Melanoma is the least common but most serious form of skin cancer. In 2013, 14,509 cases of melanoma were recorded in the UK, representing 4 per cent of all cancers. Many can be cured by surgery, but up to 20 per cent of patients will have disease that spreads beyond the primary site. Metastatic melanoma (see Figure 1) is associated with an extremely poor prognosis, with median life expectancy of eight to ten months, untreated. Those patients presenting with brain metastases fare even worse, with few surviving beyond six months.

Up until 2011, no systemic therapy had convincingly been shown to improve survival of patients with metastatic melanoma. Dacarbazine was the international standard cytotoxic chemotherapy, offering at best a 15 per cent objective response rate with no survival benefit, and treatment within a clinical trial was an accepted first-line option.

In the past five years, however, two new classes of agents – monoclonal antibodies against immune checkpoint molecules and small-molecule inhibitors of the mitogen-activated protein (MAP) kinase signalling pathway – have radically changed clinical practice, based upon randomised trials confirming overall survival benefit. This article focuses on the first of these two groups, the immune checkpoint inhibitors, including key associated toxicities and their management.
Properties of immune checkpoint inhibitors

**Ipilimumab**

Two types of immune checkpoint inhibitor are now approved by NICE for treatment of metastatic melanoma. The first of these, ipilimumab (Yervoy), is a humanised monoclonal antibody blocking the cytotoxic T lymphocyte-associated antigen 4, or CTLA-4, which works in effect by removing the brake on normal immunological controls (see Figure 2). A series of international studies have confirmed that ipilimumab generates durable disease control albeit in a minority of treated patients. Around 20% of patients treated with ipilimumab remain alive beyond three years of completing treatment, and many of these are alive and disease-free after 10 years.5 Even patients with brain metastases have the potential to benefit from this agent, with reported disease control in the brain in 24% of asymptomatic and 10% of symptomatic patients.5

Ipilimumab is straightforward to deliver to patients, the standard regimen being administered as four short 3mg/kg infusions three weeks apart. However, it has a range of complex side-effects radically different to those of conventional cytotoxic chemotherapy. Checkpoint inhibition is associated with a unique spectrum of side-effects, termed immune-related adverse events (IrAEs). IrAEs are frequent, affecting the majority of treated patients, and most commonly involve skin, gastrointestinal, liver and endocrine systems, but pretty much any type of inflammatory event may occur.

IrAEs are believed to arise from general immunological enhancement akin to autoimmunity. Their severity varies; most are mild or manageable, but around one in ten patients may experience severe, life-threatening immune-related toxicities requiring hospitalisation6 and the risk of treatment-related death is around 1 per cent.2,3,7 Most IrAEs occur within three to six months of starting treatment, but can occur up to 12 months later (see Figure 3). Currently, there is no predictive biomarker to select those patients who will benefit from ipilimumab or those who are more likely to experience toxicity.

**Pembrolizumab and nivolumab**

There are now increasing numbers of immune checkpoint molecules being identified as potential therapeutic targets. The most promising of these is the programmed cell death protein 1 receptor (PD-1). Two monoclonal antibodies that inhibit PD-1 are pembrolizumab (Keytruda) and nivolumab (Opdivo) and superior activity has recently been supported for both compared with ipilimumab.

The KEYNOTE-006 trial reported improvements in response rate (33 vs 12 per cent), progression-free disease (46 per cent vs 26 per cent progression-free at six months) and overall survival (68 vs 58 per cent one-year survival) with pembrolizumab compared with ipilimumab in metastatic melanoma patients who had received up to one line of previous treatment.8 In terms of toxicity, IrAEs were generated by pembrolizumab, but these were generally less frequent and less severe compared with ipilimumab.

The CheckMate 066 trial compared nivolumab with dacarbazine in a double-blind placebo-controlled trial and reported an extension of progression-free survival from 2.2 to 5.1 months (hazard ratio 0.43, p<0.001).9 Accumulating research suggests that pembrolizumab and nivolumab are almost identical in terms of efficacy and toxicity. The longest follow-up of heavily pretreated melanoma patients receiving nivolumab in a clinical study reported plateauing out of survival at four years and a five-year overall survival of 34 per cent,10 suggesting that durable, long-term survival can be achieved with PD-1 inhibitor monotherapy.

Most recently, the CheckMate 067 trial compared the combination of nivolumab plus ipilimumab to nivolumab or ipilimumab monotherapy in a three-arm placebo-controlled trial.11 Objective response rates were 58 vs 44 vs 19 per cent for nivolumab plus ipilimumab, nivolumab monotherapy, and ipilimumab monotherapy, respectively. Median progression-free survival was 11.5, 6.9 and
2.9 months respectively for the three arms. Of note, 56 per cent of patients treated in the combination arm experienced serious or life-threatening adverse events compared with 20 per cent treated with nivolumab and 27 per cent treated with ipilimumab.12 The data from this trial is still immature and overall survival data is not yet available, but it is clear that while the standards of care are being set, toxicity management is challenging.

Pembrolizumab and nivolumab have both been approved by NICE as monotherapy for metastatic melanoma and are rapidly replacing ipilimumab as the first-line treatment of choice for most patients with this condition. Like ipilimumab, they are administered to melanoma patients as intravenous (IV) infusions either every one or two weeks (pembrolizumab 2mg/kg) or every two weeks (nivolumab 3mg/kg). Unlike ipilimumab, duration of treatment is until disease progression occurs.

In terms of toxicity, the data are consistent in that both PD-1 inhibitors are associated with grade 3 toxicities, but these are generally less severe than those occurring with ipilimumab. However, the combination regimen, ipilimumab plus nivolumab appears to be both more active but more toxic than either single agent. The combination regimen requires both drugs (ipilimumab 3mg/kg and nivolumab 1mg/kg) to be administered concomitantly IV every three weeks for a total of 12 weeks, followed by nivolumab 3mg/kg IV maintenance therapy every two weeks until disease progression occurs. In the CheckMate 067 trial, fewer than half of all patients treated with the combination regimen got as far as nivolumab maintenance. Of note, around two-thirds of patients who stopped treatment due to toxicity achieved a response.12 The health economics of the 12-week median treatment duration and frequency of ongoing response after stopping plays out in favour of combination versus single-agent immune checkpoint inhibitors, and NICE approved this combination regimen in June 2016 for the treatment of metastatic melanoma.

Use of immune checkpoint inhibitors

Immune checkpoint inhibitors are set to change the way oncologists treat a number of solid tumours, not just melanoma: the PD-1 inhibitors appear to have broad application for a number of tumour types, since the receptor ligand, PDL-1, is expressed on a number of different types of cancer and surrounding cells. Strong positive signals have already been generated in lung13,14 and renal15 cancer clinical trials, and trials are ongoing in many other cancer types.

Priced at around £75,000 per annum per patient, key questions arise regarding the affordability of innovation, health service capacity to administer these agents to increasing numbers of patients, and optimal management pathways, since toxicity management is complex.16

Currently, systemic therapy for metastatic melanoma patients is limited to small numbers (typically one to three) of centres within each region of the UK. Patients are managed by specialist melanoma teams, who have access to acute medical support teams as needed. However, patients who become unwell at home more often call upon their GPs for help and are frequently admitted to their local hospital for urgent care. Acute oncology services geared to managing oncological emergencies are now established in all UK hospitals, but their focus to date has been on managing cytotoxic chemotherapy-induced toxicity and experience with immune checkpoint inhibitors is as yet rudimentary.

The following sections provide a summary of the most common and most serious adverse events associated with immune checkpoint inhibitors, to alert non-specialist doctors regarding when to seek advice and the immediate action to take.

### Adverse effects

#### General toxicities

Fatigue is one of the most common side-effects of immune checkpoint inhibitors, with an estimated overall frequency of around 20 per cent for the PD-1 inhibitors and 40 per cent for ipilimumab. Generally, fatigue is mild and tolerable. When fatigue is more severe, it is important to exclude an immune-related endocrine cause including thyroid, pituitary or primary adrenal insufficiency (see below). Fever, chills, arthralgia, myalgia, nausea and vomiting have also been described in up to 10 per cent of treated patients, but these are generally mild and manageable with standard supportive means.

#### Immune-related adverse events

IRAEs most commonly involve skin, gastrointestinal, liver and endocrine systems, but any body system may be affected (see Table 1).16,17 IRAEs result from the relatively nonspecific hyperstimulation of the immune system and immunosuppression using high-dose corticosteroids is, perhaps not surprisingly, usually an effective antidote. In situations where severe symptoms are not responding to corticosteroids, other immune suppressant agents typically used to treat other autoimmune condi-

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<th>Ipilimumab</th>
<th>PD-1 inhibitors</th>
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<tr>
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<td>16%</td>
<td>56%</td>
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<td>Liver</td>
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*Most common cause of death from IRAEs is colonic perforation
NR=not reported

Table 1. Rates of severe or life-threatening immune-related adverse events (IrAEs) reported in metastatic melanoma trials of immune checkpoint inhibitors
tions, in particular infliximab or mycophenolate, may be beneficial. Use of immune suppressants does not appear to affect response to immune checkpoint inhibitor therapy. Incidence and/or severity of IrAEs does not appear to correlate with treatment response.

Rash
Skin toxicity is the most common IrAE associated with immune checkpoint inhibitors. Approximately 50 per cent of patients treated with ipilimumab and 30–40 per cent of those treated with nivolumab or pembrolizumab will experience rash and/or pruritus. Skin toxicity is usually the earliest IrAE to occur after starting treatment, with onset at an average of three to four weeks after first infusion (see Figure 3). Typically, patients develop a reticuloid, maculopapular, faintly erythematous and itchy rash on the trunk or extremities. Most immune checkpoint inhibitor rashes can be treated with a good topical moisturiser or corticosteroid cream. More severe rashes may require oral corticosteroids. Vitiligo is also commonly seen. Stevens-Johnson syndrome/toxic epidermal necrolysis have been reported in rare cases.

Colitis
Diarrhoea is a common symptom in patients undergoing treatment with immune checkpoint inhibitors. In most cases, the association with commencing treatment is clear, but an infectious cause should always be considered. Immune-related colitis most commonly presents approximately six weeks into treatment, but can occur many months later. The incidence of diarrhoea is much higher in patients receiving ipilimumab compared with PD-1 inhibitors. Diarrhoea was reported in approximately 30 per cent of patients treated in the ipilimumab registration trials, but severe diarrhoea symptoms occurred in around 10 per cent of cases.

Endoscopic findings in patients receiving ipilimumab have revealed mucosal oedema with biopsies demonstrating neutrophilic, lymphocytic, or mixed neutrophilic-lymphocytic infiltrates, confirming a true colitis. Of note, a small number of treatment-related deaths associated with colitis and bowel perforation occurred in the initial trials. In view of this safety signal, management algorithms were developed to ensure rapid treatment of IrAEs. These were made available to all specialist teams using ipilimumab both pre- and postlicensing and in fact treatment-related deaths are extremely rare; much less common, for example, than cytotoxic chemotherapy-related neutropenic sepsis.

Key to patient safety is good education and information provision to patients and carers, and most now carry special alert cards. Prompt, aggressive treatment can also be life saving and local hospital teams should liaise with the specialist team for management advice if a patient is hospitalised. Patients experiencing severe diarrhoea not responding to high-dose corticosteroids within a week should receive infliximab.

Diarrhoea appears to be less frequent and severe with PD-1 inhibitors: severe or life-threatening immune-mediated colitis has been reported in only 1–2 per cent of treated patients.

Endocrinopathies
Inflammation of the pituitary, thyroid or adrenal glands as a result of checkpoint inhibition often presents with nonspecific symptoms such as nausea, headache, fatigue or vision changes. The incidence of endocrinopathies has been difficult to precisely evaluate due to variable methods of assessment, diagnosis and monitoring in different clinical trials. Even so, clinically significant endocrinopathy is typically thought to occur in up to 10 per cent of treated patients.

The pattern of endocrinopathy appears to differ between the two types of checkpoint inhibitor. Hypophysitis is more common with ipilimumab and may be confirmed on an MRI scan demonstrating a swollen pituitary gland. Corticosteroid and thyroxine replacement will be required and it appears that hormone replacement may be required in the long term. Although MRI imaging may return to normal, the gland itself appears to sustain permanent damage.

With pembrolizumab and nivolumab, the most common endocrine organ affected is the thyroid. Biochemical changes consistent with hypothyroidism are common in treated patients, who may often be asymptomatic, but thyroxine replacement is generally initiated. Whether this is required long term is as yet unclear.

The most serious endocrinopathy is adrenal insufficiency, which is, thankfully, extremely rare. A patient presenting with dehydration, hypotension and electrolyte imbalances (hyperkalaemia, hyponatraemia) constitutes a medical emergency and requires immediate hospitalisation.

The management of immune-related endocrinopathies is still in its infancy and most regions are now developing links.
with endocrinologists to assist in managing complex cases when they occur. Endocrine-related events tend to occur later than most other IrAEs; typically three to four months after starting treatment and sometimes much later.

Hepatic transaminitis
Elevations in blood levels of the liver enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), occur in 5–10 per cent of patients treated with either CTLA-4 or PD-1 inhibitors. Most episodes are asymptomatic laboratory abnormalities, but one to two per cent of patients become seriously unwell, exhibiting signs of acute liver failure including jaundice and oedema. Most cases respond well to corticosteroids, with mycophenolate being an option if unresponsive. The time to onset of liver toxicity is eight to 12 weeks after initiation of treatment, although early or delayed events have been reported.

Less common adverse effects
Less common IrAEs include pneumonitis, nephritis, uveitis and pancreatitis. A variety of neurological conditions have been documented, including several cases of Guillain-Barré syndrome. In contrast with cytotoxic chemotherapy, myelosuppression is extremely rare. However, haematological reactions including red cell aplasia, neutropenia, thrombocytopenia and acquired haemophilia A have also been reported.

Summary
Immune checkpoint inhibitors targeting CTLA-4 and PD-1 are having a dramatic impact on the care of patients with advanced melanoma and are being explored as treatments for other malignancies. Immune-related adverse events are common. These toxicities are typically transient, but occasionally can be severe or fatal. Early recognition, rapid referral and treatment with immunosuppressive agents can prove life saving.

References

Declaration of interests
Dr Corrie has served on advisory boards for Bristol Myers Squibb and Merck, Sharpe & Dohme.

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