Critical Reviews in Oncology / Hematology 132 (2018) 125–129

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Liver toxicity in the era of immune checkpoint inhibitors: A practical approach☆

Carmen Belli[a,*], Massimo Zuin[b], Luca Mazzarella[a], Dario Trapani[a], Paolo D'Amico[a], Elena Guerini-Rocco[c], Bruno Achutti Duso[a], Giuseppe Curigliano[a,d]

[a] Division of Early Drug Development for Innovative Therapies, European Institute of Oncology, via Ripamonti 435, 20141 Milan, Italy
[b] Division of Internal Medicine and Liver Unit, Department of Medicine San Paolo Hospital School of Medicine, University of Milan, via di Rudiní 8, 20142, Milan, Italy
[c] Division of Pathology, European Institute of Oncology, Via Giuseppe Ripamonti 435, 20141, Milan, Italy
[d] Department of Oncology and Hemato-Oncology, University of Milan, via Festa del Perdono 7, 20122 Milan, Italy

ARTICLE INFO

Keywords:
Immune checkpoint inhibitors
Immune-related adverse events
Drug induced liver injury
Autoimmune hepatitis

ABSTRACT

Immune checkpoint inhibitors have revolutionized the cancer treatment with an approved efficacy in different solid tumors and hematologic malignancies. These agents are increasing the indication in cancer treatment, but can be associated with serious immune-related adverse effects (IRAEs). Dermatologic and gastrointestinal toxicities are the most common IRAE followed by endocrinopathies with a different time of occurrence. Rarely cases of gastrointestinal toxicities are observed almost 2 years after initiation of the therapy. In this review we focus on liver toxicity related to these immunotherapeutic agents for which the largest amount of safety data is available. The management of drug-induced liver toxicity is very complicated and in same cases may take a long period of time to be resolved. A prompt recognition of liver IRAEs and an appropriate management of this event, requiring close collaboration with other specialist figures, could improve its treatment with evident implication on the efficacy of the therapy.

1. Introduction

In the last decade, immunotherapy went from a constituent of tumors to a mainstay in the cancer treatment. Cytotoxic T-lymphocyte antigen 4 (CTLA-4), the programmed cell death protein 1 (PD-1) and its ligands (PD-L1/PD-L2) as well as several new generation checkpoint inhibitors have proven to modulate the immune response towards cancer clearance among a variety of human malignancies and many have reached a solid placement in routine clinical practice.

CTLA-4 is a co-inhibitory receptor expressed on $CD4^+$ and $CD8^+$ T cells in early stage of T-cell activation. This receptor binds with high affinity to B7 and can compete with CD28 to further inhibit T cell activity. The binding of CTLA-4 with B7, in fact, stops the T cell from maintaining an immune response with subsequent downregulation of T helper cell (Thelp) and enhancement of regulatory T cells (Treg) immunosuppressive activities (Krummel et al., 1996; Chambers et al., 1996) Ipilimumab, a fully human IgG1 monoclonal antibody against CTLA-4, was the first checkpoint inhibitor approved for malignant melanoma (Hodi et al., 2010).

The PD-1 pathway, differently from CTLA-4 - which functions mainly in the lymph nodes -, operates in the tumor microenvironment (TME). PD-1 is a protein activated on T and B cells, natural killers (NK) and antigen-presenting cells (APC) (Keir et al., 2008). This protein interacts with PD-L1 and PD-L2 present on the surface of tumor cells as well as on the infiltrating immune milieu, including tumor associated macrophages (TAMs), dendritic cells (DC), fibroblasts, and activated T cells (Freeman et al., 2000; Dong et al., 2002; Blank et al., 2004). The binding of PD-1 with its ligands enhances T cell function, blocking T cell exhaustion and licensing for anti-tumor activity (Okazaki and Honjo, 2007; Zou and Chen, 2008; Chow, 2013). Pembrolizumab is a monoclonal antibodies targeted against PD-1, approved as first line for patient affected by non small cell lung cancer (NSCLC) expressing high levels of PD-L1 ($\geq$50%) (Reck et al., 2016) and in second and beyond lines in tumors expressing any PD-L1($\geq$1%) (Herbst et al., 2016). Nivolumab is another monoclonal antibody targeted against PD-1 and currently approved for NSCLC in the second and beyond lines (Borghaei et al., 2015; Brahmer et al., 2015). Atezolizumab is the first monoclonal antibody targeted against PD-L1 and received approval for the treatment of advanced urothelial carcinoma and metastatic NSCLC in the second-line setting and beyond, both by the end of 2016 (Bellmunt

☆ This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
* Corresponding author.
E-mail address: cbelli77@gmail.com (C. Belli).

https://doi.org/10.1016/j.critrevonc.2018.09.019
Received 18 June 2018; Received in revised form 10 July 2018; Accepted 29 September 2018

et al., 2017; Rittmeyer et al., 2017; Lee et al., 2017). Durvalumab, another anti-PD-L1, has also recently being approved for the treatment of patients with metastatic urothelial carcinoma (Powles et al., 2017) and for the treatment of patients with unresectable NSCLC that has not progressed after chemoradiation (Antonia et al., 2017). Agonist antibodies targeting immune co-stimulatory receptors are under phase II/III trials (Mayes et al., 2018) and their potential drug-related adverse events will not be specifically covered in the present time.

Agents against CTLA-4 and PD-1 or its ligand PD-L1 may be associated with serious immune-related adverse events (irAE). irAE occur as a consequence of impaired self-tolerance from loss of T-cell inhibition and may potentially hit every organ (i.e., gastrointestinal, skin, endocrine systems). In this review we focused on liver toxicity related to these immunotherapeutic agents for which the largest amount of safety data is available.

2. The irAE panorama

Anti-PD-1 and anti-PD-L1 immune-checkpoint targeted monoclonal antibodies (ICPT mAb) have a comparable toxicity profile (Pillai et al., 2018) and are compressively safer than anti-CTLA4 agents (grade 3 and 4 adverse events in 10–15% versus 20–30%) as well as ICPT mAb combinations (grade 3 and 4 adverse event rate up to 55%) (Larkin et al., 2015). The most common adverse events observed with these agents concern the gastrointestinal system, skin and endocrine glands as shown in Table 1 (Hodi et al., 2010; Borghaei et al., 2015; Larkin et al., 2015; Eggermont et al., 2015; Robert et al., 2015a; Weber et al., 2015; Robert et al., 2015b; Motzer et al., 2015; Robert et al., 2014; Garon et al., 2015; Kim et al., 2013; Wolchok et al., 2010).

The timing of irAE is similar among dermatologic and gastrointestinal systems, occurring earlier (3–4 weeks and around 6 weeks after therapy initiation respectively) when compared to hepatitis and endocrinopathies (usually after 9 weeks of therapy). Unlike anti-CTLA-4 inhibitors, the incidence of toxicities with ICPT mAb does not appear to be dose-related (Weber et al., 2017).

Diarrhea and or colitis are commonly observed gastrointestinal events and their incidence at any grade is higher in patients treated with ipilimumab and combination of ipilimumab plus nivolumab compared to agents targeting the PD-1/PD-L1 axis. Liver dysfunction *per se* is not a common adverse event, occurring in approximately 7% of patients receiving anti-CTLA-4 antibodies, in less than 6% of patient treated with nivolumab and in 30% of subjects receiving a combination of immunotherapeutic agents (Larkin et al., 2015; Robert et al., 2015a; Weber et al., 2015; Robert et al., 2015b; Kleiner and Berman, 2012). Severe (G3-G4) gastrointestinal events occurrence is comparable (1–3%) for both ipilimumab and anti-PD-1/PD-L1 agents. Rash and/or pruritus are the most frequent skin irAEs and are more commonly observed in patients treated with ipilimumab, in monotherapy or combined with other ICPT mAb. Rash typically appears as erythematosus, reticular and maculopapular lesions, localized at limbs and trunk. Toxic effects as bullous pemphigoid and Sweet syndrome are rare.

Hypophysitis and alterations of thyroid function, being hypotiroidism more common than hyperthyroidism, are the most frequent endocrinopathies occurring in patient treated with immunotherapeutic agents, in particular among ipilimumab-containing strategies. Hypophysitis is characterized by the presence of fatigue, headache, hypogonadism, hypotension, and hypoglycemia with particular radiographic findings (Spain et al., 2016). Laboratory exams show a low adrenocorticotropic and thyrotropin hormone lavels. Less commonly, luteinizing hormone, follicle-stimulating hormone, growth hormone, and prolactin levels are also found

Drug-related, immune-mediated hepatitis is often asymptomatic. However, in a small number of cases can lead to fulminant hepatitis, rapid liver failure and ultimately to death (Suzuki et al., 2011). A dose-

Table 1
Hepatic adverse events (AEs) observed on clinical trials using ICPT mAbs among diverse tumor populations; NSCL: non-small-cell lung cancer; TPS: tumor proportion score; NR: not reported; HNSCC: head and neck squamous cell carcinoma.

Trial	Primary condition (*n*)	All grades hepatic AEs (%)	Grade ≥3 hepatic AEs (%)
Ipilimumab			
Hodi et al. (2010)	First line unresectable stage III or IV melanoma (511)	13 (5.9)	4 (1.1)
(Larkin et al. (2015))	First line unresectable stage III or IV melanoma (311)	23 (7.4)	7 (2.2)
Eggermont et al. (2015)	High-risk stage III melanoma after complete resection (471)	180 (38)	45 (10)
Robert et al. (2015a)	Unresectable stage III or IV melanoma ≤1 previous systemic therapy (256)	3 (1.2)	1 (0.4)
Pembrolizumab			
Robert et al. (2015a)	Unresectable stage III or IV melanoma ≤1 previous systemic therapy (256)	8 (2.9)	8 (2.9)
Lopes et al. (2018)	First line advanced/metastatic NSCLC, with no sensitizing EGFR mutations or ALK translocations, with PD-L1 TPS ≥ 1% (636)	NR (1.4)	NR (1.1)
Reck et al. (2016)	First line stage IV NSCLC, with no sensitizing EGFR mutations or ALK translocations, with PD-L1 TPS ≥ 50% (		
Le DT and Wang (2015)	Progressive metastatic carcinoma with or without mismatch-repair deficiency (57)	3 (7)	2 (5)
(Seiwert et al. (2016))	Unresectable or metastatic HNSCC, with PD-L1 expression ≥1%	4 (6)	4 (6)
Nivolumab			
Borghaei et al. (2015)	Stage IIIb/IV or recurrent NSCLC after radiation therapy or surgical resection or progression after one prior platinum-based chemotherapy (287)	16 (6)	1 (< 1)
Larkin et al. (2015)	First line unresectable stage III or IV melanoma (313)	24 (7.6)	7 (2.3)
Weber et al. (2015)	Unresectable stage IIIc or IV metastatic melanoma; BRAF wild type progressing to anti-CTLA-4 or BRAFV600 mutated progressing to anti-CTLA-4 and a BRAF inhibitor (268)	18 (6.7)	3 (1.1)
Robert et al. (2015b)	First line unresectable stage III or IV melanoma without a BRAF mutation (206)	2 (1)	1 (0.5)
Motzer et al. (2015)	Advanced or metastatic renal-cell carcinoma with a clear-cell component who had received one or two previous regimens of antiangiogenic therapy	NR	NR
Ipilimumab + Nivolumab			
Larkin et al. (2015)	First line unresectable stage III or IV melanoma (313)	103 (32.9)	45 (14.4)
Durvalumab			
Powles et al. (2017)	Locally advanced or metastatic urothelial cancer whose disease had progressed on, were ineligible for, or refused prior chemotherapy (191)	18 (9.3)	7 (4.6)
Antonia et al. (2017)	Stage III, locally advanced, unresectable NSCLC who did not have disease progression after two or more cycles of platinum-based chemoradiotherapy (475)	NR	NR
Atezolizumab			
Rittmeyer et al. (2017)	Stage IIIb or IV NSCLC who received one to two previous cytotoxic chemotherapy regimen, at least one platinum-containing regimen (609)	NR	2 (< 1)

Fig. 1. Hepatic irAE management algorithm (JBAG et al., 2017; Brahmer et al., 2018; Puzanov et al., 2017). irAE: immune-related adverse event; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ULN: upper normal limit; ICPT mAb: immune-checkpoint targeted monoclonal antibodies.

related toxicity is observed for ipilimumab, but not for pembrolizumab and nivolumab (Common Terminology Criteria for Adverse Events (CTCAE), 2018). Liver dysfunction induced by ICPT mAb most often becomes clinically evident between 8–12 weeks after initiation of therapy; although it may occur at any time of the treatment, even 1 year after the first dose. A recent pooled analysis conducted on patients treated with nivolumab showed that those subjects experiencing any irAEs had a higher median overall response rate (Weber et al., 2017).

3. Workup and management

We recommend, initially, a systematic approach that consists of a complete anamnesis and a full physical examination. A complete blood count and metabolic panel, liver function tests, aminotransferases, exclusion of infectious causes (i.e., viral hepatitis B, C, A and E; cytomegalovirus; herpes simplex virus; parvovirus B19; adenovirus; Epstein-Barr virus), autoantibody tests (i.e., antinuclear antibody [ANA], anti–smooth muscle antibody [ASMA], liver-kidney microsomal type 1 [LKM-1] antibody, serum protein electrophoresis [SPEP]), quantitative immunoglobulins and an abdominal ultrasound are also considered part of the initial workup. A crucial reminder in the primary assessment of these patients is to collect a detailed pharmacological anamnesis, with particular emphasis on concomitant drug assumption (including alcohol) and ongoing herbal medications (JBAG et al., 2017). After exclusion of other possible conditions, we proceed to differentials amidst drug induced liver injury (DILI) associated with ICPT mAb or autoimmune hepatitis (AIH), since it can significantly drive therapeutic decisions. Remarkably, no specific image finding is diagnostic unequivocally of ICPT mAb-induced hepatitis. Notwithstanding, in severe cases, periportal edema or hepatomegaly may be observed by ultrasound (Weber et al., 2016). The differential diagnosis between AIH and DILI may be challenging since both of them are characterized by temporal relationship with drug exposure (generally 8–12 weeks after initiation of ICPT mAb). Usually, DILI may resolve almost immediately while AIH may require up to 4 years for a total resolution (Weber et al., 2016; Champiat et al., 2016). AIH and DILI may present with similar laboratory abnormalities, with AST/ALT elevation and, even if to a lesser extent, bilirubin elevation, eosinophilia and hypergammaglobulinemia. Additionally, to orient the diagnostics, the antinuclear antibodies may be useful, despite the scarce rate of positive results (Champiat et al., 2016; Michot et al., 2016) Liver biopsy for identification of histological features can eventually be decisional. For instance, DILI presents with panlobular hepatitis with neutrophil predominant infiltrate or, less commonly, biliary duct injury (Suzuki et al., 2011). AIH, instead, is characterized by periportal lymphocytic/lymphoplasmacytic infiltrate with interface hepatitis and rosettes (piecemal

necrosis), prominent lobular infiltrate (composed of mononuclear and plasma cells), emperipolesis, absence of portal lymphoid aggregates, steatosis, ground glass hepatocytes, Councilman bodies, lobular or panacinar necrosis (De Martin et al., 2018). To further stress the matter, we may refer to a simplified AIH score (Hennes et al., 2008) as a complimentary tool on the differential process.

The grading system of adverse events, as defined by the National Cancer Institute, should be referenced during the treatment and management of such events (Michot et al. (2016)). If immune-related hepatotoxicity is suspected, prompt treatment with corticosteroids (methylprednisolone 0.5 to 1 mg/kg/d or equivalent) is recommended. Interestingly, in a recent retrospective French cohort, 38% of patients who developed immune-mediated hepatitis induced by ICPT mAb did not receive any corticosteroid therapy and experienced a spontaneous improvement in liver tests (De Martin et al., 2018). Also, no ≥ G3 hepatitis was observed after reintroduction of immunotherapy in two of these patients. Another analysis derived from 128 patients treated for advanced melanoma with ICPT mAb, on which 10 (7.8%) patients experienced immune-related hepatitis. G2, G3 and G4 aminotransferase increase was reported in one, seven and two patients, respectively. Here, only 5 of these patients received therapy with steroids, with resolution of hepatitis in all cases under strict monitoring (Gauci et al., 2018). While still not supported by current guidelines, these findings point us to a more selective approach while evaluating patients as candidates for upfront steroid therapy. Based on the nature of the hepatic lesion (use of corticosteroids are highly debatable in DILI and could induce severe adverse events and decrease the efficacy of ICPT mAb) and the grade of injury as per CTCAE 4.03 (e.g., ≤G3), it is possible to consider the omission of steroid treatment in selected cases. In AIH cases presenting with features of steroid-resistance or dependence, an adjunctive benefit may be obtained with mycophenolate mofetil (500 to 1000 mg every 12 h) or, in refractory cases, tacrolimus (0.10 to 0.15 mg/kg/day (Tarhini, 2013). Infliximab is not indicated as first choice due to its increasing chance of opportunistic infection. In refractory cases with rapid clinical decompensation, antithymocyte globulin 1.5 mg/kg for 2 consecutive days has been added to steroids and mycophenolate mofetil treatment, with some success (Boutros et al., 2016). Fig. 1, reports the algorithm to be used for management of hepatitic adverse event (Brahmer et al., 2018; Puzanov et al., 2017).

In highly refractory cases of ICPT mAb-related AIH (≥G3 hepatotoxicity, as per CTCAE 4.03), the recovery phase may require more than 1 month, necessitating drug discontinuation (Friedman et al., 2016). Indeed, for grade 1–2 treatment-related hepatitis, therapy should be delayed and monitoring of liver function test should be increased in frequency, but treatment can usually be resumed provided resolution of transaminitis to grade 1 or lower.

4. Conclusions

ICPT mAb now represent a standard of care for several solid tumors. Taken into account their different toxicity profile when compared to chemotherapy, irAEs have being observed due to the increased exposure to these agents in the clinics. Liver dysfunction is not a common irAE but, when it appears as severe toxicity, the recovery phase may require more than 1 month, necessitating drug discontinuation and a scrupulous medical approach (Larkin et al., 2015; Robert et al., 2015a; Weber et al., 2015; Robert et al., 2015b; Motzer et al., 2015; Robert et al., 2014; Garon et al., 2015). In recent clinical trials, an increased susceptibility to liver dysfunction is more frequently observed in patients treated with the combination of immunotherapeutic agents and in subjects treated with anti-CTLA-4 containing strategies (Kim et al., 2013; Wolchok et al., 2010; Kleiner and Berman, 2012; Weber et al., 2017). Treatment of immune-related liver events require, in most cases, the prompt beginning of corticosteroids and, eventually, immunosuppressive agents should be considered. Despite the current clinical understanding of liver irAEs, which has led to effective treatment strategies, additional studies are needed to further evaluate the chronology of events, assess potential predictive biomarkers and unfold a more patient-oriented management.

Author declaration

None.

Acknowledgements

The authors would like to thank Camila Da Silviera Achutti Duso for help in generating the schematic figure.

References

Antonia, S.J., Villegas, A., Daniel, D., et al., 2017. Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. N. Engl. J. Med. https://doi.org/10.1056/NEJMoa1709937. NEJMoa1709937.

Bellmunt, J., Powles, T., Vogelzang, N.J., 2017. A review on the evolution of PD-1/PD-L1 immunotherapy for bladder cancer: the future is now. Cancer Treat. Rev. 54, 58–67. https://doi.org/10.1016/j.ctrv.2017.01.007.

Blank, C., Brown, I., Peterson, A.C., et al., 2004. PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8 + T cells. Cancer Res. 64 (3), 1140–1145. http://www.ncbi.nlm.nih.gov/pubmed/14871849.

Borghaei, H., Paz-Ares, L., Horn, L., et al., 2015. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. N. Engl. J. Med. 373 (17), 1627–1639. https://doi.org/10.1056/NEJMoa1507643.

Boutros, C., Tarhini, A., Routier, E., et al., 2016. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nat. Rev. Clin. Oncol. 13 (8), 473–486. https://doi.org/10.1038/nrclinonc.2016.58.

Brahmer, J., Reckamp, K.L., Baas, P., et al., 2015. Nivolumab versus Docetaxel in advanced squamous-cell non–small-cell lung cancer. N. Engl. J. Med. 373 (2), 123–135. https://doi.org/10.1056/NEJMoa1504627.

Brahmer, J.R., Lacchetti, C., Schneider, B.J., et al., 2018. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: american society of clinical oncology clinical practice guideline. J. Clin. Oncol. 4https://doi.org/10.1200/JCO.2017.77.6385. JCO.2017.77.638.

Chambers, C.A., Krummel, M.F., Boitel, B., et al., 1996. The role of CTLA-4 in the regulation and initiation of T-cell responses. Immunol. Rev. 153, 27–46. http://www.ncbi.nlm.nih.gov/pubmed/9010718.

Champiat, S., Lambotte, O., Barreau, E., et al., 2016. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. Ann. Oncol. 27 (4), 559–574. https://doi.org/10.1093/annonc/mdv623.

Chow, L.Q., 2013. Exploring novel immune-related toxicities and endpoints with immune-checkpoint inhibitors in non-small cell lung cancer. Am. Soc. Clin. Oncol. Educ. Book 33, e280–e286. https://doi.org/10.1200/EdBook_AM.2013.33.e280.

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 14, 2010. US Department of Health and Human Services. National Institutes of Health National Cancer Institute. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReferenc.

De Martin, E., Michot, J.M., Papouin, B., et al., 2018. Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. J. Hepatol. 68 (6), 1181–1190. https://doi.org/10.1016/j.jhep.2018.01.033.

Dong, H., Strome, S.E., Salomao, D.R., et al., 2002. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat. Med. 8 (8), 793–800. https://doi.org/10.1038/nm730.

Eggermont, A.M.M., Chiarion-Sileni, V., Grob, J.-J., et al., 2015. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet Oncol. 16 (5), 522–530. https://doi.org/10.1016/S1470-2045(15)70122-1.

Freeman, G.J., Long, A.J., Iwai, Y., et al., 2000. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J. Exp. Med. 192 (7), 1027–1034. http://www.ncbi.nlm.nih.gov/pubmed/11015443.

Friedman, C.F., Proverbs-Singh, T.A., Postow, M.A., 2016. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. JAMA Oncol. 2 (10), 1346–1353. https://doi.org/10.1001/jamaoncol.2016.1051.

Garon, E.B., Rizvi, N.A., Hui, R., et al., 2015. Pembrolizumab for the treatment of non–small-cell lung cancer. N. Engl. J. Med. 372 (21), 2018–2028. https://doi.org/10.1056/NEJMoa1501824.

Gauci, M.-L., Baroudjian, B., Zeboulon, C., et al., 2018. Immune-related hepatitis with immunotherapy: are corticosteroids always needed? J. Hepatol. 1–2. https://doi.org/10.1016/j.jhep.2018.03.034.

Hennes, E.M., Zeniya, M., Czaja, A.J., et al., 2008. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology 48 (1), 169–176. https://doi.org/10.1002/hep.22322.

Herbst, R.S., Baas, P., Kim, D.-W., et al., 2016. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 387 (10027), 1540–1550. https://doi.org/10.1016/S0140-6736(15)01281-7.

Hodi, F.S., O'Day, S.J., McDermott, D.F., et al., 2010. Improved survival with ipilimumab

in patients with metastatic melanoma. N. Engl. J. Med. 363 (8), 711–723. https://doi.org/10.1056/NEJMoa1003466.
JBAG, Haanen, Carbonnel, F., Robert, C., et al., 2017. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 28 (Suppl. 4), iv119–iv142. https://doi.org/10.1093/annonc/mdx225.
Keir, M.E., Butte, M.J., Freeman, G.J., Sharpe, A.H., 2008. PD-1 and its ligands in tolerance and immunity. Annu. Rev. Immunol. 26 (1), 677–704. https://doi.org/10.1146/annurev.immunol.26.021607.090331.
Kim, K.W., Ramaiya, N.H., Krajewski, K.M., et al., 2013. Ipilimumab associated hepatitis: imaging and clinicopathologic findings. Invest. New Drugs 31 (4), 1071–1077. https://doi.org/10.1007/s10637-013-9939-6.
Kleiner, D.E., Berman, D., 2012. Pathologic changes in ipilimumab-related hepatitis in patients with metastatic melanoma. Dig. Dis. Sci. 57 (8), 2233–2240. https://doi.org/10.1007/s10620-012-2140-5.
Krummel, M.F., Sullivan, T.J., Allison, J.P., 1996. Superantigen responses and co-stimulation: CD28 and CTLA-4 have opposing effects on T cell expansion in vitro and in vivo. Int. Immunol. 8 (4), 519–523. http://www.ncbi.nlm.nih.gov/pubmed/8671638.
Larkin, J., Chiarion-Sileni, V., Gonzalez, R., et al., 2015. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N. Engl. J. Med. 373 (1), 23–34. https://doi.org/10.1056/NEJMoa1504030.
Le DT, Uram J.N., Wang, H., et al., 2015. PD-1 blockade in tumors with mismatch-repair deficiency. N. Engl. J. Med. 372 (26), 2509–2520. https://doi.org/10.1056/NEJMoa1500596.
Lee, H.T., Lee, J.Y., Lim, H., et al., 2017. Molecular mechanism of PD-1/PD-L1 blockade via anti-PD-L1 antibodies atezolizumab and durvalumab. Sci. Rep. 7 (1), 1–12. https://doi.org/10.1038/s41598-017-06002-8.
Lopes, G., Wu, Y.-L., Kudaba, I., et al., 2018. Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥ 1%: Open-label, phase 3 KEYNOTE-042 study. J. Clin. Oncol. 36 suppl; abstr LBA4.
Mayes, P.A., Hance, K.W., Hoos, A., 2018. The promise and challenges of immune agonist antibody development in cancer. Nat. Rev. Drug Discov. 17 (7), 509–527. https://doi.org/10.1038/nrd.2018.75.
Michot, J.M., Bigenwald, C., Champiat, S., et al., 2016. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur. J. Cancer 54, 139–148. https://doi.org/10.1016/j.ejca.2015.11.016.
Motzer, R.J., Escudier, B., McDermott, D.F., et al., 2015. Nivolumab versus everolimus in advanced renal-cell carcinoma. N. Engl. J. Med. 373 (19), 1803–1813. https://doi.org/10.1056/NEJMoa1510665.
Okazaki, T., Honjo, T., 2007. PD-1 and PD-1 ligands: from discovery to clinical application. Int. Immunol. 19 (7), 813–824. https://doi.org/10.1093/intimm/dxm057.
Pillai, R.N., Behera, M., Owonikoko, T.K., et al., 2018. Comparison of the toxicity profile of PD-1 versus PD-L1 inhibitors in non–small cell lung cancer: a systematic analysis of the literature. Cancer 124 (2), 271–277. https://doi.org/10.1002/cncr.31043.
Powles, T., O'Donnell, P.H., Massard, C., et al., 2017. Efficacy and safety of Durvalumab in locally advanced or metastatic urothelial carcinoma. JAMA Oncol. 3 (9), e172411. https://doi.org/10.1001/jamaoncol.2017.2411.
Puzanov, I., Diab, A., Abdallah, K., et al., 2017. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J. Immunother. Cancer 5 (1), 1–28. https://doi.org/10.1186/s40425-017-0300-z.
Reck, M., Rodríguez-Abreu, D., Robinson, A.G., et al., 2016. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N. Engl. J. Med. 375 (19), 1823–1833. https://doi.org/10.1056/NEJMoa1606774.
Rittmeyer, A., Barlesi, F., Waterkamp, D., et al., 2017. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 389 (10066), 255–265. https://doi.org/10.1016/S0140-6736(16)32517-X.
Robert, C., Ribas, A., Wolchok, J.D., et al., 2014. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet 384 (9948), 1109–1117. https://doi.org/10.1016/S0140-6736(14)60958-2.
Robert, C., Schachter, J., Long, G.V., et al., 2015a. Pembrolizumab versus ipilimumab in advanced melanoma. N. Engl. J. Med. 372 (26), 2521–2532. https://doi.org/10.1056/NEJMoa1503093.
Robert, C., Long, G.V., Brady, B., et al., 2015b. Nivolumab in previously untreated melanoma without BRAF mutation. N. Engl. J. Med. 372 (4), 320–330. https://doi.org/10.1056/NEJMoa1412082.
Seiwert, T.Y., Burtness, B., Mehra, R., et al., 2016. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol. 17 (7), 956–965. https://doi.org/10.1016/S1470-2045(16)30066-3.
Spain, L., Diem, S., Larkin, J., 2016. Management of toxicities of immune checkpoint inhibitors. Cancer Treat. Rev. 44, 51–60. https://doi.org/10.1016/j.ctrv.2016.02.001.
Suzuki, A., Brunt, E.M., Kleiner, D.E., et al., 2011. The use of liver biopsy evaluation in discrimination of idiopathic autoimmune hepatitis versus drug-induced liver injury. Hepatology 54 (3), 931–939. https://doi.org/10.1002/hep.24481.
Tarhini, A., 2013. Immune-mediated adverse events associated with ipilimumab CTLA-4 blockade therapy: the underlying mechanisms and clinical management. Scientifica (Cairo) 2013, 1–19. https://doi.org/10.1155/2013/857519.
Weber, J.S., D'Angelo, S.P., Minor, D., et al., 2015. 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. 16 (4), 375–384. https://doi.org/10.1016/S1470-2045(15)70076-8.
Weber, J.S., Postow, M., Lao, C.D., Schadendorf, D., 2016. Management of adverse events following treatment with anti-programmed death-1 agents. Oncologist 21 (10), 1230–1240. https://doi.org/10.1634/theoncologist.2016-0055.
Weber, J.S., Hodi, F.S., Wolchok, J.D., et al., 2017. Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. J. Clin. Oncol. 35 (7), 785–792. https://doi.org/10.1200/JCO.2015.66.1389.
Wolchok, J.D., Neyns, B., Linette, G., et al., 2010. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol. 11 (2), 155–164. https://doi.org/10.1016/S1470-2045(09)70334-1.
Zou, W., Chen, L., 2008. Inhibitory B7-family molecules in the tumour microenvironment. Nat. Rev. Immunol. 8 (6), 467–477. https://doi.org/10.1038/nri2326.