What are Immunotherapy Side Effects?

Let us answer some of your questions.
Immunotherapy-related side effects and their management
An ESMO guide for patients

Patient information based on ESMO Clinical Practice Guidelines

This guide has been prepared to help you, as well as your family, friends and caregivers, better understand immunotherapy-related side effects and their management. It contains information on the most common toxicities associated with modern immunotherapies (known as “checkpoint inhibitors”), how your oncology team will manage these symptoms, and a few strategies you can use yourself to minimise their effects.

The medical information described in this document is based on the ESMO Clinical Practice Guideline for management of toxicities from immunotherapy, which is designed to help clinicians with the diagnosis, treatment and follow-up of these events. All ESMO Clinical Practice Guidelines are prepared and reviewed by leading experts using evidence gained from the latest clinical trials, research and expert opinion.

The information included in this guide is not intended as a replacement for your doctor’s advice. Your doctor knows your full medical history and will help guide you regarding the best treatment for you.

This guide has been developed and reviewed by:

Representatives of the European Society for Medical Oncology (ESMO):
John Haanen; Karin Jordan; Francesca Longo; Jean-Yves Douillard; Svetlana Jezdic; Claire Bramley

Representatives of the European Oncology Nursing Society (EONS): Anita Margulies; Ada Kinneally

Representative from Lung Cancer Europe: Regine Deniel Ihlen

Representative from Women Against Lung Cancer: Stefania Vallone

Representative from International Kidney Cancer Coalition: Rachel Giles

Representative from Melanoma Patient Network Europe and MelanomeFrance: Gilliosa Spurrier
2 An ESMO guide for patients
4 Immunotherapy-related side effects: A summary of key information
6 The immune system and cancer
10 The concept of immuno-oncology
13 How does modern immunotherapy differ from chemotherapy and tumour-targeted drugs?
15 What are the side effects of immunotherapy?
20 How will immunotherapy-related side effects be managed?
25 References
26 Glossary
Immunotherapy-related side effects: A summary of key information

The immune system and cancer

- The immune system consists of many different components in the body.
  - Some act as physical/chemical barriers (skin, cornea, membranes in the respiratory tract, gastrointestinal tract, urinary tract and reproductive tract).
  - Others make and/or circulate specialised immune cells (the lymphatic system, bone marrow, spleen and thymus gland).
- The role of the immune system is to defend the body against threats, including microorganisms (bacteria, viruses, fungi) and cancer cells.
- After the physical/chemical barriers of the body, the next line of defence comprises white blood cells (leucocytes) that look for, and attack, microorganisms or abnormal cells (including cancer cells).
  - T cells are white blood cells that play an important part in the acquired immune response — in which each T cell learns, remembers and is specific to a particular antigen.
  - T cells are activated via a “lock and key” mechanism enabling them to recognise, attack and kill cancer cells.
- Many cancers are probably prevented by immune system surveillance and destruction of abnormal cells, but cancer cells can outwit the immune system in various ways.

The concept of immuno-oncology

- While chemotherapy or tumour-targeted drugs directly affect the growth and proliferation of tumour cells, immuno-oncological drugs harness the body’s natural anti-cancer immune response to attack and destroy the cancer.
- Manipulation of immune checkpoints is at the leading edge of immuno-oncology.
  - Immune checkpoints are designed to turn off the immune response to prevent autoimmunity and damage to healthy cells, but cancer hijacks these mechanism by “deactivating” T cells once they have recognised the cancer, preventing attack and destruction of a cancer cell.
  - Checkpoint inhibitors such as CTLA-4 inhibitors and PD-1 pathway inhibitors (two types already available in the clinic) or PD-L1 inhibitors (one type available in the clinic) prevent this deactivation and increase the body’s anti-tumour immune response.

How does modern immunotherapy differ from chemotherapy and tumour-targeted drugs?

- Chemotherapy involves the use of one or more drugs to destroy tumour cells, based on the fact that these cells typically divide rapidly; side effects are caused by damage to normal cells, especially those that also divide rapidly, such as cells in the bone marrow, hair follicle and gastrointestinal tract.
• **Tumour-targeted drugs** specifically act against molecular targets in cancer cells identified by tissue and blood samples. These drugs are used to treat some types of cancer in selected patients based on molecular characteristics of their **tumours**. In general, it is expected that these drugs have less side effects on normal cells than **chemotherapy**, but side effects from **tumour-targeted drugs** could also be substantial and depend largely on what each drug targets.

• Because modern **immunotherapy** with **checkpoint inhibitors** blocks the body’s natural safeguards that prevent immune overactivation, it can also affect normal tissues and cause **autoimmune** side effects. These comprise a different spectrum of events compared with those associated with **chemotherapy** and **tumour-targeted drugs**, and require different management strategies.

**What are the side effects of immunotherapy?**

• Immune-related side effects arising from treatment with **checkpoint inhibitors** can affect any organ or tissue, but most commonly affect the skin, **colon**, lungs, liver and **endocrine** organs (such as the **pituitary gland** or **thyroid gland**).

• Most of these side effects are mild to moderate and reversible if detected early and addressed appropriately, so the most important action you can take is to tell your doctor or oncology team of any new or worsening symptoms, or any symptoms that are worrying you.

• Side-effects of **checkpoint inhibitor** treatment typically appear within a few weeks or months of starting treatment, but they can arise at any time during treatment – as early as days after the first infusion, but sometimes as long as 1 year after treatment has finished.

• The most common side effects for **CTLA-4 inhibitors** and **PD-1/PD-L1** pathway inhibitors are skin symptoms (like rash and itching), while **gastrointestinal** symptoms (like **diarrhoea**) seem to be more common with **CTLA-4 inhibitors** and lung symptoms and **thyroid gland** dysfunction seem to be more common with **PD-1/PD-L1** pathway inhibitors.

**How will immunotherapy-related side effects be managed?**

• **Checkpoint inhibitor**-related side effects all are managed according to some basic common principles:
  - Grade 1 (mild severity) or Grade 2 (moderate severity) events generally are managed symptomatically, without interrupting or permanently stopping treatment.
  - Patients with persistent Grade 2 symptoms may need to skip one or more treatment doses (as well as receiving symptomatic treatment), until their symptoms have improved.
  - For patients with Grade 3 (severe) or Grade 4 (very severe) symptoms, treatment will typically be discontinued and referral to a specialist – for example, a **dermatologist** for severe skin symptoms – will usually be made.

• **Oral** or **intravenous corticosteroids**, or other **immunosuppressive** drugs, are used for severe or persistent side effects; their use does not appear to compromise the efficacy of treatment with **checkpoint inhibitors**.

• If you have to permanently stop treatment with an **immune checkpoint inhibitor**, this should not negatively affect how your cancer responds.
The immune system and cancer

What is the immune system?
The human immune system comprises the lymphatic system, bone marrow, spleen and thymus gland; collectively, they produce and/or circulate specialised immune cells. The skin, cornea of the eye, and membranes lining the respiratory tract, gastrointestinal tract, urinary tract and reproductive tract act as physical/chemical barriers against microorganisms such as bacteria and viruses. The bone marrow and thymus gland are primary lymphoid organs where white blood cells are produced and/or multiply. White blood cells are a group of immune cells pivotal to effective immunity.

The immune system consists of many different components in the body, some of which act as physical/chemical barriers (skin, cornea, membranes in the respiratory tract, gastrointestinal tract, urinary tract and reproductive tract) while others make and/or circulate specialised immune cells (the lymphatic system, bone marrow, spleen and thymus gland).
What is the function of the immune system?

The immune system defends the body against infections and cancer

The role of the immune system is to defend the body against foreign or dangerous invaders, including microorganisms (bacteria, viruses, fungi) and cancer cells. To do this effectively, the immune system must be able to differentiate between self (normal cells belonging to the individual) and non-self (abnormal cells or organisms/particles that are foreign to the individual). A normal immune response comprises:

1. Recognition of potentially harmful antigens.
   - These may originate from outside the body, e.g. from invading bacteria, or from within the body, e.g. normal cells that have mutated and potentially could – or have – become malignant.
2. Activation and mobilisation of cellular and antibody defences.
3. Attack against the invader or abnormal cell.
4. Termination of the attack once the threat has been counteracted.

Besides the physical/chemical barriers of the body, another line of defence comprises white blood cells (leucocytes) that travel through the bloodstream and into tissues and organs looking for, and attacking, microorganisms or abnormal cells. There are various different types of white blood cells that perform different functions, ranging from directly attacking and killing invaders or abnormal cells, to releasing special substances that enhance the immune response by other cells.
There are many different types of leucocytes each having a specific function in the immune response. The immune response consists of two phases:

- **Innate immunity**: this is quick but not specific — a previous encounter with the invader or abnormal cell is not needed for this response. The innate response is activated in response to potentially harmful pathogens such as bacteria and viruses.

- **Acquired immunity**: this is slower but specific — the immune system “learns” to recognise the invader/abnormal cell and can attack it more efficiently the next time it encounters it. The process of acquired immunity is the basis for vaccinations.

The acquired immune system has been manipulated for its therapeutic benefit in cancer management and is therefore explained in more detail below.

The primary types of immune cells involved in the acquired immune response are B cells and T cells, which work together to destroy invaders or abnormal cells. In order to recognise foreign organisms/particles or abnormal cells, T cells require the help of specialised cells collectively called “antigen-presenting cells” — which ingest the invader or abnormal cell and break it up into smaller pieces so that antigens of the invader or abnormal cell become visible to T cells.
1. T cells can recognise antigens only after these have been processed by antigen-presenting cells, combined with major histocompatibility complex (MHC) and presented to a specialised T cell receptor (TCR) located on the surface of the T cell.

2. Presented in this way, the antigen/MHC combination acts like a “key” which fits the TCR “lock”, activating the T cell (a process called “priming”); activated T cells proliferate and differentiate into antigen-specific T cells and a small pool of memory cells (which will remember the specific antigen if encountered again, thereby ensuring a more effective immune response).

3. Activated cytotoxic T cells attack infected or cancer cells carrying the specific antigen that the T cells recognise, and kill them.

How does the immune system respond to cancer?

Many cancers are prevented by immune system surveillance and destruction of abnormal cells, without the person being aware of this. Cancer cells are clever, however, and have developed the ability to outwit or hide from the immune system in one or more ways, including:

- Hiding their identity: a cancer cell can reduce the expression of tumour antigens on its surface, making it more difficult for the immune system to identify it as being abnormal.
- Putting up a barrier: a cancer cell can express proteins on its surface that inactivate an immune cell.
- Influencing other cells: a cancer cell can influence cells close to it to release substances that suppress the immune response (and facilitate cancer cell proliferation and survival).

Cancer cells can outwit the immune system in several ways
The concept of immuno-oncology

In contrast to cancer therapies that directly affect the growth and proliferation of tumour cells – such as chemotherapy or tumour-targeted drugs – immuno-oncological drugs harness the body’s natural anti-cancer immune response, boosting its ability to attack and destroy the cancer (Kamta et al., 2017). Immuno-oncological approaches fall into two main categories:

- **Passive immunotherapy** – which facilitates and enhances the body’s existing immune response; examples include checkpoint inhibitors.
- **Active immunotherapy** – which directs the body’s immune cells to recognise, attack and destroy cancer cells; examples include anti-cancer vaccines.

Of these two approaches, the most successful so far is passive immunotherapy. Manipulation of immune checkpoints is at the leading edge of immuno-oncology. Immune checkpoints are the body’s natural defence against autoimmunity; they are designed to turn off the immune response to prevent collateral damage to healthy cells, by “deactivating” (or in some instances, destroying) activated lymphocytes such as T cells once they have recognised, attacked and destroyed a cancer cell (or microorganism). Currently, the two types of checkpoint inhibitors that are commercially available in the clinic are:

- **CTLA-4 inhibitors** – CTLA-4 is a specialised molecule that is produced by T cells during the early stages of their activation in lymphoid organs, whereupon it migrates to the cell surface and deactivates the T cell to prevent an excessive immune response (and unwanted autoimmunity). By blocking this deactivation, CTLA-4 inhibitors magnify the anti-tumour immune response (Boutros et al., 2016).

- **PD-1 pathway inhibitors** (PD-1/PD-L1 inhibitors) – PD-1 is a specialised molecule that moderates the activity of T cells later in their response to cancer, once they have arrived at the tumour site. By preventing PD-1 (the “lock”) from binding with PD-L1 (the “key”), PD-1/PD-L1 inhibitors prolong and may even reinvigorate the anti-tumour immune response. PD-1/PD-L1 provide a necessary mechanism to minimise unwanted autoimmunity and damage to peripheral tissues once the immune cells have done their job, but cancer cells can “hijack” this mechanism by producing lots of “keys” themselves, thereby suppressing the immune response (Boutros et al., 2016).
CTLA-4 inhibitors and PD-1/PD-L1 inhibitors affect T cells at different stages in their immune actions and at different locations. CTLA-4 inhibitors work at an early stage during the early deployment of T cells and primarily facilitate their sustained activation and proliferation in lymphoid organs (A), while PD-1/PD-L1 inhibitors primarily delay the later phenomenon of T cell exhaustion due to prolonged exposure to high levels of tumour antigen in and around the cancer site (and may also reinvigorate exhausted T cells, B). Adapted by permission from Macmillan Publishers Ltd: Nature Reviews Clinical Oncology (Boutros, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination), copyright (2016).

**Checkpoint inhibitors magnify the body’s natural immune response to cancer**
Several CTLA-4 inhibitors and PD-1/PD-L1 inhibitors have been approved for clinical use in various types of cancer, and they and others are continually being tested in clinical trials for other cancers. All CTLA-4 inhibitors and PD-1/PD-L1 inhibitors available so far are monoclonal antibodies – specialised, targeted proteins made in the laboratory that each bind to a specific molecule. They are all administered by injection/intravenous infusion. Mostly, they are given as a single-agent treatment but sometimes, they can be combined with chemotherapy or each other (Haanen et al., 2017).

<table>
<thead>
<tr>
<th>DRUG TYPE</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTLA-4 inhibitors</td>
<td>Ipiilimumab</td>
</tr>
<tr>
<td>PD-1 inhibitors (targeting the “lock”)</td>
<td>Nivolumab, Pembrolizumab</td>
</tr>
<tr>
<td>PD-L1 inhibitors (targeting the “key”)</td>
<td>Atezolizumab, Avelumab, Durvalumab</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>Ipiilimumab + nivolumab</td>
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Approved drugs are those that have met the requirements of the regulatory authorities in a specific country or region to prove that they are effective and safe enough to be used in daily clinical practice. Drugs that have not been approved can still be given to patients who have enrolled in a clinical trial, since these patients will be monitored very closely. Sometimes, the clinical trial will form part of the evidence needed to get a drug approved.
How does modern immunotherapy differ from chemotherapy and tumour-targeted drugs?

As with chemotherapy and tumour-targeted drugs, treatment with checkpoint inhibitors may also cause side effects but they are very different and require different management strategies.

**Chemotherapy** involves the use of one or more drugs to destroy tumour cells directly or stop cancer growth by inhibiting cancer cells ability to multiply. Chemotherapy is designed to affect cancer cells to a greater extent than normal cells, since cancer cells typically divide and multiply rapidly; however, this desired “selectivity” is not perfect, because normal cells also need to divide and multiply to replace themselves as they age — and some normal cells also divide rapidly, such as cells in the bone marrow, those lining the gastrointestinal tract, and cells in the hair follicles. This is the reason for some of the common side effects from chemotherapy, such as hair loss, nausea and vomiting, reduced white blood cell counts (leucopaenia, neutropaenia), reduced red blood cell counts (anaemia), reduced platelet counts (thrombocytopaenia), diarrhoea and mucositis. Many of these side effects go away after chemotherapy ends and normal cells recover. Different types of chemotherapy drugs may produce different ranges of side effects.

**Tumour-targeted drugs** are used for treatment of some cancer types in selected patients based on molecular characteristics of tumours determined by tissue and blood analysis. Tumour-targeted drugs can also cause side effects and their side effects profile depends largely on what the drug targets. The most common side effects from these drugs are diarrhoea, liver problems, skin problems, heart problems and high blood pressure. Because many of tumour-targeted drugs are quite new, it is still not known if they can cause long-term side effects.

The side effects from treatment with checkpoint inhibitors are caused by a form of autoimmune reaction.

Unlike chemotherapy, which directly attacks tumour cells or tumour-targeted drugs that act against molecular targets in cancer cells, modern immunotherapy with checkpoint inhibitors works “indirectly”, by harnessing the patient’s own immune system. Because it blocks the body’s natural safeguards that prevent immune overactivation, however, immunotherapy can also affect normal tissues and cause side effects.
**Immunotherapy-related side effects**

**Checkpoint inhibitors** can induce multiple immune-mediated changes that manifest as *autoimmune* side effects – which are different to side effects associated with *chemotherapy*, and therefore require different management strategies. Drugs targeting the **CTLA-4** and **PD-1** pathways have slightly different side-effect profiles, although there is considerable overlap *(June et al., 2017)*. Because **immunotherapy** drugs are new, the full range of their side effects is still not known, as well as it’s not known how long after the treatment ends they may appear.

Activated **tumour infiltrating lymphocytes (TILs)** attack the **tumour** (1), which results in **tumour cell death** but also can cause damage to nearby normal cells (2). This process releases both **tumour antigens** from the cancer and some **self-antigens** from damaged normal cells (3), which are all ingested by **antigen-presenting cells** and used to activate more **T cells** (4). As a consequence of this “mixing” effect, some **T cells** are now going to recognise and attack normal tissues, causing **autoimmune** side effects. *Adapted by permission from Macmillan Publishers Ltd: [Nature Medicine] (June, et al. Is autoimmunity the Achilles’ heel of cancer immunotherapy?), copyright (2017).*
What are the side effects of immunotherapy?

Side effects from treatment with **checkpoint inhibitors** are usually mild and reversible if reported and addressed early

What symptoms should I look out for?

Immune-related side effects (sometimes referred to as immune-related adverse effects or irAEs) arising from treatment with **checkpoint inhibitors** can affect any organ or tissue, but most commonly affect the skin, colon, lungs, liver and **endocrine** organs (such as the pituitary gland or thyroid gland) (Haanen et al., 2017). Most immune-related side effects are mild to moderate and reversible if detected early and addressed appropriately, so you should always mention any symptoms that are worrying you – as soon as you notice them – to your oncology team (Champiat et al., 2016). They will be monitoring your progress and testing your blood for signs of any side-effects without obvious symptoms in their early stages. Because side-effects to **checkpoint inhibitor** treatment can arise at any time during treatment – and sometimes also after treatment has finished – your oncology team will also advise you to look out for any of the following symptoms, and to notify them accordingly:

- **General:** fatigue is a common side effect in patients treated with **checkpoint inhibitors**. Although its cause is poorly understood, it is important to exclude thyroid, pituitary, and other endocrine disorders.
- **Skin:** extensive rash or itching.
- **Gastrointestinal:** diarrhoea especially containing blood or mucus, or severe abdominal pain.
- **Endocrine:** fatigue, weight loss, nausea/vomiting, excessive thirst or appetite, excessive and/or frequent urination.
- **Respiratory:** shortness of breath, cough.
- Any of these less common symptoms:
  - headache.
  - confusion.
  - muscle weakness or pain.
  - numbness.
  - painful or swollen joints.
  - unexplained fever.
  - tendency to bruise easily.
  - loss of vision.
Immunotherapy-related side effects

When are these side effects most likely to appear and how common are they?

Immune-related side effects to checkpoint inhibitor therapy typically occur quite early — mostly, within weeks to three months after treatment starts; however, first onset of side effects has been recorded as early as days after start to as long as one year after treatment has finished (Haanen et al., 2017). It is thought that the timeline for immune-related side effects mirrors the evolution of the body’s immune response to cancer as it is boosted by checkpoint inhibitor therapy — and eventual overactivation of this response that produces autoimmunity.

Side effects from treatment with checkpoint inhibitors typically appear within weeks or a few months of starting treatment but can persist or first appear after treatment has finished.
Side effects to PD-1 inhibitors typically appear between a few weeks and three months after treatment starts, although endocrine effects may take longer than others to manifest. (Weber J, et al: J Clin Oncol 35(7), 2017: 785-792. Reprinted with permission. © (2017) American Society of Clinical Oncology. All rights reserved.)

Overall, the most common side effects for both types of drugs are skin symptoms, while gastrointestinal symptoms seem to be more common with CTLA-4 inhibitors and lung or thyroid symptoms seem to be more common with PD-1 inhibitors (Haanen et al., 2017). Liver side effects are less common and occur with roughly similar frequencies across both types of drugs. If you are treated with a combination of a CTLA-4 inhibitor and a PD-1 inhibitor, you will be more likely to get one or more side effects.

### AFFECTED ORGAN(S) | CTLA-4 INHIBITORS | PD-1/PD-L1 INHIBITORS
--- | --- | ---
Skin | | |
Rash | 24% | 15%
Itching | 25%–35% | 13%–20%

**Gastrointestinal tract**

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<th>CTLA-4 INHIBITORS</th>
<th>PD-1/PD-L1 INHIBITORS</th>
</tr>
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</table>
Diarrhoea | 27%–54% | Very low |
Colitis | 8%–22% | |

**Lungs**

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<tr>
<th></th>
<th>CTLA-4 INHIBITORS</th>
<th>PD-1/PD-L1 INHIBITORS</th>
</tr>
</thead>
</table>
Cough/breathlessness | Very low | 20%–40%
Pneumonitis | Very low | 2%–4%
Liver | 5%–10% | 5%–10%

**Endocrine organs**

<table>
<thead>
<tr>
<th></th>
<th>CTLA-4 INHIBITORS</th>
<th>PD-1/PD-L1 INHIBITORS</th>
</tr>
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</table>
Thyroid effects | 1%–5% | 5%–10%
Hypophysitis | 1% | Very rare

*Estimated frequencies of the most common side effects to different types of checkpoint inhibitors vary but the most common events across both types of therapies involve symptoms in the skin. The majority of these side effects are mild and reversible (Adapted from Haanen et al., 2017).*
Immunotherapy-related side effects

Doctors classify side effects from any cancer therapy by assigning each event a “Grade”, on a scale of 1–4, by increasing severity. Grade 1 side effects are considered to be mild, Grade 2 moderate, Grade 3 severe, and Grade 4 very severe. However, the precise criteria used to assign a grade to a specific side effect varies depending on which side effect is being considered. The aim is always to identify and address any side effect before it becomes severe, so you should always report any worrying symptoms to your oncology team as soon as possible. Two examples of how common side effects to checkpoint inhibitor therapy are graded are as follows (Haanen et al., 2017):

**Skin rash**
- Grade 1, rash covering less than 10% of *BSA* (body surface area) with or without symptoms.
- Grade 2, rash covering 10%–30% of *BSA* with or without symptoms, affecting patient’s ability to lead a normal life.
- Grade 3, rash covering over 30% of *BSA* with or without symptoms, affecting patient’s ability to look after themselves.
- Grade 4, rash covering over 30% *BSA* with infection or other complications, requiring admission to hospital intensive care unit.
Diarrhoea

- Grade 1, fewer than three liquid stools per day more than before treatment started, patient feels well.
- Grade 2, between four and six liquid stools per day more than before treatment started, or abdominal pain, or blood in stool, or **nausea**, or night-time symptoms.
- Grades 3/4, over six liquid stools per day more than before treatment started, or symptoms occurring within 1 hour of eating; also applies to patients with Grade 1 or 2 stool frequency who also have other symptoms such as dehydration, fever, or a rapid heart rate.

Other side effects will be graded in a similar way, but using criteria specifically relevant to each side effect, which may include laboratory values from blood tests for some of them.
How will immunotherapy-related side effects be managed?

The principles for management of checkpoint inhibitor-related side effects generally are to manage Grade 1 or Grade 2 events by treating the symptoms, without interrupting or permanently stopping treatment. Patients with persistent Grade 2 symptoms may need to skip one or more treatment doses and also receive treatment for their symptoms, until their symptoms have subsided or resolved. For patients with Grade 3 or Grade 4 symptoms, treatment typically will be stopped and referral to a specialist will be arranged – for example, a dermatologist for severe skin symptoms.

The most important and effective strategy for managing side effects of checkpoint inhibitor therapy is early identification and intervention – so you should always mention new or worsening symptoms to your doctor or oncology team.

The general principle for managing side effects from treatment with checkpoint inhibitors is firstly, to identify symptoms early and address them promptly with treatment for symptoms and possibly oral steroids. Only if symptoms worsen will you be admitted to hospital for treatment with intravenous steroids or other immunosuppressive therapy. © Stéphane Champiat MD, PhD

It is very important to note that side effects which lead to permanent discontinuation of treatment with checkpoint inhibitors are relatively infrequent, and early findings suggest that treatment with intravenous corticosteroids or stronger immunosuppressive drugs (for more severe side effects) does not negatively affect how your cancer will respond to immune checkpoint therapy. Likewise, evidence suggests that even if you have to permanently stop treatment with an immune checkpoint inhibitor, this will not compromise how your cancer responds (Champiat et al., 2016).
Management of most common immune-related side effects

The table below provides a general guide regarding the typical management strategies for the most common immune-related side effects. However, this table is not intended as a replacement for your doctor’s advice. Your doctor knows your full medical history and will help guide you regarding the best treatment for you.

<table>
<thead>
<tr>
<th>GRADE</th>
<th>SYMPTOMS</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rash covering less than 10% of BSA with or without symptoms.</td>
<td>Topical moisturising cream/ointment, oral or topical antihistamines for itching (if present) and/or topical corticosteroid cream (mild strength); checkpoint inhibitor treatment can continue.</td>
</tr>
<tr>
<td>2</td>
<td>Rash covering 10%–30% of BSA with or without symptoms.</td>
<td>Topical moisturising cream/ointment, oral or topical antihistamines for itching (if present) and/or topical corticosteroid cream (medium strength); checkpoint inhibitor treatment can continue.</td>
</tr>
<tr>
<td>3</td>
<td>Rash covering less than 30% of BSA with or without symptoms.</td>
<td>Topical moisturising cream/ointment, oral or topical antihistamines for itching (if present) and/or topical corticosteroid cream (high strength); plus intravenous corticosteroids; checkpoint inhibitor treatment will be withheld, but may be restarted if symptoms reduce to Grade 1 or mild Grade 2.</td>
</tr>
<tr>
<td>4</td>
<td>Rash covering over 30% BSA with infection or other complications.</td>
<td>Intravenous corticosteroids and urgent specialist review; checkpoint inhibitor therapy must be discontinued permanently.</td>
</tr>
</tbody>
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Skin side effects (rash/itching)

Self-help measures for Grade 1/2 (mild-to-moderate) symptoms are: avoid contact with skin irritants and exposure to sun

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<tr>
<th>GRADE</th>
<th>SYMPTOMS</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fewer than three liquid stools per day more than before treatment started, feeling well.</td>
<td>Anti-diarrhoeal medication (e.g. loperamide), and oral electrolyte supplementation if required; checkpoint inhibitor treatment can continue.</td>
</tr>
<tr>
<td>2</td>
<td>Four to six liquid stools per day more than before treatment started, or abdominal pain, or blood in stool, or nausea, or night-time symptoms.</td>
<td>Oral corticosteroids and further tests (e.g. sigmoidoscopy/colonoscopy); checkpoint inhibitor treatment must be withheld until symptoms resolve.</td>
</tr>
<tr>
<td>3</td>
<td>Grades 3/4, over six liquid stools per day more than before treatment started, or symptoms occurring within 1 hour of eating; also applies to patients with Grade 1/2 stool frequency who have other symptoms such as dehydration, fever or a rapid heart rate.</td>
<td>Hospital admission, intravenous corticosteroids and further tests (e.g. sigmoidoscopy/colonoscopy if not already done); if there is no response to corticosteroids, strong immunosuppressive drugs (e.g., infliximab) can be used – checkpoint inhibitor therapy must be discontinued permanently.</td>
</tr>
<tr>
<td>4</td>
<td>None; based on findings from x-ray examination.</td>
<td>Monitored every two to three days, tests to rule out other causes; checkpoint inhibitor treatment may be delayed.</td>
</tr>
<tr>
<td>1</td>
<td>Breathlessness, cough, chest pain.</td>
<td>Antibiotics (if infection suspected), oral corticosteroids if no improvement on antibiotics or no infection found, further tests (including CT scan and bronchoscopy); checkpoint inhibitor treatment will be withheld.</td>
</tr>
<tr>
<td>2</td>
<td>Worsening symptoms, difficulty breathing.</td>
<td>Hospital admission, intravenous corticosteroids, other stronger immunosuppressive drugs if no improvement; checkpoint inhibitor treatment must be discontinued permanently.</td>
</tr>
</tbody>
</table>
### Liver side effects (hepatitis)

<table>
<thead>
<tr>
<th>GRADE</th>
<th>SYMPTOMS</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>• None; based on laboratory values from blood tests of liver enzyme levels.</td>
<td>• No immediate treatment necessary, blood tests repeated in one week’s time; <strong>checkpoint inhibitor</strong> treatment can continue.</td>
</tr>
<tr>
<td>2</td>
<td>• None; based on laboratory values from blood tests of liver enzyme levels.</td>
<td>• Blood tests repeated every three days, further liver function tests done (if liver enzyme levels rising, <strong>oral corticosteroid</strong> treatment will be given); <strong>checkpoint inhibitor</strong> treatment will be withheld but may be restarted if symptoms improve (after corticosteroids have been gradually reduced).</td>
</tr>
<tr>
<td>3</td>
<td>• Grades 3/4, tiredness, feeling unwell, mild joint or muscle pains, decreased appetite/weight loss, <strong>nausea</strong>, itching, rash, <strong>diarrhoea</strong>, bloating; may have few or even no symptoms.</td>
<td>• <strong>Oral or intravenous corticosteroids</strong>, depending on liver enzyme levels; <strong>checkpoint inhibitor</strong> therapy will be stopped.</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>• Hospital admission, <strong>intravenous corticosteroids</strong> and specialist review; <strong>checkpoint inhibitor</strong> treatment must be discontinued permanently.</td>
</tr>
</tbody>
</table>

**Endocrine side effects**

#### Thyroid

- For **hyperthyroidism** (usually transient and Grade 1 or 2), may be no symptoms if mild, various symptoms with increasing severity including nervousness, anxiety and irritability, mood swings, difficulty sleeping, persistent tiredness and weakness, sensitivity to heat, swelling in the neck from an enlarged **thyroid gland**, irregular and/or unusually fast heart rate (palpitations), twitching or trembling, weight loss.

- For **hypothyroidism** (usually Grade 1 or 2), may be no symptoms if mild, various symptoms with increasing severity including tiredness, sensitivity to cold, weight gain, **constipation**, depression, slow movements and thoughts, muscle aches and weakness, muscle cramps, dry and scaly skin, brittle hair and nails.

- For symptomatic **hyperthyroidism**, treatment is initiated with **beta-blockers**; **checkpoint inhibitor** therapy will be interrupted until symptoms resolve.

- For **hypothyroidism**, treatment is with long-term **hormone replacement therapy** (with thyroid **hormones**, depending on severity) and **oral corticosteroids** if thyroid gland inflamed; **checkpoint inhibitor** therapy may be interrupted until symptoms resolve.

- Blood tests will be done regularly for both conditions to monitor levels of thyroid **hormones**.

#### Pituitary

- For **hypophysitis** (usually Grade 1 or 2), no symptoms if mild, or any/all of various symptoms including headache, double vision, excessive thirst, production of large volumes of dilute urine, various hormonal imbalances (and related symptoms).

- **Oral or intravenous corticosteroids** and appropriate **hormone replacement therapy** (depending on severity and which set of **hormones** is affected); **checkpoint inhibitor** therapy may be continued during less severe (most) symptoms, but may be withheld for more severe symptoms.

(Adapted from Haanen et al., 2017).
Management of rare side effects

There are other side effects to checkpoint inhibitors which occur infrequently, but of which you should be aware, as follows (Haanen et al., 2017):

- **Neurological** symptoms — according to an analysis of data from many clinical trials, these occur in approximately 4%–6% of people treated with CTLA-4 inhibitors or PD-1 inhibitors, or in up to 12% if treated with both types in combination, and manifests in a wide range of different ways (including muscle weakness, numbness and breathing difficulties); treatment for symptoms of Grade 2 or higher is based mainly on increasing strength oral or intravenous corticosteroids.  

- **Rheumatological** symptoms — mild or moderate muscle or joint pain occurs in 2%–12% of people treated with checkpoint inhibitors, more commonly with PD-1 inhibitors; treatment is mainly with oral analgesics (mild-to-moderate symptoms), low-dose oral corticosteroids (moderate symptoms), or for severe symptoms, consultation with a specialist and high-dose corticosteroids or intravenous immunosuppressive drugs may be necessary. Treatment with checkpoint inhibitors may need to be interrupted or stopped, depending on symptom severity. 

- **Kidney** symptoms — fewer than 1% of people treated with CTLA-4 inhibitors or PD-1 inhibitors experience kidney problems (although approximately 5% do so if treated with the two types of checkpoint inhibitors in combination); significant impairment of kidney function is treated with intravenous corticosteroids and specialist intervention, and may require checkpoint inhibitor treatment to be interrupted or stopped. 

- **Cardiac** symptoms — seen in fewer than 1% of people treated with CTLA-4 inhibitors or PD-1 inhibitors and includes a wide range of different types; these require early referral to a cardiologist and treatment with high-dose corticosteroids or other immunosuppressive drugs. 

If you have any questions or concerns, or notice any worrying symptoms (or worsening of existing symptoms), you should inform your doctor or oncology team as soon as possible so they can address these promptly and give you the best possible care. Remember that most side effects to checkpoint inhibitors are mild and reversible if detected early, so the most important thing is to tell your doctor or oncology team about any symptoms that concern you.
References


Immunotherapy-related side effects

**GLOSSARY**

**ACQUIRED IMMUNITY**
The aspect of the body’s immune response that is learned from encountering foreign antigens

**ACTIVE IMMU NO THERAPY**
A type of immunotherapy that stimulates the person’s immune system to respond to one or more antigens by producing antibodies, e.g. a vaccine

**ANAEMIA**
A condition characterised by the shortage of red blood cells or haemoglobin (a protein in red blood cells that carries oxygen around the body)

**ANTIBIOTICS**
Drugs that fight bacterial infections

**ANTIBODY**
A blood protein produced in response to, and able to counteract, a specific antigen

**ANTI-DIARRHOEAL**
A medication that provides symptomatic relief from diarrhoea

**ANTIGEN**
A molecule capable of inducing an immune response

**ANTIGEN-PRESENTING CELL**
Any cell that can ingest and present an antigen to an immune cell in a form it recognises and responds to

**ANTIHISTAMINE**
A type of drug used to treat allergies

**ATEZOLIZUMAB**
A type of immunotherapy that blocks the interaction between PD-L1 and PD-1 on the surface of certain immune cells called T cells; this activates T cells to find and kill cancer cells. Atezolizumab is a monoclonal antibody. It is administered through a drip into a vein in your arm or chest

**AUTOIMMUNITY**
An immune response against the body’s own healthy cells and tissues

**AVELUMAB**
A type of immunotherapy that blocks the interaction between PD-L1 and PD-1 on the surface of certain immune cells called T cells; this activates T cells to find and kill cancer cells. Avelumab is a monoclonal antibody. It is administered through a drip into a vein in your arm or chest

**B CELL**
A type of white blood cell, or lymphocyte, that produces antibodies

**BACTERIA**
Microscopic single-celled organisms, some of which are capable of causing infection

**BETA-BLOCKERS**
Drugs that slow the heart rate and lower blood pressure

**BONE MARROW**
A spongy tissue found inside some bones (e.g. hip and thigh bones). It contains stem cells, which are cells that can develop into the red blood cells, white blood cells or platelets

**BRONCHOSCOPY**
A procedure by which a doctor inserts a special device into the main breathing tube (bronchus), usually via the nose or mouth, to examine the airways (including the lungs)

**BSA**
Body surface area; the measurement of the surface area of the body

**CARDIAC**
Relating to the heart

**CARDIOLOGIST**
A doctor who specialises in diseases and abnormalities of the heart

**CHECKPOINT INHIBITOR**
A type of drug that blocks certain immune response-inhibiting proteins made by immune system cells, such as T cells, and some cancer cells and thus enhances the body’s immune response

**CHEMOTHERAPY**
A type of cancer treatment using medicine that kills the cancer cells by damaging them, so that they cannot reproduce and spread

**CLINICAL TRIAL**
A study that evaluates the effects of a medical treatment or intervention

**COLITIS**
Inflammation of the colon or large intestine

**COLON**
Large intestine
GLOSSARY

**COLONOSCOPY**
A procedure in which a flexible instrument is inserted into the anus (back passage) in order to examine the colon.

**CONSTIPATION**
Difficulty emptying the bowels, usually associated with hardened faeces.

**CORNEA**
The transparent layer forming the front of the eye.

**CORTICOSTEROID**
A type of steroid drug used to relieve inflammation.

**CT SCAN**
Computed tomography; a scan using x-rays and a computer to create detailed images of the inside of your body.

**CTLA-4**
A special protein molecule that, functioning as an immune checkpoint, “turns down” an immune response once it has done its job.

**CTLA-4 INHIBITOR**
A type of drug that blocks the CTLA-4 immune checkpoint on the surface of certain immune cells called T cells; this activates T cells to find and kill cancer cells, thereby enhancing the immune response.

**CYTOTOXIC T CELL**
A type of white blood cell, or lymphocyte, able to kill infected or cancer cells.

**DERMATOLOGIST**
A doctor who specialises in diseases of the skin.

**DIARRHOEA**
Abnormal frequency of loose or liquid stools (faeces).

**DURVALUMAB**
A type of immunotherapy that blocks the interaction between PD-L1 and PD-1 on the surface of certain immune cells called T cells; this activates T cells to find and kill cancer cells. Durvalumab is a monoclonal antibody. It is administered through a drip into a vein in your arm or chest.

**ELECTROLYTE**
A substance (e.g. sodium or calcium) that regulates the flow of nutrients into, and waste products out of, cells.

**ENDOCRINE**
Relating to glands that secrete hormones into the bloodstream.

**FATIGUE**
Overwhelming tiredness.

**FUNGI**
Microscopic organisms some of which are capable of causing infection.

**GASTROINTESTINAL**
Relating to stomach and intestines.

**GASTROINTESTINAL TRACT**
The digestive tract, comprising a large muscular tube extending from the mouth to the anus (back passage) via the stomach that is responsible for digesting food and expelling waste products as stools (faeces).

**HAIR FOLLICLE**
A small sac in the skin from which hair grows from.

**HEPATITIS**
Inflammation of the liver.

**HORMONE**
A chemical messenger produced by a specialised gland in the body.

**HYPERTHYROIDISM**
Overactivity of the thyroid gland.

**HYPOPHYSIS**
Inflammation of the pituitary gland (located in the brain).

**HYPOTHYROIDISM**
Underactivity of the thyroid gland.

**IMMUNE CELL**
A cell involved in an immune response or forming part of the immune system.

**IMMUNE CHECKPOINT**
A molecule in the immune system that either turns up a signal (enhances the immune response) or turns down a signal (decreases the immune response).

**IMMUNE RESPONSE**
The reaction of cells and fluids of the body to the presence of a substance which is not recognised as a part of the body itself.

**IMMUNE SYSTEM**
The system in the body that works to ward off infection and disease.

**IMMUNO-ONCOLOGICAL**
Relating to immuno-oncology (next page).
Immunotherapy-related side effects

GLOSSARY

IMMUNO-ONCOLOGY
The discipline in medicine that uses strategies harnessing the immune system to treat cancer

IMMUNOSUPPRESSIVE
Drugs or other factors that partially or completely suppressing the immune response

IMMUNOTHERAPY
The prevention or treatment of disease with substances that stimulate (or suppress) the immune response

INFliximab
A type of drug called a monoclonal antibody that is used to treat autoimmune diseases

INNATE IMMUNITY
A non-specific type of immunity that humans are born with and which does not require a learning process or prior exposure to an antigen

INTRAvenous
Administered into a vein

IPILIMUMAb
A type of immunotherapy that blocks the CTLA-4 immune checkpoint on the surface of certain immune cells called T cells; this activates T cells to find and kill cancer cells. Ipilimumab is a monoclonal antibody. It is administered through a drip into a vein in your arm

LEUCOCYTE
A white blood cell involved in the immune response

LEUCOPAENIA
A decrease in the number of leucocytes (a type of white blood cell) in the blood, which places individuals at increased risk of infection

LOPERAMIDE
A drug used to treat diarrhoea

LYMPHATIC SYSTEM
The network of vessels through which a clear fluid called lymph drains from the tissues into the blood; it is a vital part of the immune system

LYMPHOCYTE
A type of white blood cell

LYMPHOID
Relating to cells, tissues and organs that make up the lymphatic system

MAJOR HISTOCOMPATIBILITY COMPLEX
A group of protein molecules on the surface of cells that enable the immune system to differentiate self from non-self

MALIGNANT
Malignant is another term for cancerous. Malignant cells can invade nearby tissue and spread to other parts of the body

MEMORY CELL
A long-lived lymphocyte capable of remembering and responding to a particular antigen the next time it encounters it

MICROORGANISM
A microscopic organism (e.g. a virus)

MOLECULE
The smallest physical unit of a substance

MONOClonAL ANTIBODY
A type of targeted therapy. Monoclonal antibodies recognise and attach to specific proteins produced by cells. Each monoclonal antibody recognises one particular protein. They work in different ways depending on the protein they are targeting

MUCOSITIS
The painful inflammation and ulceration of the mucous membranes lining the digestive tract

MUTATED
Relating to a permanent alteration in the DNA sequence that makes up a gene, such that the sequence differs from what is found in most people

NAUSEA
A feeling of sickness with an urge to vomit (be sick)

NEUROLOGICAL
Relating to any aspect of the nervous system

NEUTROPAENIA
An abnormally low level of neutrophils in the blood, which increases risk of infection

NIVOLUMAB
A type of immunotherapy that blocks a protein called PD-1 on the surface of certain immune cells called T cells; this activates the T cells to find and kill cancer cells. Nivolumab is a monoclonal antibody. It is administered through a drip into a vein in your arm or chest

ORAL
By mouth
PASSIVE IMMUNOTHERAPY
Interventions designed to improve upon the body’s existing immune response.

PEMBROLIZUMAB
A type of immunotherapy that blocks a protein called PD-1 on the surface of certain immune cells called T cells; this activates the T cells to find and kill cancer cells. Pembrolizumab is a monoclonal antibody. It is administered through a drip into a vein in your arm or chest.

PD-1
A special protein molecule that, functioning as an immune checkpoint, “turns down” an immune response once it has done its job.

PD-1 INHIBITOR
A type of drug that blocks the PD-1 immune checkpoint and thus enhances the immune response.

PD-L1
A special protein molecule that binds to, and activates, PD-1, in order to “turns down” an immune response.

PD-L1 INHIBITOR
A type of drug that blocks PD-L1 and thus enhances the immune response.

PITUITARY GLAND
The major endocrine gland, a pea-sized structure attached to the base of the brain.

PLATELET
A tiny blood cell that helps your body form clots to stop bleeding.

PNEUMONITIS
Inflammation of the walls of the alveoli (air sacs) in the lungs.

PROTEIN
A large molecule that makes up most of the organs and tissues of the body.

PRURITUS
Itching.

RED BLOOD CELL
The blood cells that carry oxygen around the body and remove carbon dioxide.

REPRODUCTIVE TRACT
Organ system by which humans reproduce and (in females) bear offspring.

RESPIRATORY
Relating to the respiratory tract (below).

RESPIRATORY TRACT
The passage formed by the mouth, nose, throat and lungs through which air passes during breathing.

RHEUMATOLOGICAL
Relating to the branch of medicine that deals with the study and treatment of rheumatic diseases.

SELF-ANTIGEN
A molecule that is recognised as belonging to the body and which does not normally evoke an immune response in the same person.

SIGMOIDOSCOPY
A procedure by which a doctor inserts a special device into the rectum (back passage) to examine the lower portion of the large intestine (or bowel).

SPL EN
A small organ in the abdomen that cleans the blood and is a key part of the immune system.

STEROID
See corticosteroid.

T CELL
A type of white blood cell or lymphocyte.

T CELL RECEPTOR (TCR)
A molecule on the surface of T cells that recognises antigens.

THROMBOCYTOPAENIA
A deficiency of platelets in the blood. This causes bleeding into the tissues, bruising, and slow blood clotting after injury.

THYMUS GLAND
A small organ situated in the neck that produces T cells for the immune system.

THYROID GLAND
A butterfly-shaped organ located in the lower part of the neck at the front. It releases hormones that control metabolism (the way the body uses energy).

TOPICAL
Applied directly to a particular part of the body.
Immunotherapy-related side effects

**GLOSSARY**

**TUMOUR**
A lump or growth of abnormal cells. Tumours may be benign (not cancerous) or malignant (cancerous). In this guide, the term ‘tumour’ refers to a cancerous growth, unless otherwise stated.

**TUMOUR ANTIGEN**
An antigen produced by tumour cells.

**TUMOUR-INfiltrATING LYMPHOCYTE**
White blood cells that have left the bloodstream and migrated into a tumour.

**TUMOUR-TARGETED DRUGS**
A newer type of cancer treatment using drugs that precisely identify and attack cancer cells, usually while doing little damage to normal cells.

**URINARY TRACT**
Collective term for the bladder, kidneys, ureters and urethra.

**VIRUS**
A very small microorganism that can grow and reproduce inside a living cell in the body.

**VITILIGO**
A skin disorder in which pigment is lost causing white patches on various parts of the body.

**VOMITING**
Forcible ejection of stomach contents through the mouth.

**WHITE BLOOD CELL**
A type of blood cell (leucocyte) involved in the immune response.

**X-RAY**
An imaging test, using a type of radiation that can pass through the body, that allows your doctor to see inside your body.
This guide has been prepared to help you, your friends and your family better understand the nature of immunotherapy-related side effects and their management. The medical information described in this document is based on the clinical practice guideline of the European Society for Medical Oncology (ESMO) for the management of toxicities from immunotherapy. We recommend that you ask your doctor about the types of immunotherapy available in your country for your type and stage of cancer.
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For more information, please visit www.esmo.org