accessed December 2022

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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, pulmonary and hepatic toxicities[2,3]

Frequency of any grade AEs reported with PD-1/PD-L1 inhibitors[4]

		PD-1 inhibitors (%)	PD-L1 inhibitors (%)
Dermatologic[1,4]	Rash and/or pruritus	~24 (Rash) / 13-20 (Pruritus)	~7
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, dyspnoea[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[4, 6–9]

AE, adverse event; irAE, immune-related adverse event; CTLA-4, cytotoxic T-lymphocyte-associated antigen; 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. Haanen et al. Ann Oncol 2017;28(suppl_4):iv119–iv142. 5. Khunger et al. Chest 2017;152:271–81. 6. Puzanov et al. Journal for ImmunoTherapy of Cancer 2017;5:95. 7. Davies & Duffield. ImmunoTargets and Therapy 2017;6:51–71. 8. Brahmer et al. J Clin Oncol 2018;JCO2017776385 (Epub ahead of print). 9. Aspeslagh et al. BMSO ImmunoManager. Available from: https://www.bsmo.be/immunomanager/. Accessed December 2022.

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TNF-blocking agents: selected adverse events

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

	Example
Infections	Tuberculosis, serious infections
Antibody formation	Anti-drug antibodies
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**
  - Less commonly reported with use of etanercept[1]
- **Tuberculosis**
  - Risk is lower with etanercept[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 orthopaedic surgery[4]
- **Heart failure**
  - Administration of TNF-blocking agents is contraindicated in patients with impaired cardiac function
- **Non-melanoma skin cancer**
  - Risk may be increased in patients who receive TNF-blocking agents, whatever the indication[5]
  - Increased risk of lymphoma observed in gastro-enterologic indications, but absolute numbers are small.
  - TNF-blocking agents are presently contraindicated in patients with past history of cancer

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.

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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[a] (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 reference 2

Selected AEs associated with mAbs[1]

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

[a]see next slide for more information

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. 3. Ali et al. Drug Healthc Patient Saf 2013;5:79–99.

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Monoclonal antibodies: hypersensitivity reactions

- Adverse responses can be classified into four categories of hypersensitivity (Types I–IV)[1]
- mAbs have been known to cause adverse reactions in all four categories[1]

Type of adverse reaction	Examples	Frequency	Symptoms
Type I (Immediate) hypersensitivity	Infusion syndrome Those that impact a single organ, i.e. eyes (conjunctivitis), bronchopulmonary tissue (asthma), gastrointestinal tract (gastroenteritis) and skin (urticaria, eczema) or multiple organs (anaphylaxis) Possible immediate reactions including anaphylaxis	Typical Relatively uncommon upon administration of mAbs	Flu-like symptoms, fever, chills, nausea, headache, asthenia, rash, etc. Can range from minor itching and inflammation to death Cardiovascular collapse and bronchospasm occur frequently in the course of anaphylaxis
Type II	Immune thrombocytopenia, neutopenia, hemolytic anemia	Rare	
Type III	Vasculitis, serum sickness; some pulmonary adverse events	Very rare	Symptoms of serum sickness typically appear 6–21 days after drug administration, and include lymphadenopathy and fever
Type IV (Delayed)	Delayed mucocutaneous reactions and infusion reactions/cytokine release syndrome, tumor lysis syndrome and cardiac events Delayed-type reactions include cutaneous reactions are allergic contact dermatitis, maculopapular exanthema, psoriasis	Very rare	Various Various. Generally become apparent 7–21 days after exposure

Table adapted from 1. Baldo et al. Selected content shown. Please refer to[1] for full information. For management recommendations see[2]

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

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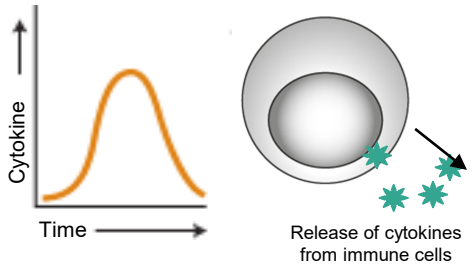
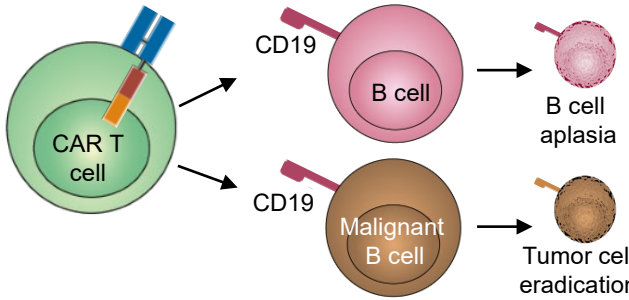
CAR T cells: selected adverse events

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

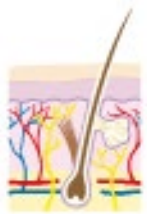


To date, the most prevalent adverse effect following infusion of CAR T cells is the onset of immune activation, known as CRS[1] (5.6% to 90% in clinical trials)[3]

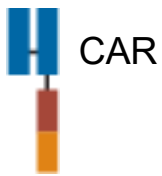


The severity of reported events for 'on-target, off-tumor' toxicity has ranged from manageable lineage depletion (B-cell aplasia) to severe toxicity (death), depending on the target[1]

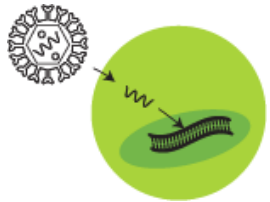
The development of neurologic toxicities, including confusion, delirium, expressive aphasia, obtundation, myoclonus and seizure has been reported in patients who received CD19-specific CAR T cells[1] (12% to 48% in clinical trials)[3]



Several dermatologic complications have also been described, including secondary cutaneous malignancies[2]



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; CRS, cytokine release syndrome; CD, cluster of differentiation..

1. Bonifant et al. Mol Ther Oncolytics 2016;3:16011. doi:10.1038/mto.2016.11. 2. Rubin et al. J Am Acad Dermatol 2016;75:1054–7. 3. Kerre. Belgian Journal of Hematology 2017;8:94–101. 4. Adkins S. J Adv Pract Oncol. 2019;10(Suppl 3):21–28. 5. Sievers S. Front Oncol. 2020 Jun 24;10:885.

Adverse events according to organ system

(focus on checkpoint inhibitors)

Immunotherapy adverse events and their management

This chapter is focused on checkpoint inhibitor-related adverse events. The type, onset and severity of immunotherapy-related adverse events varies.Healthcare providers are advised to remain vigilant for any symptoms at all times and always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

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Immune-related AEs: dermatologic

This slide is focused on CPi-related AEs The type, onset and severity of any immunotherapy-related AE varies. Always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Incidence/onset [1,2]

- ~40% of patients treated with anti-PD-1
- Early onset (3-4 weeks after treatment initiation)

Manifestations [1–3]

- Maculopapular rash and/or pruritus (trunk or extremities)
- Vitiligo
- Oral lichenoid reactions
- Dry mouth

Rare manifestations [1,2,4,5]

- Lichenoid dermatitis or psoriasis
- Bullous pemphigoid
- Dermatitis herpetiformis
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis

Management of dermatologic AEs [6]

Grade 2

- Symptomatic management: topical moisturizers, high-potency topical steroids, oral anti-histamines
- Reassess after 2 weeks. If worsened, manage as grade 3

Grade 3

- Symptomatic management: topical moisturizers, high–very high-potency topical steroids, oral anti-histamines, systemic corticosteroids (1 mg/kg/day)
- Withhold CPi
- Reassess after several days/weeks. If worsened, manage as grade 4. If symptoms grade ≤1, taper steroids over 1 month, resume CPi

Grade 4

- Permanently discontinue CPi; supportive measures

AE, adverse event; CPi; checkpoint inhibitor; PD-1, programmed cell death receptor 1.

1. Sibaud et al. Curr Opin Oncol 2016;28:254–63. 2. Boutros et al. Nat Rev Clin Oncol 2016;13:473–86. 3. Perret et al. Int J Dermatol 2017;56:527–33. 4. Mochel et al. J Cutan Pathol 2016;43:787–91. 5. Tetzlaff et al. Am J Dermatopathol 2017;39:121–9. 6. Sibaud. Am J Clin Dermatol 2017. doi: 10.1007/s40257-017-0336-3..

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This slide is focused on CPi-related AEs The type, onset and severity of any immunotherapy-related AE varies. Always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Immune-related AEs: endocrine

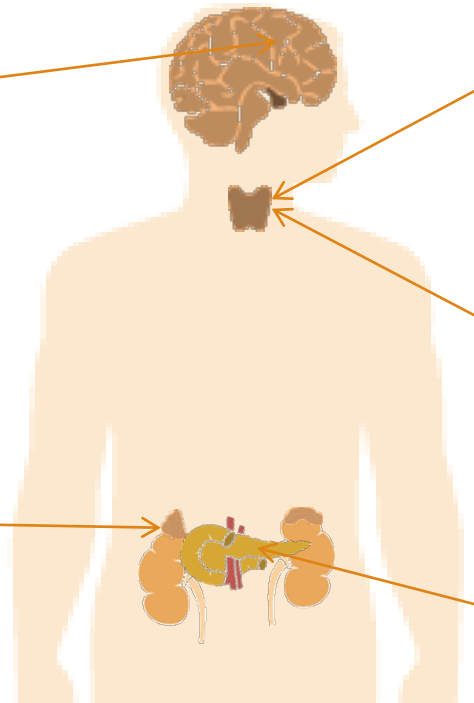
Endocrine adverse events have been reported with several immunotherapies[1,2]

Hypophysitis

- **Incidence:** 3.2–6.4%[1]
- **Management:** withhold CPi, consider administration of 1–2 mg/kg/day of oral prednisone, initiate HRT in appropriate patients[2]

Hypothyroidism

- **Incidence:** 3.8–13.2%[1]
- **Management:** consider thyroid hormone replacement in appropriate patients, consult an endocrinologist[2]



Hyperthyroidism

- **Incidence:** 1.7–8.0%[1]
- **Management:** consider beta blockers in appropriate patients, consult an endocrinologist[2]

Adrenal insufficiency

- **Incidence**: 0.7%[1]
- **Management**: hospitalization, withhold CPi, rule out sepsis, consider administration of IV corticosteroids and fluids in appropriate patients, consult an endocrinologist[2]

Type 1 diabetes mellitus

- **Incidence**: 0.2%[1]
- Monitor blood glucose regularly[3]

The management of each event is dependant upon the grade of the adverse event, and international[3,4] and national[5] guidelines should be consulted in every case

CPi, checkpoint inhibitor; IV, intravenous; HRT, hormone replacement therapy.

1. Barroso-Sousa et al. JAMA Oncol 2017. doi: 10.1001/jamaoncol.2017.3064. 2. Sznol et al. Cancer Treat Rev 2017;58:70–6. 3. Haanen et al. Ann Oncol 2017;28(suppl_4):iv119–iv142.
4. Brahmer et al. J Clin Oncol 2018; JCO2017776385. Epub ahead of print. 5. Aspeslagh et al. BMSO ImmunoManager. Available from: https://www.bsmo.be/immunomanager/. Accessed December 2022

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Immune-related AEs: gastrointestinal

This slide is focused on CPi-related AEs The type, onset and severity of any immunotherapy-related AE varies. Always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Incidence[1,2]

- Adverse events involving the gastrointestinal tract are common
- Grade 3/4 diarrhea/colitis was the most commonly observed serious adverse event reported across several trials involving CPIs

Onset[1]

- 6-7 weeks

Differential diagnosis[3-5]

- *Clostridium difficile*

Management of diarrhea and colitis[3,5]

Grade 2 (4–6 liquid stools/day over baseline)

- Withhold CPi
- Symptomatic management[a]
- Prednisolone 0.5–1 mg/kg/day or oral budesonide 9 mg od if symptoms persist for >3 days or worsen

Grade 3–4 (> 6 liquid stools/day over baseline)

- Hospitalization and isolation until infection excluded
- Withhold CPi
- Prednisolone 1–2 mg/kg/day
- Sigmoido/colonoscopy
- Infliximab if no improvement after 3 days

[a]Oral fluids, loperamide, avoid high fibre/lactose diet.

Od, once daily, CPI, checkpoint inhibitor.

1. Gelao et al. Toxins 2014;6:914–33. 2. Hodi et al. N Engl J Med 2010;363:711–23. 3.Haanen et al. Ann Oncol. 2017;28(suppl_4):iv119–iv142. 4. Samaan MA et al. Nat Rev Gastroenterol Hepatol 2018;222–234. 5. Brahmer JR et al. J Immunother Cancer 2021;9:e002435.

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This slide is focused on CPi-related AEs The type, onset and severity of any immunotherapy-related AE varies. Always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Immune-related AEs: hepatic

- Hepatic adverse events (elevated liver function enzymes and/or bilirubin) have been reported with several immunotherapies including:[1]
  - Cytokines
  - Cell therapy
  - CPi
- Combination checkpoint protein inhibition is associated with more toxicity than single agents[1,2]
- Incidence of hepatitis: 5–10%[2]
- Median time of onset: 7.4 weeks[2]

Management of hepatitis[2]

Grade 2 (ALT or AST 2-5x ULN)

- Withhold CPi – do not resume until symptoms grade ≤ 1
- Prednisolone 1 mg/kg/day if symptoms do not resolve within 1–2 weeks

Grade 3–4 (G3 - ALT or AST 5-20x ULN and G4 - ALT or AST > 20x ULN)

- Permanently discontinue CPi
- Prednisolone 1–2 mg/kg/day
- Worsening despite steroids:
  - If on oral : switch to iv
  - If on iv: add MMF 500- 1000 mg BID
  - If worse on MMF , consider adding tacrolimus

ALT, alanine transaminase AST, aspartate transaminase; BID, twice daily; Cpi, checkpoint inhibitor; G3, grade 3; G4, grade 4; MMF, mycophenolate mofetil; ULN, upper limit of normal

1. Weber et al. J Clin Oncol 2015;33:2092–9. 2. Haanen et al. Ann Oncol.2017;28(suppl_4):iv119–v142.

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Immune-related AEs: pulmonary (pneumonitis)

This slide is focused on CPi-related AEs The type, onset and severity of any immunotherapy-related AE varies. Always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Incidence[1]

- Overall: 2–4%
- Severe: 1–2%
- Observed with anti-PD-1/PD-L1 therapy, more rarely with anti-CTLA-4

Onset[1]

- Variable (very early to late)
- Median: 6–8 weeks

Assessments[1,2]

- Symptoms
- Chest X-ray
- HRCT
- Bronchoscopy with BAL
- Biopsy
- Percutaneous oximetry and PFTs

Management of suspected/documented pneumonitis[1,2]

Grade 2 (Mild to moderate new symptoms: Dyspnoea, cough, chest pain)

- Withhold immunotherapy
- Prednisolone 1 mg/kg/day or equivalent[a] (taper over ≥6 weeks)
- Follow-up at least twice weekly

Grade 3–4 (Severe new symptoms; new/worsening hypoxia; life-threatening; Difficulty in breathing, acute Respiratory Disease syndrome

- Hospitalization (consider ICU)
- Permanently discontinue immunotherapy
- Prednisolone 2–4 mg/kg/day or equivalent (taper over ≥6 weeks)
- Broad spectrum antibiotics
- Infliximab or MMF if no improvement after 2 days

[a]Exclude infection with bronchoscopy and BAL.

BAL, bronchoalveolar lavage; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; HRCT, high-resolution CT scan; ICU, intensive care unit; MMF, mycophenolate mofetil; PFTs, pulmonary function tests; PD-1, programmed cell death receptor 1; PD-L1, programmed death ligand 1.

1. Haanen et al. Ann Oncol 2017;28(suppl_4):iv119–iv142. 2. Professor J. Vansteenkiste, personal communication.

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This slide is focused on CPi-related AEs The type, onset and severity of any immunotherapy-related AE varies. Always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Immune-related AEs: renal (nephritis)

Incidence[1]

- Overall: <1%
- Combination of anti-PD-1/PD-L1 therapy with anti-CTLA-4: 4.9%

Onset[1]

- Variable (very early to late dependent on CPi

Assessments[1]

- Serum sodium
- Serum potassium,
- Creatinine
- Urea

Management of suspected/documented nephritis[1]

Grade 2 (Creatinine > 1.5-3 x baseline or > 1.5-3 x ULN)

- Withhold Cpi
- Initiate steroids (oral prednisolone 0.5-1 mg/kg)

Grade 3 (Creatinine > 3 x baseline or > 3-6 x ULN)

Grade 4 (Creatinine > 6 x ULN)

- Hospitalization (for monitoring)
- Withhold CPi
- If worsening, initiate IV (methyl)prednisolone 1-2 mg/kg (taper over 4 weeks)

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; CPi, Checkpoint inhibitor;; PD-1, programmed cell death receptor 1; PD-L1, programmed death ligand 1; ULN, upper limit of normal

1. Haanen et al. Ann Oncol 2017;28(suppl_4):iv119–iv142.

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This slide is focused on CPi-related AEs The type, onset and severity of any immunotherapy-related AE varies. Always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Immune-related AEs: cardiac

- Cardiac AEs are rare with immunotherapies, including CPis
- However, awareness and prompt referral to a cardiologist is important[1]

Published case reports of cardiotoxicity related to a CPi[1-3 a]:

Agent	N	AEs
Any (individual or combination)	10	Myocarditis, heart failure, cardiomyopathy, myocardial fibrosis, cardiac arrest cardiac conduction abnormalities
Ipilimumab + nivolumab	4	Myocarditis, myositis, cardiac conduction abnormalities
Ipilimumab then nivolumab	1	Myocarditis, myocardial fibrosis
Pembrolizumab	9	Myocarditis, cardiac conduction abnormalities, severe opthalmoplegia, myositis
Nivolumab	2	Complete heart block, Coronary vasospasm
Nivolumab	4	Myocarditis, cardiac conduction abnormalities
Ipilimumab	4	Cardiomyopathy with Takotsubo-like syndrome, pericardial effusion, Acute fibrinous pericarditis, Myocarditis, Heart Failure
Nivolumab	9	Myocarditis, myositis, insulin depend diabetes mellitus
Durvalumab + tremelimumab	1	Myocarditis
Atezolizumab	1	Myocarditis

Published guidance on the management of CPi induced cardiotoxicity is available [4-5]

[a]Table developed in collaboration with Prof. Dr Tessa Kerre

AE. adverse event; CPi, checkpoint inhibitor.

1. Jain et al. Curr Treat Options Cardiovasc Med 2017;19:36. 2. Agrawal N et al. Case Rep Oncol 2019;12:260–276 . 3. Zhou YW wt al. Front. Pharmacol. 10:1350. doi: 10.3389/fphar.2019.01350. 4.Brüstle & Heidecker. Oncotarget. 2017;8:106165–6. 5. Poto R. Expert Opin Drug Saf. 2021 Jun;20(6):685-694

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This slide is focused on CPi-related AEs The type, onset and severity of any immunotherapy-related AE varies. Always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Immune-related AEs: cardiac

- Cardiac AEs are rare with immunotherapies, including CPIs
- However, awareness and prompt referral to a cardiologist is important[1]

Selected cardiovascular adverse events reported for CPis from VigiBase WHO's global database of individual case safety reports (Jan 1, 2008, to Jan 2, 2018)[2]

	Anti-PD-1 or anti-PD-L1 Monotherapy (n=20643)* n (%)	Anti-CTLA-4 monotherapy (n=8266)* n (%)	Combination CPIs (n=2412)* n (%)
Myocarditis	84 (0,41%)	6 (0.07%)	32(1.33%)
Pericardial diseases	74 (0.36%)	13 (0.16%)	8 (0.33%)
Vasculitis Temporal Arteritis Polymyalgia Rheumatica	56 (0.27%) 7 (0.03%) 14 (0.07%)	18 (0.22%) 10 (0.12%) 1 (0-01%)	8 (0.33%) 1 (0.004%) 1 (0.004%)

Published guidance on the management of CPi induced cardiotoxicity is available [3-4]

* Total of individual case safety reports (ICSRs) reported in Vigibase for Anti-PD1/PD-Lq or Anti-CTLA-4 or CPIs Combination
CPis refers to any ICSR reported for treatment with nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, ipilimumab, or tremelimumab. Anti-PD-1 or anti-PD-L1 monotherapy refers to any ICSR associated with any of the following five drugs only when used alone: nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab. Anti-CTLA-4 monotherapy refers to any ICSR associated with ipilimumab or tremelimumab alone. Combination ICIs refers to any ICSR reported with at least one anti-PD-1 or anti-PD-L1 drug combined with an anti-CTLA-4 drug. I

AE. adverse event; CPi, checkpoint inhibitor.

1. Jain et al. Curr Treat Options Cardiovasc Med 2017;19:36. 2. Salem JE Lancet Oncol 2018; 19: 1579–89 3Brüstle & Heidecker. Oncotarget. 2017;8:106165–6. 4. Poto R. Expert Opin Drug Saf. 2021 Jun;20(6):685-694

Principles of adverse event management

(focus on checkpoint inhibitors in oncology)

Immunotherapy adverse events and their management

This chapter is focused on checkpoint inhibitor-related adverse events in oncology. The type, onset and severity of immunotherapy-related adverse events varies.Healthcare providers are advised to remain vigilant for any symptoms at all times and always refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Principles of irAE management: cooperation between all players

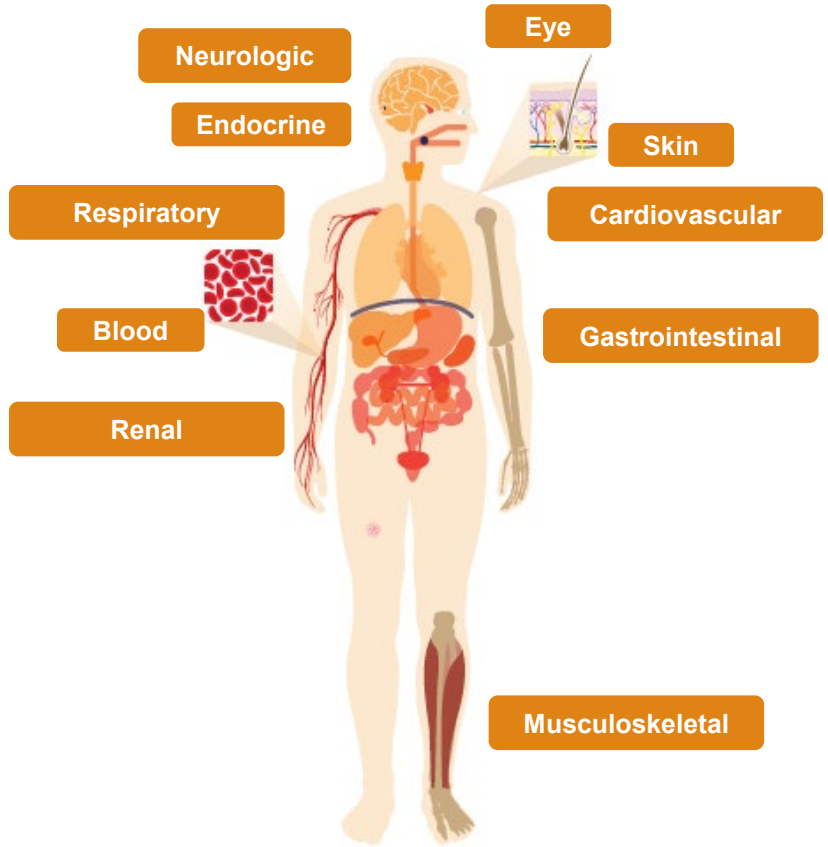
The type, onset and severity of immunotherapy-related adverse events varies. Healthcare providers are advised to remain vigilant for any symptoms at all times and refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Communication between patients, healthcare providers and oncologists is vital to successful irAE management[1,2]

Oncologist	Patient	Healthcare provider e.g. GP
Know the immune-toxicity spectrum	Be informed about possible toxicities	Be informed about possible toxicities and their onset

All individuals, patients in particular, should be aware that the onset of toxicities is usually within 3 months of starting treatment[2]

Nearly all organ systems can be affected[1,3]



Most irAEs are mild in intensity but ~10% of patients develop grade 3–4 irAEs

GP, general practitioner; irAE, immune-related adverse event.

1. Champiat et al. Ann Oncol 2016;27:559–74. 2. Haanen et al. Ann Oncol. 2017;28:iv119–iv142. 3. Postow et al. NEJM 2018;378:1586–8.

Principles of irAE management: vigilance

The type, onset and severity of immunotherapy-related adverse events varies. Healthcare providers are advised to remain vigilant for any symptoms at all times and refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Identify risk factors for irAEs[1,2]

Personal and family history of autoimmune diseases[a]

History of viral infections

Physical examination[1]

Symptoms

Laboratory tests[1,2]

CBC, CRP, serum electrolytes, renal and hepatic function, glycemia, TSH, T4, urine dipstick

Morning cortisol and ACTH, LH, FSH, estradiol and testosterone (for anti-CTLA-4 therapy)

Technical tests[1,2]

Baseline ECG, chest X-ray (plus chest CT scan and PFTs, if abnormal)

Other tests depend on patient's history and symptoms

[a]Patients with a history of autoimmune disease, especially if using immunosuppressive therapy, were not evaluated in clinical trials. Therefore, the risk/benefit ratio should be discussed in-depth with the patient before starting immunotherapy.

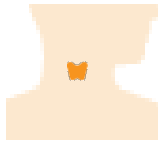
ACTH, adrenocorticotropic hormone; CBC, complete blood count; CRP, C-reactive protein; CT, computed tomography; CTLA-4, cytotoxic T lymphocyte-associated antigen; ECG, electrocardiography; FSH, follicle-stimulating hormone; irAE, immune-related adverse event; LH, luteinizing hormone; PFTs, pulmonary function tests; T4, thyroxine; TSH, thyroid-stimulating hormone.

1. Champiat et al. Ann Oncol 2016;27:559–74. 2. Haanen et al. Ann Oncol. 2017;28:iv119-iv142.

Principles of irAE management: detection and diagnosis

The type, onset and severity of immunotherapy-related adverse events varies. Healthcare providers are advised to remain vigilant for any symptoms at all times and refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

- IrAEs can develop at any time during treatment or even after immunotherapy discontinuation[1]

Early events Median time to onset: < 2 months			Late events Median time to onset: > 2 months		
					
Skin	Gastrointestinal	Hepatic	Pulmonary	Endocrine	Renal

- New symptoms or lab abnormalities should prompt a differential diagnosis among:[1]
  - Disease progression
  - Intercurrent event (mostly infections)
  - irAE
- Abnormalities need strict follow-up (frequency depends on the grade)
- Diagnostic assessments may include:[2]
  - Laboratory tests
  - Imaging tests
  - Biospy
  - (Referal to specialist)

irAE, immune-related adverse event.

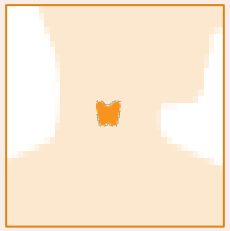
1. Champiat et al. Ann Oncol 2016;27:559–74. 2. Haanen et al. Ann Oncol. 2017;28:iv119-iv142.

Principles of irAE management: therapy for most irAEs

The type, onset and severity of immunotherapy-related adverse events varies. Healthcare providers are advised to remain vigilant for any symptoms at all times and refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

Grade	Immunotherapy[1]	Tests[2]	Therapy[1]	Corticosteroids[1,2]
1	Continue	Close monitoring of clinical and laboratory findings	Symptomatic[a]	Topical only[c]
2	Withhold	Appropriate diagnostic tests	Antibiotics[b] Oral trimethoprim/ sulfamethoxazole if long-term corticosteroids	Prednisone 0.5–1 mg/kg[d]
3	Withhold/ discontinue	Hospitalization, specialist referral, biopsy		Prednisone 1–2 mg/kg[d]
4	Discontinue			

Treatment approach for irAE-related thyroid dysfunction depends on TSH and T4 levels[2]



Condition	Treatment
Hypothyroidism	Thyroxine 0.5–1.5 µg/kg
Hyperthyroidism	Beta blockers, carbimazole
Thyroiditis	Prednisone 0.5 mg/kg

[a]For example, appropriate steroids, loperamide for diarrhea (see Champiat et al. for further guidance). [b]If infection suspected. [c]For example, for skin toxicity. [d]Dose may be increased if no improvement after 3–5 days or add-on mycophenolate (liver toxicity), infliximab (colitis and pneumonitis) or tacrolimus.

irAE, immune-related adverse event; T4, the main thyroid hormone; TSH, thyroid-stimulating hormone.

1. Champiat et al. Ann Oncol 2016;27:559–74. 2. Haanen et al. Ann Oncol. 2017;28:iv119-iv142.

Principles of irAE management: Follow-up

The type, onset and severity of immunotherapy-related adverse events varies. Healthcare providers are advised to remain vigilant for any symptoms at all times and refer to appropriate guidelines and/or organ specialists for management strategies relating to different and specific types of immunotherapies

- Except for grade 1 AEs, immunotherapy should be withheld to investigate and treat the AE (regardless of the cause)
- It is essential that, for cases of colitis, pneumonitis or any recurring event, the risk: benefit ratio is considered

When to resume or discontinue immunotherapy?

Careful discussion of the risk:benefit ratio is needed in the case of colitis, pneumonitis or any recurring event.

- Immunotherapy dose reduction is currently not recommended[1]
  - However, no dose/toxicity correlation for anti-PD-1, PD-L1 or CTLA4 (≤ 3 mg/kg)
- Retrospective data suggest that systemic immunosuppression for irAEs might not jeopardize the long-term efficacy of immunotherapy[2]
- Corticosteroid therapy should be tapered gradually, over a period of 4–6 weeks[1]

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

1. Champiat et al. Ann Oncol 2016;27:559–74. 2. Professor J. Vansteenkiste, personal communication.

Summary and key takeaways

- The toxicities of immunotherapy are as diverse as the type of treatments that have been devised, affecting most organ systems of the body to some degree[1–7]
- Hypersensitivity reactions (including infusion-related reactions) are the most common and among the most serious AEs associated with mAbs[1,2]
- While several different AEs have been reported following CAR T cell infusion[3,8-9], CRS is the most prevalent[4,9]
- Treatment with immunotherapies, especially checkpoint inhibitors, is associated with irAEs that typically are transient but occasionally can be severe or fatal[5–7]
- The most common irAEs are dermatologic, gastrointestinal, hepatic and endocrinologic toxicities, while pulmonary and cardiovascular toxicities occur less frequent, but are equally important [5–7]
- Guidelines for diagnosis, treatment and follow-up of CPi-associated irAEs have been published[7]
- In general, rapid identification of irAEs and prompt initiation of local or systemic corticosteroid immunosuppression can optimize outcomes[5–7]
- Frequent and consistent communication between patients, caregivers, healthcare providers and oncologists is vital to successful irAE management[5–7]

AE, adverse event; CPi, checkpoint inhibitor; CRS, cytokine-release syndrome; irAE, immune-related adverse event.

1, Baldo. Oncoimmunology 2013;2:e26333. 2. Guan et al. BioMed Res Int 2015;2015:428169. 3. Bonifant et al. Mol Ther Oncolytics 2016;3:16011. doi:10.1038/mto.2016.11. 4. Kerre. Belgian Journal of Hematology 2017;8:94–101. 5. Postow et al. N Engl J Med 2018;378:158–68. 6. Champiat et al. Ann Oncol 2016;27:559–74. 7. Haanen et al. Ann Oncol. 2017;28:iv119-iv142. 8 Adkins S. J Adv Pract Oncol. 2019;10(Suppl 3):21–28. 9 Sievers S. Front Oncol. 2020 Jun 24;10:885.

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