European Journal of Cancer 73 (2017) 1–8

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Review

Neurological adverse events associated with immune checkpoint inhibitors: Review of the literature

S. Cuzzubbo [a,b,*], F. Javeri [a], M. Tissier [a], A. Roumi [a], C. Barlog [a,b], J. Doridam [a,b], C. Lebbe [c], C. Belin [a,b], R. Ursu [a,b], A.F. Carpentier [a,b]

[a] *Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Avicenne, Service de Neurologie, Bobigny, France*
[b] *Université Paris 13, UFR de Santé, Médecine et Biologie Humaine, Bobigny, France*
[c] *APHP Dermatology and CIC Departments, INSERM U976, Université Paris Diderot, Sorbonne Paris Cité, Hôpital Saint Louis, Paris, France*

Received 7 November 2016; accepted 6 December 2016

KEYWORDS
Anti-PD1;
Anti-CTLA4;
Immune checkpoint inhibitors;
Neurological adverse events

Abstract Immune checkpoint inhibitors (ICIs) targeting CTLA4 and PD1 constitute a promising class of cancer treatment but are associated with several immune-related disorders. We here review the literature reporting neurological adverse events (nAEs) associated with ICIs. A systematic search of literature, up to February 2016, mentioning nAEs in patients treated with ICIs was conducted. Eligible studies included case reports and prospective trials. One case seen in our ward was also added. Within the 59 clinical trials (totalling 9208 patients) analysed, the overall incidence of nAEs was 3.8% with anti-CTLA4 antibodies, 6.1% with anti-PD1 antibodies, and 12.0% with the combination of both. The clinical spectrum of neurological disorders was highly heterogeneous. Most of these nAEs were grade 1–2 and consisted of non-specific symptoms such as headache (55%). The incidence of high grade nAEs was below 1% for all types of treatment. Headaches, encephalopathies and meningitis were the most commonly reported (21%, 19% and 15%, respectively). Among the 27 case reports, the most common nAEs were encephalopathies, meningoradiculoneuritis, Guillain-Barré like syndromes and myasthenic syndromes. The median time of nAEs onset was 6 weeks. In most cases, drug interruption and steroids led to neurological recovery, even in conditions where steroids are not usually recommended such as Guillain-Barré syndrome.

* *Corresponding author*: Service de Neurologie, Hôpital Avicenne, 125 rue de Stalingrad, 93009 Bobigny, France.
E-mail address: stefania.cuzzubbo@aphp.fr (S. Cuzzubbo).

http://dx.doi.org/10.1016/j.ejca.2016.12.001
0959-8049/

1. Introduction

Anti-CTLA4 (ipilimumab, tremelimumab) and anti-PD1 (nivolumab, pembrolizumab, lambrolizumab, pidilizumab) monoclonal antibodies enhance antitumour immunity by targeting T-cells inhibitory receptors. These antibodies, classified as immune checkpoint inhibitors (ICIs), have recently obtained approval for treatment in metastatic melanoma [1–5], non-small cell lung cancer [6–8], renal-cell carcinoma [9] and are currently under clinical trials in several other indications. Immune checkpoint inhibitors have undoubtedly been a major step forward in immunotherapy these last years, having significantly increased survival of cancer patients.

As might be expected, adverse effects (AEs) can occur through immunologic activation, that have been termed immune-related adverse events (irAEs) or, occasionally, adverse events of special interest. Grade 3 and 4 adverse events occurred in 13–55% of ipilimumab-treated patients, in 9–43% of nivolumab-treated patients, in 11–14% of pembrolizumab-treated patients and in 54–86% in ipilimumab plus nivolumab-treated patients [10]. These irAEs can potentially involve every organ system but gastrointestinal, dermatologic, hepatic, endocrine and pulmonary toxicities predominate [11,12]. Although rare, neurological adverse effects (nAEs) require prompt recognition and treatment to avoid substantial morbidity.

This review summarises the published data on neurological toxicities reported with immune checkpoint inhibitors, trying to define their incidence, timing patterns, clinical and paraclinical presentation.

2. Patients and methods

A systematic literature search, up to February 2016, mentioning treatment with immune checkpoint inhibitors on adult human beings and published in English was conducted in PubMed database, using the keywords: 'ipilimumab or tremelimumab or nivolumab or pembrolizumab or lambrolizumab or pidilizumab or anti-CTLA4 or anti-CTLA-4 or anti-PD1 or anti-PD-1' and 'clinical trials'. Observational studies were excluded. For the case reports search, the keywords used were 'safety or toxicity or sides effects or adverse events' and 'anti-CTLA4 or anti-CTLA-4 or anti-PD1 or anti-PD-1 or ipilimumab or tremelimumab or nivolumab or pembrolizumab or lambrolizumab or pidilizumab'. Abstracts in medical meetings were not searched.

To be eligible for our analysis, patients could have received previous oncologic therapies, but those who received anti-CTLA4 or anti-PD1 antibodies in combination with other treatments were not. Cases of typical myositis, uveitis and hearing loss without primary neurological involvement were excluded. Patients with brain metastases or tumoural meningitis were also excluded in case reports but trials with patients with controlled brain metastases were included.

Two investigators performed the reading and data extraction independently. They used, for each article, a standard data extraction form and re-read together the articles in the event of any discrepancy.

The incidence of neurological treatment-related AEs (nAEs) was calculated using the total number of nAEs/number of patients exposed to the drug within prospective clinical trials (phase I, II and III). The AEs grade was recorded according to version 2, 3 or 4 of the Common Terminology Criteria for Adverse Events of the National Cancer Institute, and grade ≥ 3 were considered high grade.

In case reports, patient characteristics, regimen treatment, the nature of each neurological AE, their onset, the biological and instrumental tests realised, and their outcome were recorded. Neurological AEs were classified according to the nervous system area involved: encephalopathy, myelopathy, pure meningitis, meningoradiculitis, Guillain-Barré like syndrome, peripheral neuropathy and myasthenic syndrome. Encephalopathy included all types of parenchymal lesion, such as vasculitis, stroke, multiple sclerosis, or posterior reversible encephalopathy syndrome (PRES). Neuropathy included all types of peripheral involvement (mononeuropathy, mononeuritis multiplex and polyneuropathy), except the cases in which cerebro-spinal fluid (CSF) analysis showed any abnormalities (hyperproteinorachia or pleocytosis). In these cases, the neuropathy was reclassified as a meningoradiculitis in case of pleocytosis or as a Guillain-Barré like syndrome in case of isolated hyperproteinorachia.

3. Results

3.1. Literature search

The Pubmed search identified 82 relevant publications for the present study: 59 clinical trials (totalling 9208 patients exposed to anti-CTLA4 or anti-PD1 antibodies) and 23 case reports reporting 26 cases. One case seen in our ward was added to the case reports. Among the 59 clinical trials, 37 were investigating anti-CTLA4 antibodies (7 phase I, 24 phase II, 6 phase III), 22 anti-PD1 antibodies (9 phase I, 6 phase II, 7 phase III) and 4 a combination of both (1 phase I, 1 phase II, 2 phase III; Supplementary data, Tables S1, S2 and S3). The main underlying cancers in clinical trials were melanoma (5518 treated patients), non-small-cell lung cancer (1847 treated patients) and renal-cell carcinoma (678 treated patients).

3.2. Incidence of neurological AEs in prospective trials

We first focused on patients included in prospective trials (phase I, II and III), without considering case reports, to

get an unbiased picture of the overall incidence of nAEs. Among the 9208 patients exposed to immune checkpoint inhibitors, the overall incidence of any grade nAEs was 3.8% with anti-CTLA4 antibodies, 6.1% for anti-PD1 antibodies and 12.0% with the combination of them (Table 1). However, most of these nAEs were grade 1–2 and consisted of non-specific symptoms such as headache (55%), dysgeusia (13%) or dizziness (10%; Fig. 1A). The incidence of high grade (Gr 3–4) nAEs was below 1% for all types of treatment (Table 1, Fig. 1B). The spectrum of neurological symptoms appeared to be highly heterogeneous (Fig. 1). No clear association between neurological syndromes and the ICI type (Supplementary data, Tables S4 and S5) was seen.

No clear relationship between the incidence of nAEs and drug dosage was seen in 3 studies comparing different doses of anti-CTLA4 antibodies [13–15]. For patients receiving anti-PD1 antibodies, the incidence of nAEs was higher with nivolumab at 10 mg/kg when compared with lower doses [16–19], but the reverse situation was observed with pembrolizumab [7,20–23].

3.3. Clinical presentation in case reports

We then focused on case reports (27 patients) to better define the spectrum of neurological syndromes related to immune checkpoint inhibitors therapy (Table 2). Median age of cases was 56 years old, with a range from 31 to 81 years, and there was a slight male predominance (18/27). Patients were mainly treated for melanoma (25/27 cases) with ipilimumab (21/27 cases). Overall median time of onset of nAEs was 6 weeks (1–74). The presentation was acute or sub acute in all cases. When tumour evolution was mentioned, nAEs were associated with tumour response in 11/16 patients (69%).

Peripheral nervous involvement was the most frequently described presentation in case reports (n = 13/27), even without considering myasthenic syndromes (n = 5/27). These peripheral involvements encompassed a large spectrum of overlapping diseases, ranging from focal neuropathies, peripheral neuropathies, Guillain-Barré like syndromes and meningoradiculitis. Unfortunately, electrophysiological and CSF studies were not always performed and/or reported (9/13 and 8/13 reported data, respectively), leaving the type of neuropathy (axonal, demyelinating) and precise anatomical involvement unclear. In meningoradiculitis cases, imaging showed typical cranial and/or spinal nerves enhancement in 4/6 cases. In myasthenic syndromes, anti-AchR antibodies were found in all cases, and a myositis was associated in 2 cases [24,25]. Encephalopathies cases were very heterogeneous, including demyelinating diseases with a case of

Table 1
Incidence of neurological AEs in patients included in clinical trials.

Class antibody	Drugs	Nber of pts	Incidence of any grade nAEs % (range of reported incidence)	Incidence of grade 3–4 nAEs % (range of reported incidence)	References
Anti-CTLA4	**All**	**3672**	**3.8 (0–27.3)**	**0.7 (0–7.1)**	
	Ipilimumab	*2734*	*3.0* (0–22.2)	*0.8 (0–7.1)*	[1,2,13–15,35–53]
	Tremelimumab	*938*	*6.3 (0–27.3)*	*0.3(0–3.5)*	[54–67]
Anti-PD1	**All**	**5076**	**6.1 (0–26.8)**	**0.4 (0–5.0)**	
	Nivolumab	*2536*	*5.2 (0–23.5)*	*0.4 (0–5.0)*	[5,6,8,9,16–19,68–75]
	Pembrolizumab	*2333*	*6.3 (0–26.8)*	*0.2 (0–1.7)*	[7,20–23,53,76]
	Lambrolizumab	*135*	*21.5*	*0*	[3]
	Pidilizumab	*72*	*5.6*	*5.6*	[77]
Anti-CTLA4 CTLA4 + anti-PD1	**All**	**460**	**12.0 (10.2–18.9)**	**0.7 (0–2.1)**	[4,78,79]

Bold represents the overall incidence values for anti-CTLA4, anti-PD1 treatments and association of both.
Italic represents the incidence values for each specific anti-CTLA4 or anti-PD1 drug.

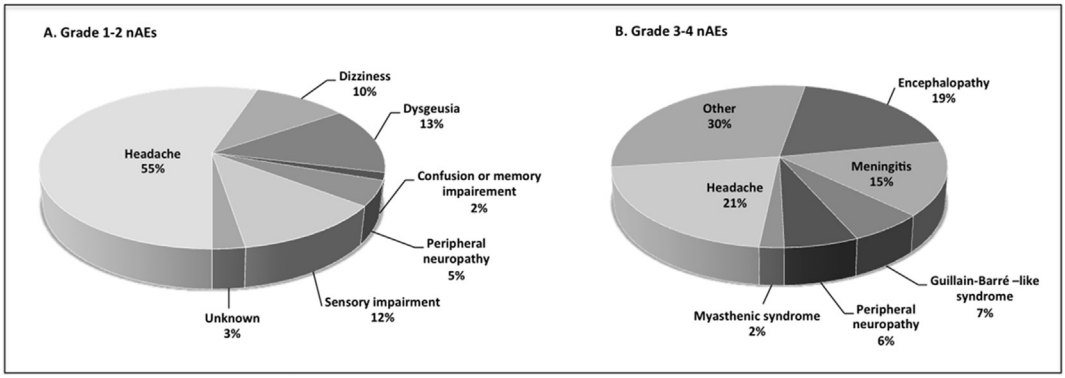

Fig. 1. Clinical pattern of neurological adverse events associated to ICIs in clinical trials. Other severe nAEs: 1 motor dysfunction [39], 3 pain in extremity [49], 1 hydrocephalus [14], 1 dizziness [47], 1 paraesthesia, 4 not specified nAEs [2,18], 2 intracranial haemorrhages, 1 glioma [77]. Two severe AEs reported respectively as disorientation and gait disorder and confusion were interpreted as encephalopathy [23,71].

Table 2
Clinical pictures of neurological AEs (nAEs) reported in case reports (n = 27).

AEs	Drug	Time to nAE onset median, days	Abnormal CSF analysis	Treatment	Outcome	References
Encephalitis (n = 6)	Anti-CTLA4: n = 2 Anti-PD1: n = 4	51 (10–518)	3/4 (pleocytosis in 2/4)	Drug discontinuation only n = 2 Steroids n = 3 Steroids + PE/IV Ig n = 1	Full recovery n = 4 Partial recovery n = 1 Death n = 1	[26–28,30,32,80]
Myelitis (n = 2)	Anti-CTLA4: n = 2	8 (45–150)	2/2 (pleocytosis in 2/2)	Steroids n = 1 Steroids + PE/IV Ig n = 1	Partial recovery n = 2	[24,81]
Meningitis (n = 1)	Anti-CTLA4: n = 1	42	1/1 (pleocytosis in 1/1)	Steroids n = 1	Full recovery n = 1	[34]
Meningoradiculitis (n = 6)	Anti-CTLA4: n = 5 Anti-CTLA4 + anti-PD1: n = 1	36 (7–72)	5/5 (pleocytosis in 5/5)	Steroids n = 3 Steroids + PE/IV Ig n = 3	Full recovery n = 2 Partial recovery n = 4	[33,82–85]
Guillain-Barré like syndrome (n = 4)	Anti-CTLA4: n = 4	42 (35–84)	3/3 (pleocytosis in 0/3)	Steroids n = 2 IV Ig only n = 1 Steroids + immunosuppr + PE n = 1	Full recovery n = 1 Partial recovery n = 1 Death n = 2	[31,86–88]
Peripheral neuropathy (n = 3)	Anti-CTLA4: n = 3	84 (35–91)	NA	Drug discontinuation only n = 1 Steroids n = 1 Steroids + immunosuppr n = 1	Full recovery n = 1 Stable n = 1 Death n = 1	[29,85,89]
Myasthenic syndrome (n = 5)	Anti-CTLA4: n = 3 Anti-PD1: n = 1 Both: n = 1	28 (12–30)	NA	Drug discontinuation only n = 1 Steroids n = 1 Steroids + PE/IV Ig n = 3	Full recovery n = 1 Partial recovery n = 2 Worsening n = 1 Death n = 1	[24,25,90,91]

exacerbation of multiple sclerosis [26], brain vasculitis [27], and PRES-like syndromes [28].

Outcome of nAEs showed a partial or complete neurological recovery in 73% of cases (20/27), with a median delay of 4 weeks. Five patients died although the relationship with the nAE was unclear in 2/5 cases [29,30]. Clinical improvement was only reported in patients for whom ICI drug was stopped. Among these patients, 12 patients (44%) received steroids in monotherapy and 8 (30%) steroids in association with intravenous immunoglobulin or plasma exchanges.

3.4. Histological analysis

In 6 cases (2 encephalitis, 1 meningitis, 1 meningoradiculitis, 1 Guillain-Barré like syndrome and 1 peripheral neuropathy), histological analysis was performed [29–34] and consistently showed inflammation with lymphocytic infiltrates supporting an immune-mediated disease. This inflammation was perivascular in 4/6 cases and involved the myenteric nervous system itself in one case of enteric neuropathy [29]. In the last case (Guillain-Barré like syndrome with severe constipation), colon biopsies revealed a high number of lymphocytic follicles [31]. Immunohistochemical analysis demonstrated the presence of both CD4+ and CD8+ T-cells [29,30,33].

4. Discussion

Immune checkpoint inhibitors have shown promising results in cancers but can possibly induce auto-immune disorders. In this study, we reviewed the neurological adverse events occurring under immune checkpoint inhibitors in oncologic patients to more clearly define their incidence and characteristics.

The most striking feature of this literature review is the extremely broad spectrum of possible syndromes, potentially involving all areas of the central and peripheral nervous system. An over-representation of grade 1–2 neuropathies was reported with anti-PD1 antibodies, but this might be biased because most patients were suffering from advanced lung cancer and had received prior neurotoxic chemotherapy regimen. Clinical trials comparing anti CTLA-4 and anti PD-1 treatments did not show a different safety profile in terms of nAEs [4,53]. In line with other organ immune-related adverse events, the median time of onset of nAEs after ICIs were started was 6 weeks. In the few cases in which histological analysis was carried out, lymphocytic infiltration was constantly found, strongly supporting an auto-immune disorder.

Severe nAEs (grade 3 and 4) appeared to be less common than other organs AEs, with an incidence slightly higher with anti-CTLA4 treatments (0.7%) than with anti-PD1 antibodies (0.4%). Surprisingly, when

considering all grades nAEs (grade 1–4), the reported incidence was higher with anti-PD1 than with anti-CTLA4 antibodies, but this difference might not be significant because most grade 1–2 nAEs consisted in subjective disorders, such as cephalalgia and dysgeusia. Cephalalgia, which is the most commonly AE reported (regardless of the grade), still represents 21% of the severe AEs. The mechanisms underlying these headaches are unclear and might be related either to non-neurological diseases such as hypophysitis or to under-diagnosed meningitis.

This latter point underlines the need for standardised investigations to accelerate the management of potentially fatal adverse events. A decisional chart for neurological investigations can be proposed (Fig. 2). In case of clinical suspicion of encephalopathy, meningitis, meningoradiculitis or Guillain-Barré like syndromes, a lumbar puncture is probably the most useful investigation to support the relationship between the nAEs and the ICI treatment. Indeed, CSF abnormalities are almost constantly found, with an elevated proteins level associated to lymphocytic pleocytosis (except for Guillain-Barré like syndromes defined by an albuminocytological dissociation), thus supporting an inflammatory-mediated disease. In pure polyneuropathy, in which case CSF analysis might be deemed inappropriate, the differential diagnosis with other causes of neuropathy is made more difficult. In such cases, a demyelinating and/or an asymmetrical pattern on electroneuromyography would be in favour of the relationship with ICI and should prompt to CSF analysis. Most of the time no auto-antibodies, including classical onco-neuronal antibodies usually seen in paraneoplastic syndromes [92], are identified. Only one recent article reported a case of encephalitis with anti-NMDA antibodies [93]. In myasthenic syndrome cases, nevertheless, the presence of serum anti-Ach Receptor antibodies was constantly found.

No standard treatment has yet been defined for neurological AEs. Clinical improvements have only been reported after the ICI drug discontinuation. Corticosensitivity is well documented in non-neurological immune-related AEs [94]. This seems to be also the case for nAEs, even in conditions where steroids are not usually recommended, such as Guillain-Barré syndromes. A commonly used protocol is oral prednisone around 1 mg/kg/day. A neurological AEs management algorithm has been proposed [78,95]. However, further studies are necessary to precise the framework in which they should be used, their dose and duration. Given the

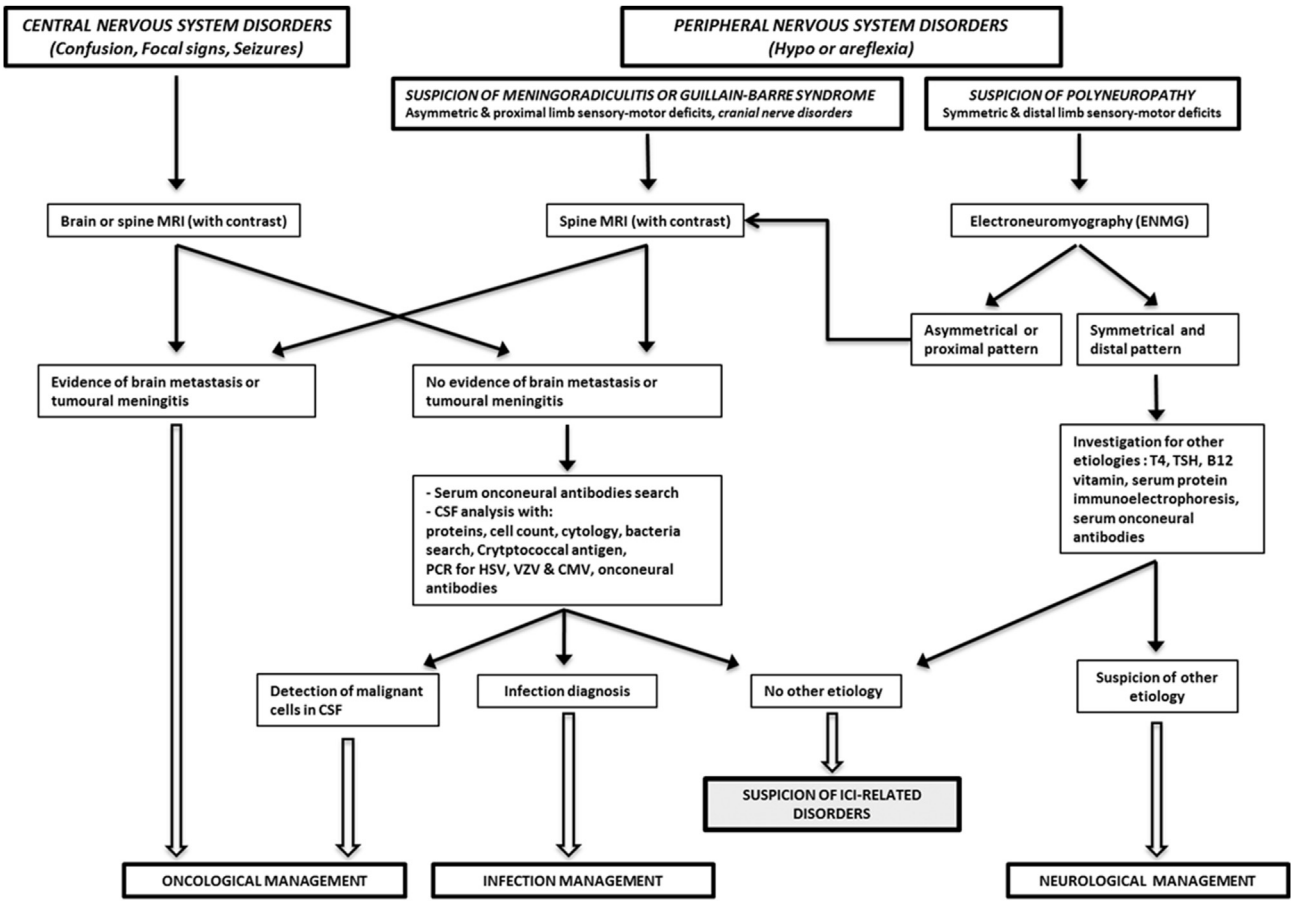

Fig. 2. Simplified diagnostic algorithm for neurological investigations.

long half-life of anti-CTLA4 and anti-PD1 antibodies (3–4 weeks), maintaining steroids for at least 3 months seems logical. Other interventions such as immunosuppressive agents or plasmaphaeresis did not prove consistent efficacy and should be more carefully evaluated. Resuming ICI after neurological recovery is a matter of debate, and a careful analysis of the benefit/risk ratio should be done on a case by case basis. Prospective trials assessing the evolution of immune disorders after resuming ICI would be of value to clarify this issue.

Our study suffered from several limitations. The incidence of neurological AEs was extracted from large clinical trials, as it cannot be deducted from case reports. Unfortunately, cases in these trials were sometimes poorly characterised, or did not benefit from extensive explorations, which may have led to diagnosis misinterpretations. Regarding clinical characterisation, it is to be remembered that ICIs and especially anti-PD1 antibodies are recent drugs, with a relatively few number of cases described at the moment. Further descriptions will probably extend the understanding of the neurological AEs spectrum and will foster their optimal management.

Conflict of interest statement

None declared.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2016.12.001.

References

[1] 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(8):711–23.
[2] 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(5):522–30.
[3] Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med 2013;369(2):134–44.
[4] 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(1):23–34.
[5] 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(4):375–84.
[6] 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(17):1627–39.
[7] 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(21):2018–28.
[8] 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(3):257–65.
[9] 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(19):1803–13.
[10] Kourie HR, Klastersky J. Immune checkpoint inhibitors side effects and management. Immunotherapy 2016;8(7):799–807.
[11] Michot JM, Bigenwald C, Champiat S, Collins M, Carbonnel F, Postel-Vinay S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer 2016;54:139–48.
[12] Tabchi S, Messier C, Blais N. Immune-mediated respiratory adverse events of checkpoint inhibitors. Curr Opin Oncol 2016;28(4):269–77.
[13] Hamid O, Schmidt H, Nissan A, Ridolfi L, Aamdal S, Hansson J, et al. A prospective phase II trial exploring the association between tumor microenvironment biomarkers and clinical activity of ipilimumab in advanced melanoma. J Transl Med 2011;9:204.
[14] 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(2):155–64.
[15] 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(8):825–30.
[16] Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 2010;28(19):3167–75.
[17] McDermott DF, Drake CG, Sznol M, Choueiri TK, Powderly JD, Smith DC, et al. Survival, durable response, and long-term safety in patients with previously treated advanced renal cell carcinoma receiving nivolumab. J Clin Oncol 2015;33(18):2013–20.
[18] 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(13):1430–7.
[19] Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366(26):2443–54.
[20] 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 2016;387(10027):1540–50.
[21] Patnaik A, Kang SP, Rasco D, Papadopoulos KP, Elassaiss-Schaap J, Beeram M, et al. Phase I study of pembrolizumab (MK-3475; anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. Clin Cancer Res 2015;21(19):4286–93.
[22] 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(8):908–18.
[23] 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(9948):1109–17.

[24] Liao B, Shroff S, Kamiya-Matsuoka C, Tummala S. Atypical neurological complications of ipilimumab therapy in patients with metastatic melanoma. Neuro Oncol 2014;16(4):589–93.
[25] Shirai T, Sano T, Kamijo F, Saito N, Miyake T, Kodaira M, et al. Acetylcholine receptor binding antibody-associated myasthenia gravis and rhabdomyolysis induced by nivolumab in a patient with melanoma. Jpn J Clin Oncol 2016;46(1):86–8.
[26] Gettings EJ, Hackett CT, Scott TF. Severe relapse in a multiple sclerosis patient associated with ipilimumab treatment of melanoma. Mult Scler 2015;21(5):670.
[27] Khoja L, Maurice C, Chappell M, MacMillan L, Al-Habeeb AS, Al-Faraidy N, et al. Eosinophilic fasciitis and acute encephalopathy toxicity from pembrolizumab treatment of a patient with metastatic melanoma. Cancer Immunol Res 2016;4(3):175–8.
[28] LaPorte J, Solh M, Ouanounou S. Posterior reversible encephalopathy syndrome following pembrolizumab therapy for relapsed Hodgkin's lymphoma. J Oncol Pharm Pract 2017 Jan;23(1):71–4.
[29] 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(2):203–5.
[30] Maurice C, Schneider R, Kiehl TR, Bavi P, Roehrl MH, Mason WP, et al. Subacute CNS demyelination after treatment with nivolumab for melanoma. Cancer Immunol Res 2015;3(12):1299–302.
[31] 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(1):77–8.
[32] Mandel JJ, Olar A, Aldape KD, Tremont-Lukats IW. Lambrolizumab induced central nervous system (CNS) toxicity. J Neurol Sci 2014;344(1–2):229–31.
[33] 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(3):440–4.
[34] Stein MK, Summers BB, Wong CA, Box HL, Cleveland KO. Meningoencephalitis following ipilimumab administration in metastatic melanoma. Am J Med Sci 2015;350(6):512–3.
[35] Ansell SM, Hurvitz SA, Koenig PA, LaPlant BR, Kabat BF, Fernando D, et al. Phase I study of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with relapsed and refractory B-cell non-Hodgkin lymphoma. Clin Cancer Res 2009;15(20):6446–53.
[36] Bashey A, Medina B, Corringham S, Pasek M, Carrier E, Vrooman L, et al. CTLA4 blockade with ipilimumab to treat relapse of malignancy after allogeneic hematopoietic cell transplantation. Blood 2009;113(7):1581–8.
[37] Hersh EM, O'Day SJ, Powderly J, Khan KD, Pavlick AC, Cranmer LD, et al. A phase II multicenter study of ipilimumab with or without dacarbazine in chemotherapy-naive patients with advanced melanoma. Investig New Drugs 2011;29(3):489–98.
[38] Hodi FS, Lee S, McDermott DF, Rao UN, Butterfield LH, Tarhini AA, et al. Ipilimumab plus sargramostim vs ipilimumab alone for treatment of metastatic melanoma: a randomized clinical trial. JAMA 2014;312(17):1744–53.
[39] 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(7):700–12.
[40] Le DT, Lutz E, Uram JN, Sugar EA, Onners B, Solt S, et al. Evaluation of ipilimumab in combination with allogeneic pancreatic tumor cells transfected with a GM-CSF gene in previously treated pancreatic cancer. J Immunother 2013;36(7):382–9.
[41] Maki RG, Jungbluth AA, Gnjatic S, Schwartz GK, D'Adamo DR, Keohan ML, et al. A pilot study of anti-CTLA4 antibody ipilimumab in patients with synovial sarcoma. Sarcoma 2013;2013:168145.
[42] McDermott D, Haanen J, Chen TT, Lorigan P, O'Day S. Efficacy and safety of ipilimumab in metastatic melanoma patients surviving more than 2 years following treatment in a phase III trial (MDX010-20). Ann Oncol 2013;24(10):2694–8.
[43] O'Day SJ, Maio M, Chiarion-Sileni V, Gajewski TF, Pehamberger H, Bondarenko IN, et al. Efficacy and safety of ipilimumab monotherapy in patients with pretreated advanced melanoma: a multicenter single-arm phase II study. Ann Oncol 2010;21(8):1712–7.
[44] Robert C, Schadendorf D, Messina M, Hodi FS, O'Day S. Efficacy and safety of retreatment with ipilimumab in patients with pretreated advanced melanoma who progressed after initially achieving disease control. Clin Cancer Res 2013;19(8):2232–9.
[45] Royal RE, Levy C, Turner K, Mathur A, Hughes M, Kammula US, et al. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother 2010;33(8):828–33.
[46] Slovin SF, Higano CS, Hamid O, Tejwani S, Harzstark A, Alumkal JJ, et al. Ipilimumab alone or in combination with radiotherapy in metastatic castration-resistant prostate cancer: results from an open-label, multicenter phase I/II study. Ann Oncol 2013;24(7):1813–21.
[47] Small EJ, Tchekmedyian NS, Rini BI, Fong L, Lowy I, Allison JP. A pilot trial of CTLA-4 blockade with human anti-CTLA-4 in patients with hormone-refractory prostate cancer. Clin Cancer Res 2007;13(6):1810–5.
[48] Weber J, Hamid O, Amin A, O'Day S, Masson E, Goldberg SM, et al. Randomized phase I pharmacokinetic study of ipilimumab with or without one of two different chemotherapy regimens in patients with untreated advanced melanoma. Cancer Immun 2013;13:7.
[49] Weber JS, O'Day S, Urba W, Powderly J, Nichol G, Yellin M, et al. Phase I/II study of ipilimumab for patients with metastatic melanoma. J Clin Oncol 2008;26(36):5950–6.
[50] Yamazaki N, Kiyohara Y, Uhara H, Fukushima S, Uchi H, Shibagaki N, et al. Phase II study of ipilimumab monotherapy in Japanese patients with advanced melanoma. Cancer Chemother Pharmacol 2015;76(5):997–1004.
[51] Zimmer L, Eigentler TK, Kiecker F, Simon J, Utikal J, Mohr P, et al. Open-label, multicenter, single-arm phase II DeCOG-study of ipilimumab in pretreated patients with different subtypes of metastatic melanoma. J Transl Med 2015;13:351.
[52] Zimmer L, Vaubel J, Mohr P, Hauschild A, Utikal J, Simon J, et al. Phase II DeCOG-study of ipilimumab in pretreated and treatment-naive patients with metastatic uveal melanoma. PloS One 2015;10(3):e0118564.
[53] 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(26):2521–32.
[54] 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(11):1104–11.
[55] 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(4):301–9.
[56] Camacho LH, Antonia S, Sosman J, Kirkwood JM, Gajewski TF, Redman B, et al. Phase I/II trial of tremelimumab in patients with metastatic melanoma. J Clin Oncol 2009;27(7):1075–81.
[57] Chung KY, Gore I, Fong L, Venook A, Beck SB, Dorazio P, et al. Phase II study of the anti-cytotoxic T-lymphocyte-associated antigen

4 monoclonal antibody, tremelimumab, in patients with refractory metastatic colorectal cancer. J Clin Oncol 2010;28(21):3485–90.
[58] Comin-Anduix B, Lee Y, Jalil J, Algazi A, de la Rocha P, Camacho LH, et al. Detailed analysis of immunologic effects of the cytotoxic T lymphocyte-associated antigen 4-blocking monoclonal antibody tremelimumab in peripheral blood of patients with melanoma. J Transl Med 2008;6:22.
[59] Huang RR, Jalil J, Economou JS, Chmielowski B, Koya RC, Mok S, et al. CTLA4 blockade induces frequent tumor infiltration by activated lymphocytes regardless of clinical responses in humans. Clin Cancer Res 2011;17(12):4101–9.
[60] Joshua AM, Monzon JG, Mihalcioiu C, Hogg D, Smylie M, Cheng T. A phase 2 study of tremelimumab in patients with advanced uveal melanoma. Melanoma Res 2015;25(4):342–7.
[61] Kirkwood JM, Lorigan P, Hersey P, Hauschild A, Robert C, McDermott D, et al. Phase II trial of tremelimumab (CP-675,206) in patients with advanced refractory or relapsed melanoma. Clin Cancer Res 2010;16(3):1042–8.
[62] Ralph C, Elkord E, Burt DJ, O'Dwyer JF, Austin EB, Stern PL, et al. Modulation of lymphocyte regulation for cancer therapy: a phase II trial of tremelimumab in advanced gastric and esophageal adenocarcinoma. Clin Cancer Res 2010;16(5):1662–72.
[63] Ribas A, Chesney JA, Gordon MS, Abernethy AP, Logan TF, Lawson DH, et al. Safety profile and pharmacokinetic analyses of the anti-CTLA4 antibody tremelimumab administered as a one hour infusion. J Transl Med 2012;10:236.
[64] Ribas A, Kefford R, Marshall MA, Punt CJ, Haanen JB, Marmol M, et al. Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. J Clin Oncol 2013;31(5):616–22.
[65] Robert L, Tsoi J, Wang X, Emerson R, Homet B, Chodon T, et al. CTLA4 blockade broadens the peripheral T-cell receptor repertoire. Clin Cancer Res 2014;20(9):2424–32.
[66] Straatsma BR, Nusinowitz S, Young TA, Gordon LK, Chun MW, Rosen C, et al. Surveillance of the eye and vision in clinical trials of CP-675,206 for metastatic melanoma. Am J Ophthalmol 2007;143(6):958–69.
[67] von Euw E, Chodon T, Attar N, Jalil J, Koya RC, Comin-Anduix B, et al. CTLA4 blockade increases Th17 cells in patients with metastatic melanoma. J Transl Med 2009;7:35.
[68] 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(4):311–9.
[69] 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(2):123–35.
[70] 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(18):2004–12.
[71] Hamanishi J, Mandai M, Ikeda T, Minami M, Kawaguchi A, Murayama T, et al. Safety and antitumor activity of anti-PD-1 antibody, nivolumab, in patients with platinum-resistant ovarian cancer. J Clin Oncol 2015;33(34):4015–22.
[72] 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(4):320–30.
[73] 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(10):1020–30.
[74] Ulmeanu R, Antohe I, Anisie E, Antoniu S. Nivolumab for advanced non-small cell lung cancer: an evaluation of a phase III study. Expert Rev Anticancer Ther 2016;16(2):165–7.
[75] Weber JS, Kudchadkar RR, Yu B, Gallenstein D, Horak CE, Inzunza HD, et al. Safety, efficacy, and biomarkers of nivolumab with vaccine in ipilimumab-refractory or -naive melanoma. J Clin Oncol 2013;31(34):4311–8.
[76] 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(26):2509–20.
[77] 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(33):4199–206.
[78] Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015;372(21):2006–17.
[79] Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013;369(2):122–33.
[80] Conry RM, Sullivan JC, Nabors 3rd LB. Ipilimumab-induced encephalopathy with a reversible splenial lesion. Cancer Immunol Res 2015;3(6):598–601.
[81] O'Kane GM, Lyons TG, Colleran GC, Ahmad MW, Alken S, Kavanagh EC, et al. Late-onset paraplegia after complete response to two cycles of ipilimumab for metastatic melanoma. Oncol Res Treat 2014;37(12):757–60.
[82] Ali S, Lee SK. Ipilimumab therapy for melanoma a mimic of leptomeningeal metastases. Am J Neuroradiol 2015;36(12):E69–70.
[83] Bompaire F, Mateus C, Taillia H, De Greslan T, Lahutte M, Sallansonnet-Froment M, et al. Severe meningo-radiculo-neuritis associated with ipilimumab. Investig New Drugs 2012;30(6):2407–10.
[84] Luke JJ, Lezcano C, Hodi FS, Murphy GF. Antitumor granuloma formation by CD4+ T cells in a patient with rapidly progressive melanoma experiencing spiking fevers, neuropathy, and other immune-related toxicity after treatment with ipilimumab. J Clin Oncol 2015;33(6):e32–5.
[85] Thaipisuttikul I, Chapman P, Avila EK. Peripheral neuropathy associated with ipilimumab: a report of 2 cases. J Immunother 2015;38(2):77–9.
[86] Altman AL, Golub JS, Pensak ML, Samy RN. Bilateral facial palsy following ipilimumab infusion for melanoma. Otolaryngol Head Neck Surg 2015;153(5):894–5.
[87] Bot I, Blank CU, Boogerd W, Brandsma D. Neurological immune-related adverse events of ipilimumab. Pract Neurol 2013;13(4):278–80.
[88] Wilgenhof S, Neyns B. Anti-CTLA-4 antibody-induced Guillain-Barre syndrome in a melanoma patient. Ann Oncol 2011;22(4):991–3.
[89] Jinnur P, Lim KG. Severe acute orthopnea: ipilimumab-induced bilateral phrenic nerve neuropathy. Lung 2015;193(4):611–3.
[90] Johnson DB, Saranga-Perry V, Lavin PJ, Burnette WB, Clark SW, Uskavitch DR, et al. Myasthenia gravis induced by ipilimumab in patients with metastatic melanoma. J Clin Oncol 2015;33(33):e122–4.
[91] Loochtan AI, Nickolich MS, Hobson-Webb LD. Myasthenia gravis associated with ipilimumab and nivolumab in the treatment of small cell lung cancer. Muscle Nerve 2015;52(2):307–8.
[92] Hoftberger R, Rosenfeld MR, Dalmau J. Update on neurological paraneoplastic syndromes. Curr Opin Oncol 2015;27(6):489–95.
[93] Williams TJ, Benavides DR, Patrice KA, Dalmau JO, de Avila AL, Le DT, et al. Association of autoimmune encephalitis with combined immune checkpoint inhibitor treatment for metastatic cancer. JAMA Neurol 2016;73(8):928–33.
[94] Weber JS, Dummer R, de Pril V, Lebbe C, Hodi FS. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. Cancer 2013;119(9):1675–82.
[95] Hottinger AF. Neurologic complications of immune checkpoint inhibitors. Curr Opin Neurol 2016 Dec;29(6):806–12.