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Complications of Treatment

# Management of toxicities of immune checkpoint inhibitors

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ABSTRACT

Immune checkpoint inhibition with the anti-CTLA-4 antibody ipilimumab and the anti-PD-1 antibodies nivolumab and pembrolizumab has improved survival in metastatic melanoma, lung cancer and renal cancer. Use of these agents holds promise in other malignancies. The augmented immune response enabled by these agents has led to a particular group of side effects called immune-related adverse events (irAEs). The main irAEs include diarrhea, colitis, hepatitis, skin toxicities and endocrinopathies such as hypophysitis and thyroid dysfunction. The anti-PD-1 antibodies have a different toxicity profile to ipilimumab with fewer high grade events. This article identifies the rates of common and uncommon irAEs associated with each immune checkpoint inhibitor (ICPI) and their timing of onset, focusing mainly on the experience in melanoma and lung cancer. An approach to management for each class of irAE is provided.



## Introduction

Immune checkpoint inhibitors (ICPIs) have changed the landscape of advanced cancer treatment during the last few years. Blockade with antibodies against cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death-protein 1 (PD-1) or its ligand (PD-L1) augment the immunologic reaction against tumour cells in several cancer types.

CTLA-4 is part of the B7:CD28 immunoglobulin family found on the surface of T-cells and transmits an inhibitory signal to the T-cell. Ipilimumab is a fully human monoclonal antibody against CTLA-4 binding of which leads to deactivation of the inhibitory signal of the T-cell [1]. PD-1 is expressed on T-cells and binds to its ligands PD-L1 and PD-L2 that are expressed on cancer cells and other immune cells. Antibodies against PD-1, such as nivolumab, pembrolizumab and pidilizumab, or PD-L1, such as MEDI4736 and MPDL3280A increase the anti-tumour T-cell response by blocking the interaction of PD1 and PD-L1 to prevent T-cell inactivation [1].

Immune-related adverse events (irAEs) from ICPIs occur as a consequence of impaired self-tolerance from loss of T-cell inhibition. They can potentially involve every organ system but gastrointestinal, dermatologic, hepatic and endocrine toxicities predominate. These side effects are generally manageable but can be fatal in some cases [2–5]. Their appearance may be subclinical and early diagnosis and management present challenges for the physician.

This article will focus on published toxicity data in phase II and III studies, the majority of which comes from trials in advanced melanoma, and present an approach to management of the main irAEs.

## Overview of treatment with immune checkpoint inhibitors in various malignancies

### *Melanoma*

The greatest evidence for the use of ICPIs comes from studies in advanced melanoma. In the metastatic setting, ipilimumab [2,6], nivolumab [7,8] and pembrolizumab [5,9] are all associated with a substantial survival advantage over cytotoxic chemotherapy in both pre-treated and treatment-naïve patients. Pembrolizumab and nivolumab are superior to ipilimumab in the first-line setting with regards to overall and progression-free survival respectively [5,10]. Combination immunotherapy with nivolumab and ipilimumab results in a higher response rate and longer time to progression than either agent alone [10]. Ipilimumab also improves recurrence free survival in patients with resected stage III melanoma [4]. Other ICPIs such as anti-PD-L1 agents show promise in melanoma, possibly with a better toxicity profile [11]. Rates of irAEs associated with ICPIs in advanced melanoma are shown in Table 1.

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**Table 1**
Immune-related adverse event rates associated with immune checkpoint inhibitors in advanced melanoma.

| | Pembrolizumab (2 mg/kg 2- and 3-weekly) [5] | | Nivolumab (3 mg/kg 2-weekly) [7,8,10] | | Ipilimumab (3 mg/kg 3-weekly) [5,10] | | Ipilimumab + Nivolumab (3 mg/kg + 1 mg/kg every 3 weeks) [10] | |
|---|---|---|---|---|---|---|---|---|
| | All grade | Grade 3/4 | All grade | Grade 3/4 | All grade | Grade 3/4 | All grade | Grade 3/4 |
| Diarrhoea (%) | 14–17 | 1–3 | 11–19 | 0–2 | 23–33 | 3–6 | 44 | 9 |
| Colitis (%) | 2–4 | 1–3 | 1 | <1 | 8–12 | 7–9 | 12 | 8 |
| Hepatitis* (%) | 1–2 | 1–2 | 3–6 | 2–3 | 1–7 | 0–2 | 30 | 19 |
| Pruritus (%) | 14 | 0 | 16–19 | <1 | 25–35 | <1 | 33 | 2 |
| Rash (%) | 13–15 | 0 | 9–22 | <1 | 15–21 | 1–2 | 28 | 3 |
| Vitiligo (%) | 9–11 | 0 | 5–11 | 0 | 2–4 | 0 | 7 | 0 |
| Pneumonitis (%) | <1 | <1 | 1–2 | <1 | 0–2 | <1 | 6 | 1 |
| Hypothyroidism (%) | 9–10 | <1 | 4–9 | 0 | 2–4 | 0 | 15 | <1 |
| Hyperthyroidism (%) | 3–7 | 0 | 2–4 | <1 | 1–2 | <1 | 10 | 1 |
| Hypophysitis (%) | <1 | <1 | <1 | <1 | 2–4 | 2 | 8 | 2 |
| Renal injury (%) | 1 | 0 | 1 | <1 | <1 | <1 | NR | NR |
| Rheumatological (%) | | | | | | | | |
| Myalgia | 2–7 | <1 | 4 | 0 | 2 | <1 | NR | NR |
| Arthralgia | 9–12 | <1 | 6–8 | 0 | 5 | <1 | 11 | <1 |
| Arthritis | 0–2 | 0 | | NR | 0 | 0 | | NR |
| Myositis | | 0 | | NR | NR | NR | | NR |
| Uveitis (%) | <1 | 0 | NR | NR | 0 | 0 | NR | NR |
| Neurological (%) | 1 | 0 | 1 | NR | 1 | <1 | NR | NR |
| Cardiac (%) | NR | 1–2 | 0** | NR | NR | NR** | NR | NR |
| Fatigue (%) | 19–21 | 0 | 34 | 0–1 | 15 | 1 | 35 | 4 |
| Haematological (%) | | | | | | | | |
| Anaemia | 1–2 | 0 | 4 | NR | <1 | <1 | NR | NR |
| Neutropenia | NR | NR | NR | 0 | 0 | 0 | NR | NR |
| Thrombocytopenia | NR | NR | NR | **0 | NR | NR | NR | NR |

NR = not reported
* Deemed to be any elevation of ALT or AST.
** G5 event.

*Lung cancer and mesothelioma*

After promising results in early trials [14,15], three phase III studies demonstrated superior survival with anti-PD-1 blockade (nivolumab and pembrolizumab) compared to chemotherapy in previously treated patients with squamous and non-squamous lung cancer [16–18]. Nivolumab was approved in the United States (US) for treatment of squamous NSCLC in March 2015. A phase III trial comparing nivolumab with chemotherapy in treatment naive patients is recruiting (NCT02041533). Table 2 details the rates of irAEs in these trials.

Tremelimumab showed clinical activity with an acceptable safety profile in advanced malignant mesothelioma [20,21]. In April 2015 tremelimumab was granted Orphan Drug Designation in the US for treatment of malignant mesothelioma.

**Table 2**
Immune-related adverse events associated with immune checkpoint inhibitors in advanced lung cancer.

| | Pembrolizumab (2 mg/kg or 10 mg/kg every 3 weeks or 10 mg every 2 weeks) [17,19] | | Nivolumab (3 mg/kg every 2 weeks) [14,16,18] | |
|---|---|---|---|---|
| | All grade | Grade 3/4 | All grade | Grade 3/4 |
| Diarrhoea (%) | 8 | 1 | 8–10 | 0–3 |
| Colitis (%) | 1 | 1 | 1 | <1 |
| Hepatitis* (%) | 1–3 | <1 | 1–3 | <1 |
| Pruritus (%) | 11 | 0 | 6–8 | 0–1 |
| Rash (%) | 10 | 0.2 | 4–11 | 0–1 |
| Vitiligo (%) | NR | 0 | NR | NR |
| Pneumonitis (%) | 5 | 2** | 3–5 | 1–3 |
| Hypothyroidism (%) | 8 | <1 | 4–7 | 0 |
| Hyperthyroidism (%) | 2–4 | 0 | 1–2 | 0 |
| Hypophysitis (%) | <1 | <1 | NR | NR |
| Renal injury (%) | <1 | 0 | 0–4 | 1 |
| Rheumatological (%) | | | | |
| Myalgia | 3 | 0 | 2–5 | 0–1 |
| Arthralgia | 9 | <1 | 5 | NR |
| Arthritis | NR | NR | NR | NR |
| Uveitis (%) | NR | NR | NR | NR |
| Neurological (%) | NR | NR | NR | 1 |
| Cardiac (%) | NR | NR | 1 | 0 |
| Fatigue (%) | 14 | 1 | 16 | 1–4 |
| Haematological (%) | | | | |
| Anaemia | 3 | 1 | 2 | 1 |

* Deemed to be any elevation of ALT or AST.
** Includes a G5 event.

*Renal cancer*

Activity of nivolumab has been demonstrated in pre-treated patients with metastatic renal cell carcinoma in both phase 2 and 3 trials [22,23]. When compared with everolimus, it improves response rates, progression-free and overall survival [23]. Overall nivolumab is well-tolerated, with grade 3/4 events occurring in 19%. Common all-grade side effects included fatigue, nausea, pruritus and diarrhea [23].

*Lymphoma*

Anti-PD-1 antibodies such as nivolumab and pidilizumab show promise in the treatment of Hodgkin's [24] and follicular lymphoma [25] respectively. Nivolumab may also have a role in maintenance after autologous stem cell transplant in diffuse large B cell lymphoma [26]. Relative to ICPI studies in epithelial malignancies, higher rates of haematological toxicity are attributed to these agents, although no grade 3 and 4 adverse events were reported in two of these studies [25,26] and affected only one patient in the other [24].

*Other malignancies*

Immune checkpoint blockade is being evaluated in a range of malignancies. In docetaxel-pretreated patients with metastatic

prostate cancer who received radiotherapy, overall ipilimumab was not shown to be superior to placebo in terms of overall survival [3]. Clinical benefit in colorectal cancer associated with mismatch repair deficiency has been established [27]. Several trials are ongoing looking at the efficacy of ICPIs in the management of bladder, gastric, pancreatic, squamous head and neck, ovarian and triple negative breast cancer.

## General approach to management of irAEs

The disadvantage of an augmented immune response driven by T cell activation is the potential autoimmune-related inflammation of normal tissues. In most circumstances, this may be managed with immune-modulatory medications (IMM). When treating patients with ICPIs it is important to remain open-minded to the possibility of irAEs, both rare and common, and develop a careful approach to their assessment and management. This includes comprehensive education of patients and care-givers on recognition of irAEs. Regular contact with specialty teams, including dedicated nurses, and establishing clear communication pathways for patient reporting of potential irAEs is important. Management of serious irAEs should be undertaken in a hospital familiar with ICPIs and their toxicity profile. Input from other specialties may be required for difficult cases.

Knowledge of the timing of onset of the suspected irAE is helpful. In melanoma patients treated with ipilimumab, dermatological irAEs usually develop during the first few weeks on treatment whereas diarrhea and colitis tend to occur between weeks 5 and 10, liver toxicity from week 7 to 14 and hypophysitis after 6 weeks [28]. Most ipilimumab-related irAEs occur during the induction period [29]. In a pooled analysis of patients treated with nivolumab, 54% of whom had prior ipilimumab, median onset of skin irAEs was at 5 weeks, gastrointestinal at 7.3 weeks, hepatic at 7.7 weeks, pulmonary at 8.9 weeks, endocrine at 10.4 weeks and renal irAEs at 15.1 weeks [30]. Pembrolizumab has a median onset of moderate to severe toxicity around 9 weeks, as compared to 6 weeks with ipilimumab [5]. It is possible for patients exposed to ICPIs to develop late-onset irAEs, which may occur after treatment has been completed [31,32].

Standard practice in clinical trials is to grade side effects according to Common Terminology Criteria for Adverse Events (CTCAE) and these may also be used in the clinic. Whilst CTCAE provide a useful framework, they may underestimate some of the irAEs such as pituitary dysfunction. We will use these criteria (CTCAE version 4.0 [33]) for discussion of management in this paper.

Steroids are administered when the severity of an irAE warrants reversal of inflammation. Other immunomodulatory medications (IMM) used in steroid-refractory cases include the anti-TNF-alpha antibody infliximab, the anti-metabolite mycophenylate mofetil and the calcineurin inhibitors tacrolimus and cyclosporine. T-cell depleting antibodies such as anti-thymocyte globulin have been effective in rare cases [34]. Table 3 describes the mechanism of action of commonly used IMMs. Liaison with other specialties is also important to collaborate expertise in immunosuppression strategies beyond steroids.

**Table 3**
Mechanism of action of immune modulating medications.

| Drug | Key mechanism of action |
|---|---|
| Steroids | Multiple effects on T cells, B cells and phagocytes through inhibition of transcription of interleukins, reduction in synthesis of cytokines, inhibition of neutrophil apoptosis and reduced macrophage function |
| Infliximab | Antibody that inhibits binding of the inflammatory cytokine tumour necrosis factor alpha (TNF-α) to its receptors |
| Mycophenylate mofetil | Inhibits inosine monophosphate dehydrogenase (IMPDH), an enzyme involved in nucleotide production, particularly in activated lymphocytes |
| Tacrolimus and Cyclosporine | Calcineurin inhibitors that limit transcription of interleukin 2 (IL-2), involved in T cell proliferation |

## Immune checkpoint inhibitor adverse events and management

### *Diarrhoea and enterocolitis*

Diarrhoea is one of the most frequent AEs related to ICPIs. It occurs at any grade in 23–33% of patients treated with ipilimumab, 8–19% of those managed with anti-PD-1 antibodies and 44% with the combination of ipilimumab and nivolumab [5,7,8,10,19]. Grade 3 and 4 diarrhoea is most prevalent with the combination approach (9%) [10]. The term colitis is used to describe diarrhoea associated with abdominal pain, per rectal bleeding or mucous, or when imaging findings confirm large bowel inflammation. Enteritis, though reported with ipilimumab [35], is rare. Coeliac disease has also been described [36]. Deaths from ipilimumab at a dose of 10 mg/kg have occurred due to intestinal perforation from colitis in around 1% of patients [3,4] and therefore urgent assessment and management is required in moderate and severe cases of diarrhea.

In patients treated with both ipilimumab and nivolumab, median onset of diarrhoea is at 7 weeks [37] whereas it appears to be around 6 months with pembrolizumab [38].

Computed tomography (CT) imaging findings associated with ICPI induced colitis include mesenteric engorgement and bowel wall thickening [39]. Histopathology of ipilimumab-induced colitis reveals a pattern distinct from inflammatory bowel disease with dysregulation of GI mucosal immunity [40]. The descending colon is usually involved and on microscopy an inflammatory cell infiltrate with cryptitis may be evident; granulomas, a hallmark of Crohn's disease, have not been described.

Management of ICPI diarrhea and colitis depends on the severity of the symptoms and treatment should be interrupted if they are moderate or meet criteria for Grade 2 (see Table 4). In a patient with associated abdominal pain or if diarrhea frequency exceeds 6 episodes per day, steroids should be initiated. Sigmoidoscopy-proven colitis with failure of improvement after 48 to 72 h warrants infliximab administration. In all cases stool cultures should be sent to exclude infection, abdominal imaging with X-ray or CT obtained, and electrolytes monitored. Ophthalmologic examination is recommended as ocular inflammation can be associated with colitis [41].

If diarrhea or colitis recurs despite treatment, discontinuation of the ICPI must be considered. The risks versus benefits of administering a different ICPI after grade 3 toxicity must be carefully discussed with the patient. Use of other immunosuppressants such as tacrolimus or mycophenylate mofetil can be considered in steroid- and infliximab-refractory cases. Colectomy may be needed in select cases and surgical involvement should occur early in patients who are very unwell with colitis.

### *Hepatitis*

Although various trials of ICPIs have used the terms *hepatitis* and *raised transaminases* to describe liver dysfunction, for the purpose of this article we will refer to any derangement in liver function (raised alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with or without elevated bilirubin) due to an ICPI as immune-related hepatitis. Onset typically occurs between 6 and 14 weeks after initiation of therapy. Ipilimumab hepatitis occurs in 1–7% whereas hepatitis due to anti-PD-1 agents

**Table 4**
Management of immune-related diarrhoea, colitis and hepatitis.

| | Grade 1 (mild) | Grade 2 (moderate) | Grade 3 (severe) | Grade 4 (life threatening) |
|---|---|---|---|---|
| Diarrhoea and Enterocolitis | *<4 bowel actions per day over baseline; mild:* supportive measures such as increasing oral fluid, anti-motility agents such as loperamide | *4–6 bowel actions per day over baseline; moderate:* withhold ICPI. As per Grade 1 if patient is well. If no improvement in 5 days, or if worsening of symptoms, commence steroids at a dose of 0.5–1 mg/kg per day of prednisolone (or IV equivalent) and continue until symptoms improve to G1. If no improvement occurs, manage as per G3. Steroids can be tapered over 2–4 weeks. Sigmoidoscopy and biopsy can be considered and may assist in determining the duration of steroid taper based on the macroscopic and microscopic inflammation evident | *⩾7 bowel actions per day over baseline; severe symptoms:* admit patient to hospital for intravenous hydration and clinical observation as appropriate. Commence steroids at 1–2 mg/kg prednisolone or IV equivalent. If no improvement in 2–3 days, commence infliximab 5 mg/kg and continue steroids. Infliximab is contraindicated in patients with sepsis or a perforation. Sigmoidoscopy and biopsy recommended to exclude other causes. Once symptoms resolve to G1, taper steroids over minimum 1 month (up to 3 months for severe cases). Infliximab may be re-administered at 2 and 6 weeks if symptoms persist or recur. Dietician input recommended | *Life threatening consequences, urgent intervention indicated:* management as per G3. Involve gastroenterologist and surgeon in management. Permanently discontinue ICPI |
| Hepatitis | *ALT/AST up to 3 times ULN:* continue ICPI. Send viral serology looking for hepatitis A, B C and CMV and iron studies to look for underlying haemochromatosis. Advise against excessive alcohol intake | *3 to 5 times ULN:* withhold ICPI. Product information (Ipi, Nivo, Pembro) recommends initiation of steroids with prednisolone 1–2 mg/kg/day or IV equivalent. If patient is well, it is reasonable to re-check liver function every 2 days and initiate steroids if no improvement or worsening. Taper steroids over 4 weeks once liver function G1 or at baseline | *5 to 20 times ULN:* as per Grade 2 except that steroids should be initiated immediately. Ipilimumab should be permanently discontinued. Consider permanent discontinuation of anti-PD-1 drugs | >20 times ULN: as per Grade 3. Permanently discontinue ICPI |

ADL = activities of daily living; IV = intravenous.

and the combination occurs in 1–6% and 30% respectively [5,7,8,10,19]. Grade 3 hepatitis occurs in 1–2% for both ipilimumab and anti-PD-1 agents and 14% in the combination [5,7,8,10,19]. In our experience, hepatitis is usually asymptomatic and is detected on routine blood tests. Fulminant hepatitis has been reported with ipilimumab [37] and there are reports of presentation with jaundice and hepatic failure [34].

Our approach to diagnosis and management of suspected ICPI-related hepatitis is to exclude other causes of liver injury such as medications, alcohol and viral hepatitis. Imaging should also be undertaken to rule out disease progression. Albumin and coagulation studies should be requested to assess synthetic function. As there may be delays in obtaining serological results, initiation of steroids should not be delayed if there is no other apparent cause or if the patient is compromised.

Management of hepatitis is outlined in Table 4. Steroid therapy should be initiated in patients with ALT or AST values greater than 5 times the upper limit of normal.

If hepatitis does not respond to steroids, mycophenylate mofetil should be introduced at 500–1000 mg bd. Input from a hepatologist is advised in severe steroid-refractory cases. Failing mycophenylate, anti-thymocyte globulin has been successfully used in one case report [34].

### *Other GI*

Aside from enterocolitis and hepatitis, other recognised gastrointestinal irAEs include pancreatitis [38,42], inflammatory enteric neuropathy with constipation [43] and esophagitis [37]. A pragmatic approach to diagnosis is required and acknowledgement that exclusion of autoimmune-related inflammation is usually easier than confirmation. Use of steroids in moderate to severe cases is recommended at a dose of 1–2 mg/kg/day of prednisolone or IV equivalent.

### *Dermatologic*

Skin toxicity from ICPIs, ranging from rash to pruritus to vitiligo, is common and often occurs within the first few weeks of treatment [28,30]. Delayed onset has also been reported [44]. It is more prevalent in patients with advanced melanoma than other malignancies. In a meta-analysis of patients treated with ipilimumab, 24.3% developed a rash, 2.4% was high-grade [45]. Vitiligo, noted in up to 10% of melanoma patients managed with ICPIs [5,7,8,10], in particular with anti-PD-1 agents, has not been reported in lung cancer or renal cancer studies [14,16,19,22]. This may be explained by development of anti-melan-A T cells that are specific to an anti-melanoma immune response [46]. Vitiligo can be a predictive factor for durable response [47,48]. Pruritus is more common with ipilimumab (up to 35%) [5,10] but still impacts 6–20% of patients treated with anti-PD-1 across several malignancies [5,8,10,16,19,22], with rates as high as 15–19% in melanoma [4,6,7].

Severe skin toxicity (grades 3 and 4) is rare, although cases of Stevens Johnson syndrome, toxic epidermal necrolysis [37] and drug rash with eosinophilia and systemic symptoms (DRESS) [49] have been reported. Sweet syndrome due to ipilimumab, responsive to steroids, has been described [50,51]. Combination immunotherapy has yielded the highest rate of severe skin toxicity (2.9%) [10]. Most of these patients received steroids and resolution

occurred in 2–6 weeks. In a pooled analysis of patients on nivolumab, skin toxicity had the longest duration of the irAEs when IMM was required [30].

Differential diagnoses include contact dermatitis, viral rashes and vasculitis. Dermatological opinion is advisable if there is uncertainty. Biopsies are often feasible and histology may vary depending on the mechanism of inflammation. Perivascular lymphocytic infiltrates [52] or in the case of Sweet syndrome, dermal neutrophilic infiltration [51], have been reported.

Management of ICPI rash is described in detail in Table 5. Full supportive measures with emollient creams, avoidance of chemicals and sun protection is recommended for all patients. Topical steroids may be very effective for mild to moderate symptoms but in severe cases prednisolone or methylprednisolone may be indicated.

### *Pulmonary*

Generally pneumonitis is an uncommon side effect of immune checkpoint inhibitors. With nivolumab, pneumonitis was less frequent in melanoma patients (around 2%) [8,15,16] than in renal cancer and NSCLC patients (around 5%) [13,17]. Cases of treatment-related deaths from pulmonary toxicity are described [18]. Similar frequencies were shown with pembrolizumab in melanoma and NSCLC patients, with one death described in a patient with NSCLC [10,14,19]. Ipilimumab monotherapy results in pneumonitis in up to 5%, although a higher number of patients with dyspnoea or cough are described [2,7,8,10]. The combination of ipilimumab and nivolumab is associated with the highest rate of pneumonitis (5–10% (any grade) and 2% grade 3/4) [7,8,20].

While asymptomatic pneumonitis may be observed and treatment continued, the presence of any symptoms warrants interruption of immune-checkpoint delivery and initiation of steroid treatment (see Table 5 for detailed management).

### *Endocrine*

Endocrine toxicity from ICPIs ranges from common asymptomatic changes in thyroid function tests to an adrenal crisis. With ipilimumab, onset is usually from 7 weeks and with nivolumab median onset is 10 weeks [28,53]. Contrary to dermatologic, gastrointestinal and hepatic irAEs, there is no data on histopathological findings.

#### *Thyroid dysfunction*

Hypothyroidism is more common with anti-PD-1 antibodies than ipilimumab 3 mg/kg (4–10% versus 2–4% respectively) and is rarely severe [5,8,10]. We see this occur commonly after subclinical hyperthyroidism. A higher rate of 9% was reported with ipilimumab given at 10 mg/kg [4], but not at Grade 3 or 4 severity.

**Table 5**
Management of other immune-related adverse events.

| | Grade 1 (mild) | Grade 2 (moderate) | Grade 3 (severe) | Grade 4 (life threatening) |
|---|---|---|---|---|
| Rash | *<10% BSA:* symptomatic management with anti-histamines for pruritus and topical steroid cream for localised pruritus and rash; continue ICPI if responding or stable | *10–30% BSA:* if tolerable, as per G1; if intolerable, initiate systemic steroids (eg oral prednisolone 0.5–1 mg/kg daily with a 1–2 week wean) and delay treatment until G1 and steroids <10 mg. If symptoms persist or recur consider skin biopsy and withholding drug | *>30% BSA:* obtain a skin biopsy and dermatology consult. Initiate systemic steroids with 1 mg/kg of prednisolone or IV equivalent, with a 4 week taper. Withhold treatment until G1 | *No formal definition.* Management as per Grade 3. Permanently discontinue ICPI |
| Pneumonitis | *Asymptomatic; clinical or diagnostic observations; no intervention needed:* delay drug administration. Consider steroids (e.g. prednisone 1 mg/kg/day PO or methylprednisolone 1 mg/kg/day IV). Follow-up: reassess management after 3 weeks: if completely resolved or non-drug related continue treatment. If worsens treat as grade 2 or 3/4 | *Symptomatic; medical intervention indicated; limits instrumental ADLs:* delay drug administration. Consider hospitalisation, daily monitoring of symptoms. Steroids recommended (e.g. prednisone 1–2 mg/kg/day PO or methylprednisolone 1–2 mg/kg/day IV). Consider empiric antibiotics (if suspicious for concurrent infection). Follow-up: reassess management every 1–3 days. If improving taper steroids and continue treatment if symptoms resolve completely. If worsens treat as grade 3/4 | *Severe symptoms; limits self-care ADLs; oxygen indicated:* discontinue drug administration. Hospitalisation. High dose steroids with methylprednisolone (e.g. 1 g/day IV). Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy with biopsy. Reassess management daily. If not improving after 48 h or worsening, administer additional immunosuppressive therapy (e.g. infliximab, mycophenolate, immunoglobulins). If improving, taper steroids. Discontinue treatment permanently | *Life-threatening respiratory compromise; urgent intervention indicated (eg intubation):* as per Grade 3. Intensive care support required |
| Thyroid dysfunction | *Asymptomatic, no intervention needed:* monitor only | *Symptomatic or intervention indicated:* for hypothyroidism, commence levothyroxine. For hyperthyroidism, seek endocrinology input, start propranolol or atenolol for symptoms; steroids or carbimazole may be indicated pending underlying mechanism | *Severe symptoms:* as per grade 2. Hospitalisation and specialist input are recommended. Initiate prednisolone 1–2 mg/kg or IV equivalent | *Life threatening consequences:* as per grade 3 |
| Nephritis | *Creatinine > 1–1.5 × baseline; proteinuria 1+, <1.0g/24 h:* monitor renal function, promote hydration and cessation of nephrotoxic drugs | *Creatinine > 1.5–3.0 × baseline; proteinuria 2+, 1.0–3.4 g/24 h:* exclude non-immune causes, commence prednisolone 0.5–1 mg/kg. If worsens, manage as per grade 3 and discontinue ICPI | *Creatinine > 3.0 × baseline; ⩾3.5 g/24 h:* initiate prednisolone 1–2 mg/kg or IV equivalent. Consider renal biopsy. Discontinue ICPI | *Creatinine > 6.0 × ULN:* as per G3 |

Usually thyroid hormone replacement with levothyroxine can be instituted at a dose of 1–1.5 mcg/kg and ICPI treatment may be continued without interruption.

Hyperthyroidism is less common (1–7%) and may be due to transient thyroiditis preceding hypothyroidism, such as in Hashimoto's, or much less commonly due to TSH-receptor antibody development and Grave's disease. Thyroid function tests, autoantibodies such as TSH-receptor antibody and a nuclear medicine thyroid uptake scan should be performed in the work-up where appropriate.

Management of hyperthyroidism depends on the mechanism. Symptoms such as tachycardia and tremor may be alleviated with beta-blockers. Steroids should be instigated if the patient is very symptomatic. Thyroid suppressive medication such as carbimazole should be used in syndromes resembling Grave's disease. In our experience many patients have a subclinical thyroiditis that does not warrant any specific treatment.

An approach to the management of thyroid dysfunction is described in Table 5.

*Hypophysitis*

Pituitary inflammation, or hypophysitis, is much more common with ipilimumab (up to 4% at 3 mg/kg, 13% at 10 mg/kg) [4,5,10] than anti-PD-1 antibodies (less than 1%) [5,8,10]. Combination of nivolumab with ipilimumab resulted in hypophysitis in 8% [10]. It usually occurs between 6 and 13 weeks [54] but late presentations up to 19 months post treatment have been noted [31]. Symptoms may be vague with mild fatigue, arthralgias, behavioural change and loss of libido due to hormone insufficiency. They may also be severe with headache and visual change due to gland oedema or profound dizziness and nausea from an adrenal crisis. Because of the non-specific nature of many presentations, hypophysitis is probably under-diagnosed [31,55]. A male predominance (65%) is reported [54,56].

Thyroid function should be assessed regularly as low TSH may be an early indicator prior to symptom development. A pituitary axis should be tested in any suspected cases (morning cortisol, ACTH, TSH, LH and FSH, estradiol in women and testosterone in men, in addition to prolactin). It is possible to have one or more axes affected. Diabetes insipidus has also been attributed to ipilimumab-induced hypophysitis [57]. In a single-centre series of 19 cases of hypophysitis, the main MRI finding was pituitary enlargement; nodularity was also seen [31]. Some patients had a normal pituitary gland on their initial MRI but in one case atrophy was noted on follow-up suggesting inflammation and fibrosis had occurred. The timing of imaging in this study was not disclosed and it is feasible that if MRI images are obtained after commencement of high dose steroid treatment, normal findings may be expected.

In addition to hypothyroidism, hypophysitis is one of the few irAEs that is not usually reversible and patients often require long-term hormone replacement [32]. Recovery of the pituitary-thyroid axis is reported to occur in 37–85% whereas the pituitary-adrenal axis is unlikely [54,56]. Whether or not introduction of high dose steroids prevents loss of endocrine function from destructive inflammation is unknown.

As hypophysitis is not an adverse event as defined by CTCAE version 4.0, a pragmatic approach to management based on a patient's symptoms is reasonable.

Asymptomatic: image pituitary with MRI; institute hormone replacement only (as discussed with an Endocrinologist). Cortisol replacement should be administered for a week prior to levothyroxine initiation.

Symptomatic: (eg headaches, visual disturbance, hypotension): initiate prednisolone 1–2 mg/kg or IV equivalent and image pituitary with MRI. If hypotensive, IV therapy is indicated. Taper steroids over 2 to 4 weeks followed by hormone replacement.

*Other endocrine irAEs*

Hyperglycemia from type 1 diabetes mellitus has occurred following pembrolizumab [58] and a case of diabetic ketoacidosis has complicated nivolumab therapy [42]. Primary adrenal insufficiency due to ipilimumab has been described [31]. Though not reported in the literature, primary ovarian failure and epididymo-orchitis may occur in theory and therefore young patients should be made aware of potential impact on sexual function, future infertility and longer-term effects of sex-hormone deficiency such as osteoporosis and cardiovascular disease.

*Renal injury*

Elevated creatinine, autoimmune and interstitial nephritis are all recognised as irAEs of ICPIs, although they are not common (0–4%) [5,8,10,14,16,19,22]. Interestingly no renal events were reported with combination immunotherapy [10]. The highest reported rate of renal impairment was 4% in a Phase II lung cancer nivolumab trial [14,16] but no high grade events were reported. Kidney injury due to ipilimumab-induced lupus nephritis has also been described [59]. Early detection is important as renal injury is not always reversible [42].

Suggested management of immune-related renal impairment is outlined in Table 5.

*Neurological*

Although rare and occurring in no more than 3% of patients (3% with a 10 mg/kg dose of ipilimumab [4], <1% in other studies [5,8,10,14,16,19,22]), neurological irAEs require prompt recognition and treatment to avoid substantial morbidity. Median onset in one adjuvant ipilimumab trial was at 13 weeks [4]. Myasthenia gravis and Guillain Barre syndrome (including one fatal case) have been reported with ipilimumab [37,60], nivolumab [42] and pembrolizumab [16]. Posterior reversible leukoencephalopathy [61], radiculoneuropathy [62], Bell's palsy [32] and aseptic meningitis [49] have been reported with ipilimumab. Pembrolizumab has also been associated with central nervous system toxicity [63]. A range of neurological events have been described with nivolumab, including polyneuropathy [14], facial and abducens nerve paresis and demyelination [42].

For all but very mild (grade 1) neurological symptoms attributed to ICPIs, treatment should be withheld until the nature of the adverse event is understood. Early neurological consultation is advised. High dose steroid therapy with oral prednisolone (1 mg/kg) or IV equivalent should be instituted sooner rather than later if there is any doubt. MRI, nerve conduction studies and lumbar puncture may assist in diagnosis. Failing response to steroids, plasmapheresis or intravenous immunoglobulin may be required in myasthenic syndromes or for primary management of Guillain Barre Syndrome.

*Rheumatological*

Myalgias and arthralgias are commonly reported AEs with ICPIs (2–12% [5,8,10,14,16,19,22]), especially with anti-PD-1 agents. Higher grade toxicity occurs infrequently (1%) [5,30]. A pattern associated with inflammatory rheumatological conditions (ie morning stiffness, synovitis, proximal weakness) may be elicited. Two cases of polyarticular inflammatory arthritis have been reported [64], characterised by synovitis and tenosynovitis and managed with bisphosphonates and salazopyrin. Vasculitis [14], polymyositis, myositis [37] and temporal arteritis [65] have also been described.

For mild symptoms we suggest analgesia with paracetamol or non-steroidal anti-inflammatories. Moderate symptoms may

respond to prednisolone at a low dose of 10–20 mg per day. Severe symptoms warrant higher dose steroids (prednisolone 1 mg/kg) and early rheumatological consultation.

*Ocular*

An uncommon but recognised toxicity of ICPIs is ocular toxicity. Uveitis, conjunctivitis, iritis and Grave's ophthalmopathy have all been reported. Irritative eye symptoms or blurred vision should prompt early ophthalmologic review.

Management of mild to moderate symptoms that are not associated with visual change includes use of topical steroid eye drops. If symptoms do not improve, the ICPI should be discontinued. Any substantial or impending visual loss necessitates prompt initiation of steroids, either oral prednisolone at 1–2 mg/kg or an IV equivalent.

*Other toxicities*

In addition to the irAEs described above, cardiac and haematological side effects have been described. Myocarditis, including a fatal case [4], and pericarditis [37] have been attributed to ipilimumab, as was a fatal cardiac arrest in a patient on ipilimumab [10]. A case of Takotsubo cardiomyopathy was also reported in association with ipilimumab treatment [66]. In this case management was not detailed beyond beta-blockade and causal attribution remained questionable. Pembrolizumab has also been associated with myocarditis presenting as acute cardiac failure [67].

Haematologic toxicity is more commonly attributed to ICPIs in lymphoma studies, which may represent a reporting bias. Drug-induced neutropenia was thought to be the cause of death in one patient on nivolumab [10]. Grade 3 myelodysplasia was reported in a patient with Hodgkin's lymphoma treated with nivolumab. Pembrolizumab has been associated with low grade anemia and neutropenia [5]. Haemolytic anemia, red cell aplasia and acquired haemophilia A have all been reported as AEs related to ipilimumab [37,68,69]. In one patient with severe anemia and leucopenia after treatment with ipilimumab, bone marrow biopsy revealed lymphocyte infiltration without evidence of another malignancy [68]. This case was successfully reversed with high dose steroids in addition to support with granulocyte-monocyte colony stimulating factor (GM-CSF).

Fatigue is the most commonly reported AE in many of the ICPI trials, though rarely at a high grade (see Tables 1 and 2). It is essential to exclude secondary causes such as hypothyroidism and hypoadrenalism. Short courses of prednisolone at doses of 10–20 mg may be effective in managing intolerable cases.

Sarcoidosis may complicate ICPI treatment and has been reported with ipilimumab at both 3 mg/kg and 10 mg/kg [70–76]. Visceral and even neurosarcoid findings have been noted [73,76]. In some cases it has been associated with prolonged remissions [70,76]. If doubt exists as to the nature of new lymphadenopathy in an otherwise well and responding patient, a tissue diagnosis should be obtained to avoid unnecessary anti-neoplastic treatment. Treatment with steroids (ie prednisolone 1–2 mg/kg) may be required, such as in the case of symptomatic neurosarcoidosis, but in an asymptomatic patient observation may be appropriate.

*Considerations with prolonged immunosuppression*

Treatment with steroids and other IMMs for prolonged periods may be associated with short-term side effects such as opportunistic infection, insomnia, mood disturbance, gastritis, diabetes and hypertension in addition to long-term side effects such as osteoporosis. Although there are no firm guidelines in the solid-organ malignancy population, we recommend prophylaxis against pneumocystis jirovecii pneumonia in patients who receive greater than 25 mg prednisolone per day for more than four weeks. We also suggest occasional blood sugar monitoring to screen for diabetes. Many patients will require supportive antacid medications to reduce associated heartburn. Optimisation of vitamin D levels is important as well as education regarding osteoporosis minimisation in those who receive steroids for greater than 3 months [77].

## Discussion

Immune-checkpoint inhibitors have improved overall survival in a number of malignancies and have an established role in the treatment of advanced melanoma, non-small cell lung cancer and renal cancer. They commonly cause irAEs, some of which are severe, but are usually reversible with early recognition and specialised management. Algorithms for the management of irAEs have been developed and these provide a framework within which individual clinicians may exercise their discretion. Where possible, histological or serological confirmation should be sought to clarify the nature of the autoimmune process as this may differ. For example, hyperthyroidism may be mediated by thyroiditis or Grave's disease and this impacts on management. One challenge lies in deciding when to instigate next-line immunosuppression after steroids. Given the potential for fatal perforation in those with colitis, we advocate use of infliximab sooner rather than later. Prospective trials of management strategies are lacking in this field and are required to advance knowledge. These need to incorporate prolonged durations of follow-up to identify possible late complications.

The newer anti-PD-1 antibodies such as nivolumab and pembrolizumab are more tolerable than ipilimumab (grade 3 and 4 AEs in 10–15% versus 20–30% respectively) and certainly have fewer side effects than combination ipilimumab/nivolumab (grade 3 and 4 AE rate 55%). The irAE profile also differs between anti-PD-1 and anti-CTLA-4 agents. Thyroid dysfunction, arthralgias and myalgias, vitiligo and rash are all more common with nivolumab and pembrolizumab [5,7–10], whereas diarrhea, colitis, hypophysitis and pruritus are more common with ipilimumab [5,10]. Fatigue, rash and hepatitis occur at similar rates with both classes of drug when used as monotherapy. Combination ipilimumab/nivolumab is undoubtedly the most toxic regimen with diarrhea, hepatitis, pruritus and rash accounting for most of the side effects. Nonetheless, the majority of grade 3 and 4 toxicities from combination treatment resolve, except for skin and endocrine effects (86% and 46% resolution rates, respectively) [10].

Interestingly, there appears to be a positive correlation between dose and toxicity for ipilimumab, but not for pembrolizumab or nivolumab. Higher doses of ipilimumab (ie 10 mg/kg) appear to increase rates of irAEs in melanoma, though we await results from a trial of 3 mg/kg versus 10 mg/kg in the advanced setting to directly compare the two (NCT02279862) [12]. In the adjuvant melanoma trial comparing 10 mg/kg of ipilimumab with placebo, the grade 3 irAE rate was 37% and grade 4 was 6%, compared to 20–27% grade 3 and 4 events with 3 mg/kg [4,5,10]. No significant differences in toxicity have been noted between melanoma cohorts randomized to pembrolizumab 10 mg/kg or 2 mg/kg [13]. Rates of AEs from nivolumab at 3 mg/kg and 10 mg/kg appear very similar [22,78]. An analysis in melanoma patients of long-term nivolumab safety with evaluations up to 2 years, did not reveal cumulative toxicities with ongoing treatment. In fact, most AEs occurred within the first 6 months. This is reassuring, especially as the optimal duration of anti-PD-1 treatments is yet to be established.

One of the greatest points of contention is whether irAEs, representative of an activated immune response, are associated with improved disease-specific outcomes. This is balanced against the theoretically detrimental effect of dampening the immune response when IMMs are required. Higher grade events have been associated with a greater response and survival in some small studies [52,79,80]. A retrospective evaluation of 139 patients of ipilimumab given at varying doses also found irAEs to be predictive of response and survival and the highest response rate was seen in those who had grade 3 and 4 toxicity [81]. In patients treated with ipilimumab at 10 mg/kg, use of steroids did not appear to alter clinical benefit [82]. The most comprehensive dataset involved a retrospective review of 298 patients treated with ipilimumab of whom 35% required a systemic steroid for management of irAEs. Time to treatment failure and overall survival were no worse in the steroid-requiring group [83]. In a recent pooled analysis of patients treated with nivolumab, those experiencing any AE had an overall response rate by RECIST 1.1 criteria higher than the median (48.6 versus 31.4%) but those who experienced any grade 3 or 4 toxicity actually had a slightly worse response rate (27.8%) [30]. Overall, physicians should not hesitate to use IMMs to appropriately manage irAEs and patients can be reassured that there is no clear data to suggest any detrimental impact.

Select irAEs are more common in certain tumour types. Pneumonitis appears more prevalent in lung cancer patients and this may be explained by pre-existing inflammation from smoking or environmental carcinogens. Melanoma patients exclusively develop vitiligo and appear to have higher rates of colitis, although the latter may be reporting bias when it comes to the anti-PD-1 agents, due in part to greater experience with ipilimumab. Determining predictive biomarkers for other irAEs is an area of ongoing and future research. As ICPIs become more widely used in other malignancies, we may unearth novel irAEs. Anti-PD-L1 antibodies do not appear to cause as many high-grade irAEs [11], but this statement cannot be made conclusively due to lack of data.

True contraindications to use of a second ICPI, when the first has been complicated by severe toxicity, have not been established. Whilst most clinical trials of ICPIs after first-line treatment excluded patients who had a prior Grade 3 or 4 toxicity and mandated a minimum 4 week period between different agents, practice outside of trials differs according to the judgment of the physician. Treatment with nivolumab after ipilimumab appears to be safe, with 8% experiencing severe AEs in a pooled analysis [30]. In 21 patients with prior ipilimumab-induced grade 3–4 irAEs, but who were not treated with infliximab, only 2 had a subsequent dose limiting (and different) irAE with nivolumab [53]. Atypical irAEs have been reported in case series when ipilimumab follows anti-PD-1 treatment [84] but there is little data at present from which to draw conclusions as access to anti-PD-1 antibodies in the first-line setting has been limited to recently reported clinical trials [5,7,10]. Ipilimumab re-treatment does not seem to result in any increased toxicity, but it is not clear whether patients with prior Grade 3 or 4 toxicity were included in the re-treated cohorts [85,86]. In our opinion, the best strategy remains an informed discussion with the patient regarding the risk versus benefit of rechallenge with an ICPI in the context of prior severe irAEs, especially when balanced with the prospect of death from metastatic disease. Patients may also be prepared to accept greater toxicity than their physicians for a relatively small perceived benefit [87].

Excluded from clinical trials, 'real-world' treatment of patients with pre-existing auto-immune conditions will undoubtedly occur when the perceived benefit exceeds the risk. Administration of ipilimumab to two renal transplant patients was achieved without graft rejection [88] and has also been administered to patients with ulcerative colitis [89], multiple sclerosis and rheumatoid arthritis [90]. In a series of 12 patients with autoimmune conditions, reported in abstract form [91], half had a flare of their underlying condition, all managed with steroids. Response rate was 17% and median overall survival 22 months, both comparable with phase III trial results.

The advent of immune checkpoint blockade has improved survival in patients with melanoma, lung and renal cancer with further benefits anticipated in a range of other malignancies. As patients live longer and cure of advanced malignancy is within reach, a new set of survivorship issues may arise for management. There may also be sequelae due to an interplay between late effects of radiotherapy in addition to immunotherapy [32]. Thoughtful management of short and medium-term irAEs is important in optimising quality of life and long-term outcomes.

## Conflict of interest

There are no specific conflicts of interests to declare for any of the authors (L. Spain, S. Diem, J. Larkin).

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## References

[1] Curran MA, Montalvo W, Yagita H, Allison JP. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proc Natl Acad Sci USA 2010;107:4275–80.
[2] Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.
[3] Kwon ED, Drake CG, Scher HI, Fizazi K, Bossi A, van den Eertwegh AJ, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 2014;15:700–12.
[4] Eggermont AM, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, Schmidt H, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet Oncol 2015;16:522–30.
[5] Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015;372:2521–32.
[6] Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364:2517–26.
[7] Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320–30.
[8] Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015;16:375–84.
[9] Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol 2015;16:908–18.
[10] Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23–34.
[11] Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366:2455–65.
[12] Wolchok JD, Neyns B, Linette G, Negrier S, Lutzky J, Thomas L, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol 2010;11:155–64.
[13] Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet 2014;384:1109–17.
[14] Rizvi NA, Mazieres J, Planchard D, Stinchcombe TE, Dy GK, Antonia SJ, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol 2015;16:257–65.
[15] Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, et al. Overall survival and long-term safety of nivolumab (anti-programmed death 1

antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. J Clin Oncol 2015;33:2004–12.
[16] Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015;373:123–35.
[17] Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2015;373:1627–39.
[18] Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015;373:1627–39.
[19] Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018–28.
[20] Calabro L, Morra A, Fonsatti E, Cutaia O, Amato G, Giannarelli D, et al. Tremelimumab for patients with chemotherapy-resistant advanced malignant mesothelioma: an open-label, single-arm, phase 2 trial. Lancet Oncol 2013;14:1104–11.
[21] Calabro L, Morra A, Fonsatti E, Cutaia O, Fazio C, Annesi D, et al. Efficacy and safety of an intensified schedule of tremelimumab for chemotherapy-resistant malignant mesothelioma: an open-label, single-arm, phase 2 study. Lancet Respir Med 2015;3:301–9.
[22] Motzer RJ, Rini BI, McDermott DF, Redman BG, Kuzel TM, Harrison MR, et al. Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial. J Clin Oncol 2015;33:1430–7.
[23] Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1803–13.
[24] Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 2015;372:311–9.
[25] Westin JR, Chu F, Zhang M, Fayad LE, Kwak LW, Fowler N, et al. Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, phase 2 trial. Lancet Oncol 2014;15:69–77.
[26] Armand P, Nagler A, Weller EA, Devine SM, Avigan DE, Chen YB, et al. Disabling immune tolerance by programmed death-1 blockade with pidilizumab after autologous hematopoietic stem-cell transplantation for diffuse large B-cell lymphoma: results of an international phase II trial. J Clin Oncol 2013;31:4199–206.
[27] Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509–20.
[28] Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 2012;30:2691–7.
[29] Ibrahim R, Berman DM, DePril V, Humphrey RW, Chen T, Messina M, et al. Ipilimumab safety profile: Summary of findings from completed trials in advanced melanoma. American Society Clinical Oncology (ASCO); J Clin Oncol, (Suppl.; abstr 8583), Chicago, 2011.
[30] Weber J, Antonia S, Topalian SL, Schadendorf D, Larkin J, Sznol M, et al. Safety profile of nivolumab (NIVO) in patients (pts) with advanced melanoma (MEL): a pooled analysis. American Society Clinical Oncology (ASCO); J Clin Oncol 33, (Suppl.; abstr 9018), Chicago, 2015.
[31] Ryder M, Callahan M, Postow MA, Wolchok J, Fagin JA. Endocrine-related adverse events following ipilimumab in patients with advanced melanoma: a comprehensive retrospective review from a single institution. Endocr Relat Cancer 2014;21:371–81.
[32] Johnson DB, Friedman DL, Berry E, Decker I, Ye F, Zhao S, et al. Survivorship in immune therapy: assessing chronic immune toxicities, health outcomes, and functional status among long-term ipilimumab survivors at a single referral center. Cancer Immunol Res 2015;3:464–9.
[33] U.S.D.o.H.a.H. Services. Common Terminology Criteria for Adverse Events; Version 4.0; 2009. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.
[34] Chmiel KD, Suan D, Liddle C, Nankivell B, Ibrahim R, Bautista C, et al. Resolution of severe ipilimumab-induced hepatitis after antithymocyte globulin therapy. J Clin Oncol 2011;29:e237–40.
[35] Venditti O, De Lisi D, Caricato M, Caputo D, Capolupo GT, Taffon C, et al. Ipilimumab and immune-mediated adverse events: a case report of anti-CTLA4 induced ileitis. BMC Cancer 2015;15:87.
[36] Gentile NM, D'Souza A, Fujii LL, Wu TT, Murray JA. Association between ipilimumab and celiac disease. Mayo Clin Proc 2013;88:414–7.
[37] Bristol Myers Squibb. Yervoy (Ipilimumab) Product Information; 2015. http://packageinserts.bms.com/pi/pi_yervoy.pdf.
[38] Merck Sharp & Dohme Corp. Keytruda (Pembrolizumab) Product Information; 2015. http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf.
[39] Kim KW, Ramaiya NH, Krajewski KM, Shinagare AB, Howard SA, Jagannathan JP, et al. Ipilimumab-associated colitis: CT findings. AJR Am J Roentgenol 2013;200:W468–74.
[40] Berman D, Parker SM, Siegel J, Chasalow SD, Weber J, Galbraith S, et al. Blockade of cytotoxic T-lymphocyte antigen-4 by ipilimumab results in dysregulation of gastrointestinal immunity in patients with advanced melanoma. Cancer Immun 2010;10:11.
[41] Robinson MR, Chan CC, Yang JC, Rubin BI, Gracia GJ, Sen HN, et al. Cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma: a new cause of uveitis. J Immunother 2004;27:478–9.
[42] Bristol Myers Squibb. Opdivo (Nivolumab) Product Information; 2015. http://packageinserts.bms.com/pi/pi_opdivo.pdf.
[43] Bhatia S, Huber BR, Upton MP, Thompson JA. Inflammatory enteric neuropathy with severe constipation after ipilimumab treatment for melanoma: a case report. J Immunother 2009;32:203–5.
[44] Ludlow SP, Kay N. Delayed dermatologic hypersensitivity reaction secondary to ipilimumab. J Immunother 2015;38:165–6.
[45] Minkis K, Garden BC, Wu S, Pulitzer MP, Lacouture ME. The risk of rash associated with ipilimumab in patients with cancer: a systematic review of the literature and meta-analysis. J Am Acad Dermatol 2013;69:e121–8.
[46] Klein O, Ebert LM, Nicholaou T, Browning J, Russell SE, Zuber M, et al. Melan-A-specific cytotoxic T cells are associated with tumor regression and autoimmunity following treatment with anti-CTLA-4. Clin Cancer Res 2009;15:2507–13.
[47] Pavlick A, Ott PA, Kannan R, Madden KM, Sorlie C, Escano C, et al. Hair depigmentation as an indicator of durable response to CTLA-4 therapy. American Society Clinical Oncology (ASCO); J Clin Oncol, (Suppl.; abstr 8571), Chicago, 2010.
[48] Hua C, Boussemart L, Mateus C, Routier E, Boutros C, Cazenave H, et al. Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab. JAMA Dermatol 2016;152:45–51.
[49] Voskens CJ, Goldinger SM, Loquai C, Robert C, Kaehler KC, Berking C, et al. The price of tumor control: an analysis of rare side effects of anti-CTLA-4 therapy in metastatic melanoma from the ipilimumab network. PLoS ONE 2013;8:e53745.
[50] Kyllo RL, Parker MK, Rosman I, Musiek AC. Ipilimumab-associated Sweet syndrome in a patient with high-risk melanoma. J Am Acad Dermatol 2014;70:e85–6.
[51] Gormley R, Wanat K, Elenitsas R, Giles J, McGettigan S, Schuchter L, et al. Ipilimumab-associated Sweet syndrome in a melanoma patient. J Am Acad Dermatol 2014;71:e211–3.
[52] Attia P, Phan GQ, Maker AV, Robinson MR, Quezado MM, Yang JC, et al. Autoimmunity correlates with tumor regression in patients with metastatic melanoma treated with anti-cytotoxic T-lymphocyte antigen-4. J Clin Oncol 2005;23:6043–53.
[53] Weber J, Gibney G, Yu B, Cheng P, Martinez A, Kroeger J, et al. Survival, biomarker, and toxicity analysis of nivolumab (NIVO) in patients that progressed on ipilimumab (IPI). American Society Clinical Oncology (ASCO); J Clin Oncol 33, (Suppl.; abstr 9055), Chicago, 2015.
[54] Corsello SM, Barnabei A, Marchetti P, De Vecchis L, Salvatori R, Torino F. Endocrine side effects induced by immune checkpoint inhibitors. J Clin Endocrinol Metab 2013;98:1361–75.
[55] Torino F, Barnabei A, Paragliola RM, Marchetti P, Salvatori R, Corsello SM. Endocrine side-effects of anti-cancer drugs: mAbs and pituitary dysfunction: clinical evidence and pathogenic hypotheses. Eur J Endocrinol 2013;169:R153–64.
[56] Albarel F, Gaudy C, Castinetti F, Carre T, Morange I, Conte-Devolx B, et al. Long-term follow-up of ipilimumab-induced hypophysitis, a common adverse event of the anti-CTLA-4 antibody in melanoma. Eur J Endocrinol 2015;172:195–204.
[57] Dillard T, Yedinak CG, Alumkal J, Fleseriu M. Anti-CTLA-4 antibody therapy associated autoimmune hypophysitis: serious immune related adverse events across a spectrum of cancer subtypes. Pituitary 2010;13:29–38.
[58] Martin-Liberal J, Furness AJ, Joshi K, Peggs KS, Quezada SA, Larkin J. Anti-programmed cell death-1 therapy and insulin-dependent diabetes: a case report. Cancer Immunol Immunother 2015;64:765–7.
[59] Fadel F, El Karoui K, Knebelmann B. Anti-CTLA4 antibody-induced lupus nephritis. N Engl J Med 2009;361:211–2.
[60] Gaudy-Marqueste C, Monestier S, Franques J, Cantais E, Richard MA, Grob JJ. A severe case of ipilimumab-induced guillain-barre syndrome revealed by an occlusive enteric neuropathy: a differential diagnosis for ipilimumab-induced colitis. J Immunother 2013;36:77–8.
[61] Maur M, Tomasello C, Frassoldati A, Dieci MV, Barbieri E, Conte P. Posterior reversible encephalopathy syndrome during ipilimumab therapy for malignant melanoma. J Clin Oncol 2012;30:e76–8.
[62] Manousakis G, Koch J, Sommerville RB, El-Dokla A, Harms MB, Al-Lozi MT, et al. Multifocal radiculoneuropathy during ipilimumab treatment of melanoma. Muscle Nerve 2013;48:440–4.
[63] Mandel JJ, Olar A, Aldape KD, Tremont-Lukats IW. Lambrolizumab induced central nervous system (CNS) toxicity. J Neurol Sci 2014;344:229–31.
[64] Chan MM, Kefford RF, Carlino M, Clements A, Manolios N. Arthritis and tenosynovitis associated with the anti-PD1 antibody pembrolizumab in metastatic melanoma. J Immunother 2015;38:37–9.
[65] Goldstein BL, Gedmintas L, Todd DJ. Drug-associated polymyalgia rheumatica/giant cell arteritis occurring in two patients after treatment with ipilimumab, an antagonist of ctla-4. Arthritis Rheumatol 2014;66:768–9.
[66] Geisler BP, Raad RA, Esaian D, Sharon E, Schwartz DR. Apical ballooning and cardiomyopathy in a melanoma patient treated with ipilimumab: a case of takotsubo-like syndrome. J Immunother Cancer 2015;3:4.
[67] Laubli H, Balmelli C, Bossard M, Pfister O, Glatz K, Zippelius A. Acute heart failure due to autoimmune myocarditis under pembrolizumab treatment for metastatic melanoma. J Immunother Cancer 2015;3:11.

[68] Simeone E, Grimaldi AM, Esposito A, Curvietto M, Palla M, Paone M, et al. Serious haematological toxicity during and after ipilimumab treatment: a case series. J Med Case Rep 2014;8:240.
[69] Delyon J, Mateus C, Lambert T. Hemophilia A induced by ipilimumab. N Engl J Med 2011;365:1747–8.
[70] Vogel WV, Guislain A, Kvistborg P, Schumacher TN, Haanen JB, Blank CU. Ipilimumab-induced sarcoidosis in a patient with metastatic melanoma undergoing complete remission. J Clin Oncol 2012;30:ee7–ee10.
[71] Tissot C, Carsin A, Freymond N, Pacheco Y, Devouassoux G. Sarcoidosis complicating anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody biotherapy. Eur Respir J 2013;41:246–7.
[72] Reule RB, North JP. Cutaneous and pulmonary sarcoidosis-like reaction associated with ipilimumab. J Am Acad Dermatol 2013;69:e272–3.
[73] Murphy KP, Kennedy MP, Barry JE, O'Regan KN, Power DG. New-onset mediastinal and central nervous system sarcoidosis in a patient with metastatic melanoma undergoing CTLA4 monoclonal antibody treatment. Oncol Res Treat 2014;37:351–3.
[74] Eckert A, Schoeffler A, Dalle S, Phan A, Kiakouama L, Thomas L. Anti-CTLA4 monoclonal antibody induced sarcoidosis in a metastatic melanoma patient. Dermatology 2009;218:69–70.
[75] Berthod G, Lazor R, Letovanec I, Romano E, Noirez L, Mazza Stalder J, et al. Pulmonary sarcoid-like granulomatosis induced by ipilimumab. J Clin Oncol 2012;30:e156–159.
[76] Andersen R, Norgaard P, Al-Jailawi MK, Svane IM. Late development of splenic sarcoidosis-like lesions in a patient with metastatic melanoma and long-lasting clinical response to ipilimumab. Oncoimmunology 2014;3:e954506.
[77] Heffernan MP, Saag KG, Robinson JK, Callen JP. Prevention of osteoporosis associated with chronic glucocorticoid therapy. JAMA 2006;295:1300–3.
[78] Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol 2014;32:1020–30.
[79] Yousaf N, Davidson M, Goode E, Thomas C, Hung R, Gore M, et al. The cost of ipilimumab toxicity: a single-centre analysis. Melanoma Res 2015;25:259–64.
[80] Yang JC, Hughes M, Kammula U, Royal R, Sherry RM, Topalian SL, et al. Ipilimumab (anti-CTLA4 antibody) causes regression of metastatic renal cell cancer associated with enteritis and hypophysitis. J Immunother 2007;30:825–30.
[81] Downey SG, Klapper JA, Smith FO, Yang JC, Sherry RM, Royal RE, et al. Prognostic factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. Clin Cancer Res 2007;13:6681–8.
[82] Amin A, DePril V, Hamid O, Wolchok J, Maio M, Neyns B, et al. Evaluation of the effect of systemic corticosteroids for the treatment of immune-related adverse events (irAEs) on the development or maintenance of ipilimumab clinical activity. American Society Clinical Oncology (ASCO); J Clin Oncol, (Suppl.; abstr 9037), Chicago, 2009.
[83] Horvat TZ, Adel NG, Dang TO, Momtaz P, Postow MA, Callahan MK, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at memorial sloan kettering cancer center. J Clin Oncol 2015;33:3193–8.
[84] Danlos FX, Pages C, Roux J, Jebali M, Gornet JM, Bagot M, et al. Atypical severe immune-related adverse effects resulting from sequenced immunotherapy in melanoma. Melanoma Res 2015;25:178–9.
[85] Chiarion-Sileni V, Pigozzo J, Ascierto PA, Simeone E, Maio M, Calabro L, et al. Ipilimumab retreatment in patients with pretreated advanced melanoma: the expanded access programme in Italy. Br J Cancer 2014;110:1721–6.
[86] Lebbe C, Weber JS, Maio M, Neyns B, Harmankaya K, Hamid O, et al. Survival follow-up and ipilimumab retreatment of patients with advanced melanoma who received ipilimumab in prior phase II studies. Ann Oncol 2014;25:2277–84.
[87] Krammer R, Heinzerling L. Therapy preferences in melanoma treatment–willingness to pay and preference of quality versus length of life of patients, physicians and healthy controls. PLoS ONE 2014;9:e111237.
[88] Lipson EJ, Bodell MA, Kraus ES, Sharfman WH. Successful administration of ipilimumab to two kidney transplantation patients with metastatic melanoma. J Clin Oncol 2014;32:e69–71.
[89] Bostwick AD, Salama AK, Hanks BA. Rapid complete response of metastatic melanoma in a patient undergoing ipilimumab immunotherapy in the setting of active ulcerative colitis. J Immunother Cancer 2015;3:19.
[90] Kyi C, Carvajal RD, Wolchok JD, Postow MA. Ipilimumab in patients with melanoma and autoimmune disease. J Immunother Cancer 2014;2:35.
[91] Johnson DB, Khushalani NI, Puzanov I, Mudigonda T, Kaufman H, Sosman JA, et al. Ipilimumab in metastatic melanoma patients with pre-existing autoimmune disorders. American Society Clinical Oncology (ASCO); J Clin Oncol 33, (Suppl.; abstr 9019), Chicago, 2015.