Front. Med. 2021, 15(1): 33–42
https://doi.org/10.1007/s11684-019-0735-3

REVIEW

# Advances on immune-related adverse events associated with immune checkpoint inhibitors

Yong Fan[1], Yan Geng[1], Lin Shen[2], Zhuoli Zhang (✉)[1]

[1]*Department of Rheumatology and Clinical Immunology, Peking University First Hospital, Beijing 100034, China;* [2]*Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing 100142, China*

© Higher Education Press 2020

**Abstract** **Immunotherapy has recently led to a paradigm shift in cancer therapy, in which immune checkpoint inhibitors (ICIs) are the most successful agents approved for multiple advanced malignancies. However, given the nature of the non-specific activation of effector T cells, ICIs are remarkably associated with a substantial risk of immune-related adverse events (irAEs) in almost all organs or systems. Up to 90% of patients who received ICIs combination therapy experienced irAEs, of which majority were low-grade toxicity. Cytotoxic lymphocyte antigen-4 and programmed cell death protein-1/programmed cell death ligand 1 inhibitors usually display distinct features of irAEs. In this review, the mechanisms of action of ICIs and how they may cause irAEs are described. Some unsolved challenges, however really engrossing issues, such as the association between irAEs and cancer treatment response, tumor response to irAEs therapy, and ICIs in challenging populations, are comprehensively summarized.**

**Keywords** cancer; immunotherapy; immune checkpoint inhibitors; immune-related adverse events; review

## Introduction

With increasing incidence and mortality, cancer has been a major public health problem and one of the leading causes of death worldwide [1,2]. In the past decades, the paradigm of cancer therapy has a dramatic revolution. Immunotherapy is rapidly advancing and can be currently considered as the "fifth pillar" of cancer therapy, joining the ranks of surgery, cytotoxic chemotherapy, radiation, and targeted therapy [3]. In 2013, cancer immunotherapy was cited by *Science* as top 1 breakthrough in medicine. The American Society of Clinical Oncology named immunotherapy as its Breakthrough of the Year for three years in a row (2016–2018 annual report). Immunotherapy, also referred to as biologic therapy or biotherapy, is an area of cancer treatment that uses the ability of an individual's immune system to fight cancer. It comes in various forms, including cytokines, cancer vaccines, adoptive cell transfer, oncolytic viruses, and most notably certain monoclonal antibodies identified as immune checkpoint inhibitors (ICIs). Given the interest generated by their recent and tremendous success, this article focuses on ICIs.

Received April 6, 2019; accepted October 31, 2019
Correspondence: Zhuoli Zhang, zhuoli.zhang@126.com

## ICIs and their mechanisms for cancer therapy

Immunotherapy with ICIs is one of the most exciting areas of new discoveries and treatments for cancer [4]. Immune checkpoints have succeeded in attracting great attention of people worldwide when the Nobel Prize in Physiology or Medicine 2018 was awarded jointly to James Allison and Tasuku Honjo for their discovery of cancer therapy by inhibition of negative immune regulation. In general, the immune system relies on T cells to fight cancer. These specialized cells are extremely powerful and have the potential to damage cancer cells and healthy cells. Normal T cell activation requires two signals to become fully activated. The primary signal (signal 1) occurs when the antigen-major histocompatibility complex (MHC) that is presented by the antigen-presenting cell (APC) binds to the

T cell receptor (TCR). However, signal 1 by itself is insufficient to enable T cell activation. A second signal (signal 2) occurs when a costimulator called CD28 binds to B7 (CD80 and CD86) on the surface of the APC. Following this interaction, T cells are activated and perform various effector functions (e.g., killing of tumor cells). Several inhibitory molecules in T cells, named immune checkpoints, function to maintain a balance of immunity. Cytotoxic lymphocyte antigen-4 (CTLA-4) was the first described immune checkpoint that was expressed on T cell surface only after T cell activation. However, CTLA-4 has high homology to CD28 and binds to B7 molecules with much higher affinity than CD28, inhibiting T cell activation. Programmed cell death protein-1 (PD-1) is another negative regulatory receptor expressed on the T cell surface that generally binds to either programmed cell death ligand 1 (PD-L1; expressed widely in multiple tissues and tumor cells) or PD-L2 (restricted to professional APCs). Tumors co-opt certain immune-checkpoint pathways as a major mechanism of immune resistance. In the tumor microenvironment, immune-checkpoint molecules, such as CTLA-4, PD-1, and its ligand PD-L1, are remarkably overexpressed [5], which suppress the activation of T cells and result in the exhaustion of immune response (Fig. 1). Therefore, these immune checkpoints are important immunotherapeutic targets, with checkpoint blockades releasing this immune suppression and reactivating cytotoxic T cells that can destroy tumor cells [6]. Other immune-checkpoint targets, such as lymphocyte activation gene 3, T cell immunoglobulin-3, B and T lymphocyte attenuator, and V-domain Ig suppressor of T cell activation, have also been studied extensively.

Currently, the US Food and Drug Administration has approved seven ICIs for the treatment of various solid tumors and hematological malignancies, including anti-CTLA-4 antibody (ipilimumab), anti-PD-1 antibody (pembrolizumab, nivolumab, cemiplimab), and anti-PD-L1 antibody (atezolizumab, durvalumab, avelumab) (Table 1). ICIs have brought revolutionary changes in the treatment of multiple advanced cancers, and the list of treatment indications has been likely extended as the years go by, even as a first-line therapy [7,8]. Despite the impressive therapeutic benefits, ICIs may induce profound immune toxicities called immune-related adverse events (irAEs). irAEs are side effects that can develop during or after treatment with ICIs. They are called "immune-related" because they develop as a result of a highly active immune response, which can damage healthy tissue or cause autoimmune or inflammatory disorders. The Common Terminology Criteria for Adverse Events is one of the most useful tools that is helping researchers to recognize and grade irAEs. Given the increasing prescription of ICIs, knowledge of irAEs is important for physicians in multiple clinical disciplines [9].

## irAEs: characteristics and potential mechanisms

Given that ICIs block inhibitory signaling pathways mainly in T cells, the enhancement of immune response induced by "artificial" mediators can also directly attack normal host tissues, thereby potentially facilitating autoimmune activity against any organ [10]. Compared with toxicities resulting from traditional chemotherapy, irAEs tend to have a relatively delayed onset and be inflammatory or autoimmune in nature [11,12]. Notably, irAEs can develop at any time during treatment, even after the cessation of ICIs. In summary, irAEs are broken down into two major categories: frequently reported (dermatologic, gastroenterological, hepatic, endocrine, respiratory, and rheumatologic/musculoskeletal) and uncommon (cardiovascular, hematologic, renal, neurologic, and ophthalmologic) types based on the frequency of occurrence in clinical practice [13–15]. Most irAEs are reversible, except for the effects on the endocrine system, which may be permanent [16]. A recent systematic analysis of AE frequencies with the use of ICIs in RCTs revealed that the overall AEs occurred in 74% of cancer patients treated with PD-1/PD-L1 inhibitors, 89% in the CTLA-4 inhibitor group, 90% in the ICI combination group, and 89% in the ICI plus chemotherapy group. Furthermore, AEs with grade $\geqslant 3$ were reported in 14% of patients treated with PD-1/PD-L1 inhibitors, 34% of patients treated with CTLA-4 inhibitor, 55% of patients treated with ICI combinations, and 46% of patients treated with combinations of ICIs and chemotherapy. The rates of AEs leading to treatment withdrawal were 6% for PD-1/PD-L1 inhibitors, 21% for CTLA-4 inhibitor, 38% for ICI combinations, and 13% for combinations of ICIs and chemotherapy. Of note, different frequencies of irAEs across ICIs may be due to their different mechanisms of action. In general, CTLA-4 controls the amplitude of immunologic response at early stages of T cell activation, whereas PD-1/PD-L1 pathways act at later stages, limiting T cell activity in the peripheral tissues [17]. Therefore, anti-CTLA-4 agents usually take effect by enhancing T cell priming, whereas the blockade of PD-1 or PD-L1 is thought to act by reinvigorating pre-existing CD8 T cell responses [18]. These differences can partly explain the increased frequency and severity of irAEs associated with anti-CTLA-4 agents. Although these irAEs are potentially fatal, deaths are uncommon, occurring in $< 1.5\%$ of cases with irAEs [19]. However, fatal ICI-associated irAEs, especially for cardiovascular toxicities, need to be alert and urgently investigated [20].

Interestingly, CTLA-4 and PD-1/PD-L1 inhibitors usually display distinct patterns of tissue-specific irAEs [21,22]. Ipilimumab, an anti-CTLA-4 antibody, is often associated with colitis (25%–30%), dermatitis (25%), and

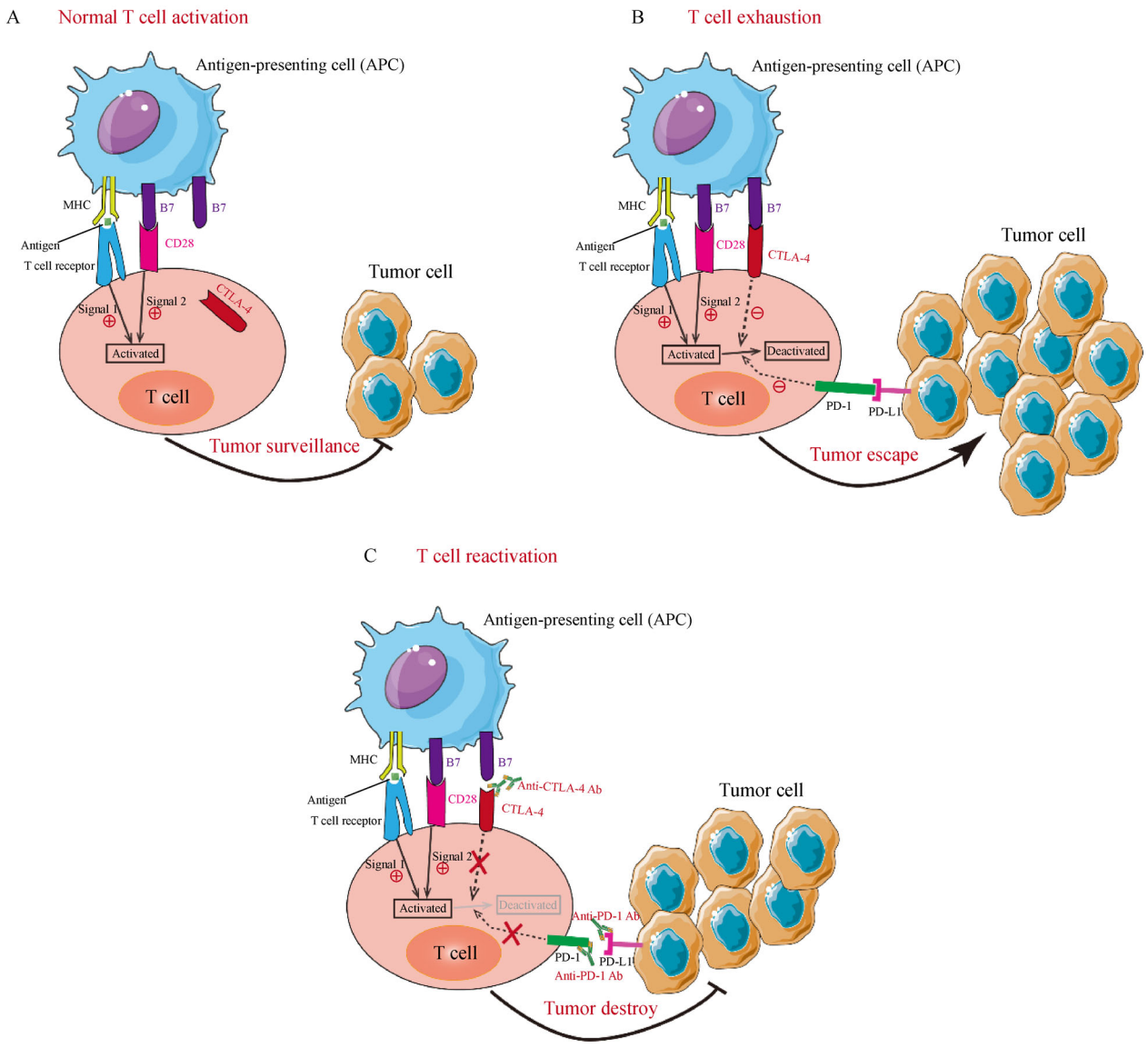


**Fig. 1** Schematic of ICIs in cancer therapy. (A) Normal T cell activation requires two signals to become fully activated. The primary signal (signal 1) occurs when the MHC that is presented by the APC binds to the TCR. However, signal 1 by itself is insufficient to enable T cell activation. A second signal (signal 2) occurs when a costimulator called CD28 binds to B7 (CD80 and CD86) on the surface of the APC. Following this interaction, T cells are activated and perform various effector functions (e.g., killing of tumor cells). (B) Several inhibitory molecules in T cells, named immune checkpoints, function to maintain a balance of immunity. CTLA-4 was the first described immune checkpoint that was expressed on T cell surface only after T cell activation. However, CTLA-4 has high homology to CD28 and binds to B7 molecules with much higher affinity than CD28, inhibiting T cell activation. PD-1 is another negative regulatory receptor expressed on the T cell surface that generally binds to either PD-L1 (expressed widely in multiple tissues and tumor cells) or PD-L2 (restricted to professional APCs). Under pathological conditions, the over-activation of both CTLA-4 and PD-1/PD-L1 pathways can suppress the activation of T cells and result in the exhaustion of immune response. (C) Blocking CTLA-4 and PD-1/PD-L1 inhibitory signal pathways by using specific antibodies (known as ICIs) diminishes the threshold for T cell activation and boosts anti-tumor activity by re-invigorated T cells but may also cause immune-related adverse events.

hypophysitis (5%–15%), whereas dermatitis (10%–20%), thyroiditis (10%–15%), and pneumonitis (3%–5%) are the most common AEs reported in patients treated with PD-1/PD-L1 inhibitors [9,19,23]. The primary cancer may also determine the type of irAEs. Colitis and skin irAEs are more often associated with melanoma [24], whereas pneumonitis occurs more frequently in patients with hematologic malignancies and lung cancer [25]. In addition, the irAE risk of anti-CTLA-4 appears to be dose dependent [26], whereas cumulative toxicities with prolonged exposure to anti-PD-1 antibodies are not observed [21,27]. Overall, the frequency and severity of

**Table 1** Overview of ICIs approved by the FDA (until April 2019)

| Drug name | Targeted | Year of FDA approval | Trademark | Company name | Indications |
|---|---|---|---|---|---|
| Ipilimumab | Anti-CTLA-4 antibody | 2011 | Yervoy | Bristol-Myers Squibb | Melanoma, renal cell carcinoma, colorectal cancer |
| Pembrolizumab | Anti-PD-1 antibody | 2014 | Keytruda | Merck Sharp & Dohme | Melanoma, non-small cell lung cancer, head and neck squamous cell cancer, classical Hodgkin lymphoma, primary mediastinal large B cell lymphoma, urothelial carcinoma, microsatellite instability-high cancer, gastric cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma |
| Nivolumab | Anti-PD-1 antibody | 2014 | Opdivo | Bristol-Myers Squibb | Melanoma, non-small cell lung cancer, small cell lung cancer, renal cell carcinoma, classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer, hepatocellular carcinoma |
| Cemiplimab | Anti-PD-1 antibody | 2018 | Libtayo | Regeneron Pharmaceuticals | Cutaneous squamous cell carcinoma |
| Atezolizumab | Anti-PD-L1 antibody | 2016 | Tecentriq | Genentech | Urothelial carcinoma, non-small cell lung cancer, triple-negative breast cancer, small cell lung cancer |
| Durvalumab | Anti-PD-L1 antibody | 2017 | Imfinzi | AstraZeneca | Urothelial carcinoma, non-small cell lung cancer |
| Avelumab | Anti-PD-L1 antibody | 2017 | Bavencio | EMD Serono | Merkel cell carcinoma, urothelial carcinoma |

irAEs of anti-CTLA-4 are greater than those of anti-PD-1/PD-L1 treatment, and their combination even exacerbates the frequency of irAEs.

The precise pathophysiology of irAEs remains uncertain, although preclinical, translational, and clinical studies have provided insights into their potential mechanisms. Of note, immune cells play vital roles in the anti-tumor features of ICIs. The early increased diversity of T cell repertoire after ipilimumab therapy is closely correlated with the development of irAEs [28]. In four cases of pneumonitis in patients treated with ICIs, the T cell repertoire in inflamed lung lesions and tumors overlapped significantly [29], suggesting that cross-reactive T cells against a tumor and a related antigen in normal tissue might be involved in irAE pathogenesis. After ICI combination therapy, a dramatic decline of circulating B cells and an increase in $CD21^{low}$ B cells and plasmablasts were observed. The early change of B cell subsets is a strong predictor of irAEs, suggesting that B cells might also be important contributors to autoimmunity following ICI therapy [30]. Using whole-blood gene-expression profiling in melanoma patients treated with ipilimumab, researchers noted that the neutrophil-activation markers CD177 and CEACAM1 were associated with gastrointestinal irAE [31]. Apart from immune cells, cytokines are also important regulators of host immune activity. Lim and colleagues analyzed the expressions of 65 cytokines in longitudinal plasma samples collected prior to therapy and during treatment in melanoma patients treated with ICIs alone or combination. Eleven cytokines were significantly upregulated in patients with severe irAEs, and the integration of these 11 cytokines into a single toxicity score (CYTOX) effectively predicted irAEs associated with ICIs [32]. Furthermore, serum levels of IL-6, IL-17, and sCD163 are significantly associated with irAEs in cancer patients treated with ICIs [33–35]. Hasan *et al*. recently demonstrated that human leukocyte antigen (HLA) genes are strongly associated with the development of pruritus (HLA-DRB1*11:01) or colitis (HLA-DQB1*03:01) during ICI therapy, suggesting a genetic etiology of irAEs [36]. Various bacterial species in the stool (specifically for colitis), preexisting autoantibodies, and polymorphisms in immune genes (such as CTLA-4, PD-1) may also predict toxicity, although their predictive capacities and underlying mechanisms require further investigation. Despite the tremendous long-lasting efficacy of ICIs in cancer treatment, irAEs remain considerable problems, as they may be fatal unexpectedly [37]. The potential mechanisms of irAEs are still poorly elucidated and may be related to a combination of genetic predisposition, environmental insults, and preexisting smoldering inflammation [38]. Whether irAEs are representative of *de novo* events or rather indicative of underlying immune-mediated diseases is unclear. Early recognition and intervention are critical for severe irAEs, and many patients require treatment interruption, discontinuation, and/or immunosuppressive agents, such as glucocorticoids, immunosuppressants, tumor necrosis factor inhibitors, or other biologics (e.g., IL-6 and IL-17 blockades).

ICI therapy using antibodies targeting CTLA-4 and PD-1/PD-L1 has demonstrated profound clinical efficacy for multiple malignancies. Nevertheless, an increasing number

of issues are of great interest to both clinicians and scientists.

## Are irAEs associated with the treatment response of ICIs?

Although the precise pathophysiology of irAEs remains unclear, the occurrence of irAEs may represent the reinvigoration of immune system to some extent. Whether irAEs can predict the anti-tumor response to ICIs remains controversial and worthy of further investigations. The association between irAEs and efficacy of ICIs was first described in metastatic melanoma in 2007 [39]. The majority (62%, 86 of 139) of metastatic melanoma patients treated with CTLA-4 blockade developed irAEs, which were associated with an increased probability of objective antitumor response ($P = 0.0004$). Furthermore, patients with complete anti-tumor responses had more severe irAEs. However, in another study, irAEs were observed in 254 out of 298 patients (85%) treated with a standard dose of ipilimumab. When comparing the outcomes of patients without irAEs and with irAEs of any grade, no differences in time to treatment failure and overall survival were observed [40]. In addition, a phase I/II study of ipilimumab revealed no significant association between irAEs and clinical response ($P = 0.45$) [41]. A landmark analysis of patients after 3 months of ipilimumab treatment also revealed no difference in overall survival between patients with and without irAEs [42]. Nevertheless, a very recent publication suggested that patients with irAEs respond better than those without irAEs. To evaluate the impact of irAEs on clinical outcomes, Cortellini *et al*. conducted a multi-center retrospective study based on a large cohort of patients with advanced non-small cell lung cancer and treated with PD-1 inhibitors. They found that irAEs were concordantly related to higher overall response rate, longer overall response rate and longer overall survival compared with those without irAEs [43]. Subsequently, increasing number of studies demonstrated that the occurrence of irAEs could predict clinical benefit of ICIs in non-small cell lung cancer and melanoma [44–46]. Furthermore, Kaplan–Meier and multivariate Cox regression analysis showed that irAEs are associated with improved progression-free survival (hazard ratio of 0.33, $P < 0.001$). This association did not appear to be altered by the use of systemic corticosteroids [47]. Kostine *et al*. reported that patients with rheumatic irAEs had a higher anti-tumor response rate than those without irAEs (85.7% vs. 35.3%; OR = 8.8 (95% CI 3.2 to 29.8), $P < 0.0001$) and a trend toward a higher response rate than those with non-rheumatic irAEs (85.7% vs. 75.1%, $P = 0.18$) [48]. Moreover, a recent study revealed not only a strong relationship between overall irAEs and good oncological response to PD-1 inhibitors but also a stronger association of rheumatic irAEs with good oncological response (OR = 11.16, 95% CI 2.65–46.98) than non-cutaneous irAEs (RR = 2.03, 95% CI 1.27–3.22) [49].

Intriguingly, some specific AEs (e.g., skin irAEs) may be definitely associated with treatment efficacy. Several studies involving patients with melanoma have shown an association between vitiligo and beneficial clinical outcomes [50,51]. In 67 melanoma patients treated with pembrolizumab, 17 patients (25%) developed vitiligo. The objective response rates were 71% and 28% in patients with and without vitiligo ($P = 0.002$), respectively [51]. Other studies evaluated the association of skin irAEs and outcomes. Time to progression was significantly better in patients who experienced skin irAEs than those who did not. Similarly, cutaneous irAEs (rash and vitiligo) were found to be correlated with statistically significant overall survival benefit in melanoma patients treated with nivolumab ($P = 0.004$ and $P = 0.028$, respectively) [52]. These findings suggested a predictive role of skin irAE occurrence in patients receiving PD-1 inhibitors. Of note, most of these aforementioned studies were retrospective and vulnerable to several forms of appraisal bias. To determine whether irAEs are beneficial, more well-designed and long-term studies are needed. The general consensus at the moment is that irAEs are not required for ICI treatment benefit [53], but irAEs might be "the cream on the top of the cake."

## Does corticosteroid use decrease the efficacy of ICIs?

Considering the biological hypothesis that immunosuppressive therapy may compromise the antitumor response, clinicians have wondered whether corticosteroids and immunosuppressive agents used to treat irAEs may decrease the efficacy of ICIs. Unfortunately, there has been no high-quality, prospective study to answer this question so far. *In vitro*, PD-1 expression is upregulated by high-dose corticosteroids in both mouse and human activated T cells [54]. Even low doses of corticosteroids markedly impair the antitumor activity of tumor-infiltrating lymphocytes [55]. Steroids do not entirely eliminate the possibility of response to ICIs; however, the apparent low rate of benefit is observed in the corticosteroid group [56]. Among 98 melanoma patients with ipilimumab-induced hypophysitis, those who received high doses of glucocorticoids had reduced survival, suggesting a potential negative effect of high-dose glucocorticoid on the efficacy of ICIs after the occurrence of an irAE [57]. A case report published in the *New England Journal of Medicine* also demonstrated that interleukin-17 blockade dramatically decreased the antitumor efficacy of pembrolizumab in a patient with metastatic colon cancer [58]. However, an increasing number of retrospective studies have shown that systemic use of steroids for irAEs does not appear to lessen the antitumor effects. A pooled retrospective analysis including 576 melanoma patients treated with nivolumab

monotherapy showed that 71% experienced any-grade irAEs, and approximately 24% received systemic immune-modulating agents to manage these irAEs. The objective response rates were similar in patients who received systemic immune-modulating agents with those who did not [59]. Data from a large cancer center in the USA revealed that systemic corticosteroid therapy for an irAE is necessary for 35% (103 in 298) of patients, and more importantly the overall survival and time to treatment failure were not affected by the use of systemic corticosteroids [40]. Moreover, a study also showed no worse outcomes in patients with ipilimumab-related diarrhea who were treated with infliximab compared with other medications [60]. Recently, a comprehensive meta-analysis including 27 articles suggested that the concomitant administration of corticosteroids and ICIs may not necessarily lead to poor clinical outcomes [61]. Interestingly, Hinrichs *et al*. indicated that glucocorticoids did not interfere with the antitumor response of immunotherapy in a melanoma mouse model *in vivo* [62]. Currently, most of these irAEs can be managed by counteracting lymphocyte activation with steroids. All guidelines from the American Society of Clinical Oncology, the European Society for Medical Oncology, and the Society for Immunotherapy of Cancer recommend corticosteroids as the first choice in the management of irAEs [15,63,64]. The beneficial response of ICIs can persist despite the use of immunosuppressive agents to treat irAEs seems to have reached consensus at present. Whether the use of corticosteroids, especially high-dosage, long-term therapy, will negate the anti-tumor response of ICI therapy still lacks high-quality evidence and remains unclear. Further investigations in this field must be carried out.

## Can cancer patients with preexisting autoimmune disorders (ADs) be treated with ICIs?

Patients with a history of ADs have been excluded from all clinical trials with ICI therapy and therefore have lost potential opportunities to fight with advanced malignancy. Immune-mediated inflammatory diseases are at high risk to develop cancer. Up to 13.5% of patients with lung cancer have concurrent AD, suggesting the urgency of exploring ICIs in this population [65]. By antagonizing immune inhibitory pathways, ICI treatments were thought to potentially worsen AD. Indeed, evidence shows that cancer patients with preexisting or underlying AD would experience increased flares of AD and irAEs. Johnson and colleagues enrolled 30 advanced melanoma patients with AD who received anti-CTLA4 therapy. Half of them experienced no toxicity, whereas 10 (33%) patients experienced $\geqslant$ grade 3 irAEs. Eight (27%) patients who experienced exacerbations of their autoimmune condition were managed with corticosteroids [66]. Similar results were observed in patients with advanced melanoma and preexisting AD receiving anti-PD1 therapy. Twenty (38%) patients had flares of AD requiring immunosuppression therapy, and only two (4%) patients discontinued treatment due to flares [67]. A systematic review showed that the exacerbation of prior AD occurred in half of the reported patients, and one third of patients with AD experienced *de novo* irAEs, indicating that the frequency of *de novo* irAEs may be similar in patients with and without AD. Most irAEs are easily managed with corticosteroids, with some (16%) requiring more aggressive immunosuppressive agent therapy. More than half of the patients did not require discontinuation of ICI therapy [68]. Very recently, a large multicenter "real-world" observational study demonstrated that the incidence of irAEs of any grade was significantly higher in anti-PD-1-treated patients with pre-existing AD compared with patients without (65.9% vs. 39.9%, $P < 0.0001$); however, no significant differences in grade 3/4 irAEs were observed between these two subgroups (9.4% vs. 8.8%, $P = 0.8663$) [69]. Danlos *et al*. also revealed a significantly increased risk of irAEs in patients with pre-existing AD receiving anti-PD1 therapy; however, the effectiveness of ICIs was the same as those patients without AD [70]. Available information derived mainly from case series and retrospective studies with cancer and preexisting AD suggest the feasible use of ICIs when cancer is life-threating [53]. Although these patients are at increased risk for exacerbations of AD and occurrence of irAEs, these events are generally not harmful. A careful balance between toxicity and efficacy and close monitoring are necessary; however, preexisting AD is not an absolute contraindication to ICI therapy [71].

## Is it safe to restart ICI therapy in patients who ever developed irAEs?

In the clinic, physicians may easily be confused about whether it is safe to restart ICI therapy in patients who ever developed irAEs. Unfortunately, no prospective data from clinical trials can answer this question. A retrospective study involving patients with melanoma showed that anti-PD-1 could be safely restarted after a serious ipilimumab-related irAE requiring immunosuppression treatment. The overall response rate was 40%. Among 67 patients, 2 (3%) had a recurrence of the same ipilimumab irAEs, and 23 (34%) developed new irAEs (14 with grade 3–4 irAEs); however, no treatment-related death occurred [67]. In another retrospective study, 38 patients with non-small cell lung cancer who had serious anti-PD-(L)1-related irAEs were rechallenged with PD-1/PD-L1 blockades. Half of them had no further irAEs, 26% had recurrence of the initial irAE, and 26% had a new irAE. Most recurrent/new irAEs were mild (58% grade 1–2) and manageable (84% resolved or improved to grade 1); however, two treatment-related deaths occurred [72]. Furthermore, Simonaggio *et al*. focused on ICI rechallenge in 40 patients with a broad

spectrum of cancers treated with anti-PD-1 or anti-PD-L1 agents. A total of 17 patients (42.5%) experienced a recurrence of the same type of irAE, and five patients (12.5%) experienced a different type of irAE. The severity distribution for the second irAE was 38% for grade 2, 48% for grade 3, and 14% for grade 4, which were not more severe than the initial event [73]. Thus, the effect and safety of ICI rechallenge seem to be acceptable.

Combined ICI therapy (CTLA-4 plus PD-1/PD-L1) induces high rate of irAEs. Interestingly, Pollack *et al*. demonstrated that anti-PD-1 rechallenge after severe irAEs during combined CTLA-4/PD-1 therapy for metastatic melanoma caused relatively low rate of initial irAE (in 18% of patients) or new different irAE (21%) [74], which indicated that anti-PD-(L)1 rechallenge appears to be feasible and safe (with close monitoring). Nevertheless, the question of whether to rechallenge remains crucial and has not been discussed in practical guidelines. Associated factors or biomarkers that can predict ICI rechallenge had not been fully evaluated. From the perspective of some experts, rechallenge is considered possible only after the grade of the irAE is reverted to 0 or 1 [73]. Eventually, a decision to restart treatment with ICIs (mainly PD-(L)1 blockades) should likely depend on the severity of the prior irAE, the availability of alternative treatment options, and the overall status of the cancer. An absolute contra-indication to restart treatment with ICIs is life-threatening toxicity, particularly cardiac, pulmonary, or neurologic toxicity. Of note, safety should be one of the most important considerations when reinitiating ICI therapy after an irAE. The rechallenge should be first assessed with regard to each patient's individual risk–benefit ratio. Further investigations are needed to define the detailed criteria for ICI rechallenge.

## Conclusions

ICI therapy by targeting CTLA-4 and PD-1/PD-L1 has revolutionized the treatment of many types of advanced cancer. Nevertheless, given the nature of non-specific activation of T cells, ICIs are associated with a substantial risk of irAEs. IrAEs are usually tolerable with low-grade toxicity but can be fatal. Further understanding of the pathophysiology of ICIs and identifying reliable biomarkers to predict the treatment efficacy and toxicity are important. In daily practice, clinicians should consider these available data when making treatment decisions in challenging patients (e.g., cancer patients with pre-existing autoimmune diseases and irAEs) and balancing the risks of toxicity with potential benefits. Close collaborations among oncologists, organ specialists, and clinical immunologists are vital for properly managing irAEs and improving the long-term survival of cancer patients.

## Acknowledgements

This work was supported by the Beijing Natural Science Foundation (No.7184251) and National Natural Science Foundation of China (Nos. 91442120 and 81771740).

## Compliance with ethics guidelines

Yong Fan, Yan Geng, Lin Shen, and Zhuoli Zhang declare that they have no financial conflicts of interest. This manuscript is a review article and does not involve a research protocol requiring approval by a relevant institutional review board or ethics committee.

## References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136(5): E359–E386
2. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. CA Cancer J Clin 2016; 66(2): 115–132
3. Urruticoechea A, Alemany R, Balart J, Villanueva A, Viñals F, Capellá G. Recent advances in cancer therapy: an overview. Curr Pharm Des 2010; 16(1): 3–10
4. Brower V. Checkpoint blockade immunotherapy for cancer comes of age. J Natl Cancer Inst 2015; 107(3): 107
5. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature 2011; 480(7378): 480–489
6. Inthagard J, Edwards J, Roseweir AK. Immunotherapy: enhancing the efficacy of this promising therapeutic in multiple cancers. Clin Sci (Lond) 2019; 133(2): 181–193
7. Pai-Scherf L, Blumenthal GM, Li H, Subramaniam S, Mishra-Kalyani PS, He K, Zhao H, Yu J, Paciga M, Goldberg KB, McKee AE, Keegan P, Pazdur R. FDA Approval Summary: pembrolizumab for treatment of metastatic non-small cell lung cancer: first-line therapy and beyond. Oncologist 2017; 22(11): 1392–1399
8. Zhou Y, Chen C, Zhang X, Fu S, Xue C, Ma Y, Fang W, Yang Y, Hou X, Huang Y, Zhao H, Hong S, Zhang L. Immune-checkpoint inhibitor plus chemotherapy versus conventional chemotherapy for first-line treatment in advanced non-small cell lung carcinoma: a systematic review and meta-analysis. J Immunother Cancer 2018; 6 (1): 155
9. Johnson DB, Chandra S, Sosman JA. Immune checkpoint inhibitor toxicity in 2018. JAMA 2018; 320(16): 1702–1703
10. Michot JM, Bigenwald C, Champiat S, Collins M, Carbonnel F, Postel-Vinay S, Berdelou A, Varga A, Bahleda R, Hollebecque A, Massard C, Fuerea A, Ribrag V, Gazzah A, Armand JP, Amellal N, Angevin E, Noel N, Boutros C, Mateus C, Robert C, Soria JC, Marabelle A, Lambotte O. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer 2016; 54: 139–148
11. Thompson JA, Schneider BJ, Brahmer J, Andrews S, Armand P, Bhatia S, Budde LE, Costa L, Davies M, Dunnington D, Ernstoff MS, Frigault M, Hoffner B, Hoimes CJ, Lacouture M, Locke F,

Lunning M, Mohindra NA, Naidoo J, Olszanski AJ, Oluwole O, Patel SP, Reddy S, Ryder M, Santomasso B, Shofer S, Sosman JA, Wahidi M, Wang Y, Johnson-Chilla A, Scavone JL. Management of immunotherapy-related toxicities, version 1.2019. J Natl Compr Canc Netw 2019; 17(3): 255–289

12. Kong YC, Flynn JC. Opportunistic autoimmune disorders potentiated by immune-checkpoint inhibitors anti-CTLA-4 and anti-PD-1. Front Immunol 2014; 5: 206
13. El Osta B, Hu F, Sadek R, Chintalapally R, Tang SC. Not all immune-checkpoint inhibitors are created equal: meta-analysis and systematic review of immune-related adverse events in cancer trials. Crit Rev Oncol Hematol 2017; 119: 1–12
14. Calabrese LH, Calabrese C, Cappelli LC. Rheumatic immune-related adverse events from cancer immunotherapy. Nat Rev Rheumatol 2018; 14(10): 569–579
15. Puzanov I, Diab A, Abdallah K, Bingham CO 3rd, Brogdon C, Dadu R, Hamad L, Kim S, Lacouture ME, LeBoeuf NR, Lenihan D, Onofrei C, Shannon V, Sharma R, Silk AW, Skondra D, Suarez-Almazor ME, Wang Y, Wiley K, Kaufman HL, Ernstoff MS; Society for Immunotherapy of Cancer Toxicity Management Working Group. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer 2017; 5(1): 95
16. Chang LS, Barroso-Sousa R, Tolaney SM, Hodi FS, Kaiser UB, Min L. Endocrine toxicity of cancer immunotherapy targeting immune checkpoints. Endocr Rev 2019; 40(1): 17–65
17. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012; 12(4): 252–264
18. Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. Nature 2017; 541(7637): 321–330
19. Arnaud-Coffin P, Maillet D, Gan HK, Stelmes JJ, You B, Dalle S, Péron J. A systematic review of adverse events in randomized trials assessing immune checkpoint inhibitors. Int J Cancer 2019; 145(3): 639–648
20. Moslehi JJ, Salem JE, Sosman JA, Lebrun-Vignes B, Johnson DB. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. Lancet 2018; 391(10124): 933
21. Wang PF, Chen Y, Song SY, Wang TJ, Ji WJ, Li SW, Liu N, Yan CX. Immune-related adverse events associated with anti-PD-1/PD-L1 treatment for malignancies: a meta-analysis. Front Pharmacol 2017; 8: 730
22. Bertrand A, Kostine M, Barnetche T, Truchetet ME, Schaeverbeke T. Immune related adverse events associated with anti-CTLA-4 antibodies: systematic review and meta-analysis. BMC Med 2015; 13(1): 211
23. Boutros C, Tarhini A, Routier E, Lambotte O, Ladurie FL, Carbonnel F, Izzeddine H, Marabelle A, Champiat S, Berdelou A, Lanoy E, Texier M, Libenciuc C, Eggermont AM, Soria JC, Mateus C, Robert C. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nat Rev Clin Oncol 2016; 13(8): 473–486
24. Khoja L, Day D, Wei-Wu Chen T, Siu LL, Hansen AR. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. Ann Oncol 2017; 28(10): 2377–2385
25. Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, Chaft JE, Segal NH, Callahan MK, Lesokhin AM, Rosenberg J, Voss MH, Rudin CM, Rizvi H, Hou X, Rodriguez K, Albano M, Gordon RA, Leduc C, Rekhtman N, Harris B, Menzies AM, Guminski AD, Carlino MS, Kong BY, Wolchok JD, Postow MA, Long GV, Hellmann MD. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. J Clin Oncol 2017; 35(7): 709–717
26. Wolchok JD, Neyns B, Linette G, Negrier S, Lutzky J, Thomas L, Waterfield W, Schadendorf D, Smylie M, Guthrie T Jr, Grob JJ, Chesney J, Chin K, Chen K, Hoos A, O'Day SJ, Lebbé C. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol 2010; 11(2): 155–164
27. Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, Brahmer JR, Lawrence DP, Atkins MB, Powderly JD, Leming PD, Lipson EJ, Puzanov I, Smith DC, Taube JM, Wigginton JM, Kollia GD, Gupta A, Pardoll DM, Sosman JA, Hodi FS. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol 2014; 32(10): 1020–1030
28. Oh DY, Cham J, Zhang L, Fong G, Kwek SS, Klinger M, Faham M, Fong L. Immune toxicities elicted by CTLA-4 blockade in cancer patients are associated with early diversification of the T-cell repertoire. Cancer Res 2017; 77(6): 1322–1330
29. Läubli H, Koelzer VH, Matter MS, Herzig P, Dolder Schlienger B, Wiese MN, Lardinois D, Mertz KD, Zippelius A. The T cell repertoire in tumors overlaps with pulmonary inflammatory lesions in patients treated with checkpoint inhibitors. OncoImmunology 2018; 7(2): e1386362
30. Das R, Bar N, Ferreira M, Newman AM, Zhang L, Bailur JK, Bacchiocchi A, Kluger H, Wei W, Halaban R, Sznol M, Dhodapkar MV, Dhodapkar KM. Early B cell changes predict autoimmunity following combination immune checkpoint blockade. J Clin Invest 2018; 128(2): 715–720
31. Shahabi V, Berman D, Chasalow SD, Wang L, Tsuchihashi Z, Hu B, Panting L, Jure-Kunkel M, Ji RR. Gene expression profiling of whole blood in ipilimumab-treated patients for identification of potential biomarkers of immune-related gastrointestinal adverse events. J Transl Med 2013; 11(1): 75
32. Lim SY, Lee JH, Gide TN, Menzies AM, Guminski A, Carlino MS, Breen EJ, Yang JYH, Ghazanfar S, Kefford RF, Scolyer RA, Long GV, Rizos H. Circulating cytokines predict immune-related toxicity in melanoma patients receiving anti-PD-1-based immunotherapy. Clin Cancer Res 2019; 25(5): 1557–1563
33. Valpione S, Pasquali S, Campana LG, Piccin L, Mocellin S, Pigozzo J, Chiarion-Sileni V. Sex and interleukin-6 are prognostic factors for autoimmune toxicity following treatment with anti-CTLA4 blockade. J Transl Med 2018; 16(1): 94
34. Tarhini AA, Zahoor H, Lin Y, Malhotra U, Sander C, Butterfield LH, Kirkwood JM. Baseline circulating IL-17 predicts toxicity while TGF-β1 and IL-10 are prognostic of relapse in ipilimumab neoadjuvant therapy of melanoma. J Immunother Cancer 2015; 3 (1): 39
35. Fujimura T, Sato Y, Tanita K, Kambayashi Y, Otsuka A, Fujisawa Y, Yoshino K, Matsushita S, Funakoshi T, Hata H, Yamamoto Y, Uchi H, Nonomura Y, Tanaka R, Aoki M, Imafuku K, Okuhira H, Furudate S, Hidaka T, Aiba S. Serum levels of soluble CD163 and

CXCL5 may be predictive markers for immune-related adverse events in patients with advanced melanoma treated with nivolumab: a pilot study. Oncotarget 2018; 9(21): 15542–15551

36. Hasan Ali O, Berner F, Bomze D, Fässler M, Diem S, Cozzio A, Jörger M, Früh M, Driessen C, Lenz TL, Flatz L. Human leukocyte antigen variation is associated with adverse events of checkpoint inhibitors. Eur J Cancer 2019; 107:8–14
37. Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, Zhao S, Das S, Beckermann KE, Ha L, Rathmell WK, Ancell KK, Balko JM, Bowman C, Davis EJ, Chism DD, Horn L, Long GV, Carlino MS, Lebrun-Vignes B, Eroglu Z, Hassel JC, Menzies AM, Sosman JA, Sullivan RJ, Moslehi JJ, Johnson DB. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. JAMA Oncol 2018; 4(12): 1721–1728
38. Johnson DB, Balko JM. Biomarkers for immunotherapy toxicity: are cytokines the answer? Clin Cancer Res 2019; 25(5): 1452–1454
39. Downey SG, Klapper JA, Smith FO, Yang JC, Sherry RM, Royal RE, Kammula US, Hughes MS, Allen TE, Levy CL, Yellin M, Nichol G, White DE, Steinberg SM, Rosenberg SA. Prognostic factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. Clin Cancer Res 2007; 13(22 Pt 1): 6681–6688
40. Horvat TZ, Adel NG, Dang TO, Momtaz P, Postow MA, Callahan MK, Carvajal RD, Dickson MA, D'Angelo SP, Woo KM, Panageas KS, Wolchok JD, Chapman PB. 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(28): 3193–3198
41. Weber JS, O'Day S, Urba W, Powderly J, Nichol G, Yellin M, Snively J, Hersh E. Phase I/II study of ipilimumab for patients with metastatic melanoma. J Clin Oncol 2008; 26(36): 5950–5956
42. Owen DH, Wei L, Bertino EM, Edd T, Villalona-Calero MA, He K, Shields PG, Carbone DP, Otterson GA. Incidence, risk factors, and effect on survival of immune-related adverse events in patients with non-small-cell lung cancer. Clin Lung Cancer 2018; 19(6): e893–e900
43. Cortellini A, Chiari R, Ricciuti B, Metro G, Perrone F, Tiseo M, Bersanelli M, Bordi P, Santini D, Giusti R, Grassadonia A, Di Marino P, Tinari N, De Tursi M, Zoratto F, Veltri E, Malorgio F, Garufi C, Russano M, Anesi C, Zeppola T, Filetti M, Marchetti P, Berardi R, Rinaldi S, Tudini M, Silva RR, Pireddu A, Atzori F, Iacono D, Migliorino MR, Porzio G, Cannita K, Ficorella C, Buti S. Correlations between the immune-related adverse events spectrum and efficacy of anti-PD1 immunotherapy in NSCLC patients. Clin Lung Cancer 2019; 20(4): 237–247.e1
44. Toi Y, Sugawara S, Kawashima Y, Aiba T, Kawana S, Saito R, Tsurumi K, Suzuki K, Shimizu H, Sugisaka J, Ono H, Domeki Y, Terayama K, Nakamura A, Yamanda S, Kimura Y, Honda Y. Association of immune-related adverse events with clinical benefit in patients with advanced non-small-cell lung cancer treated with nivolumab. Oncologist 2018; 23(11): 1358–1365
45. RogadoJ, Sánchez-Torres JM, Romero-Laorden N, Ballesteros AI, Pacheco-Barcia V, Ramos-Leví A, Arranz R, Lorenzo A, Gullón P, Donnay O, Adrados M, Costas P, Aspa J, Alfranca A, Mondéjar R, Colomer R. Immune-related adverse events predict the therapeutic efficacy of anti-PD-1 antibodies in cancer patients. Eur J Cancer 2019; 109: 21–27
46. Okada N, Kawazoe H, Takechi K, Matsudate Y, Utsunomiya R, Zamami Y, Goda M, Imanishi M, Chuma M, Hidaka N, Sayama K, Kubo Y, Tanaka A, Ishizawa K. Association between immune-related adverse events and clinical efficacy in patients with melanoma treated with nivolumab: a multicenter retrospective study. Clin Ther 2019; 41(1): 59–67
47. Shafqat H, Gourdin T, Sion A. Immune-related adverse events are linked with improved progression-free survival in patients receiving anti-PD-1/PD-L1 therapy. Semin Oncol 2018; 45(3): 156–163
48. Kostine M, Rouxel L, Barnetche T, Veillon R, Martin F, Dutriaux C, Dousset L, Pham-Ledard A, Prey S, Beylot-Barry M, Daste A, Gross-Goupil M, Lallier J, Ravaud A, Forcade E, Bannwarth B, Truchetet ME, Richez C, Mehsen N, Schaeverbeke T; FHU ACRONIM. Rheumatic disorders associated with immune checkpoint inhibitors in patients with cancer-clinical aspects and relationship with tumour response: a single-centre prospective cohort study. Ann Rheum Dis 2018; 77(3): 393–398
49. Liew DFL, Leung JLY, Liu B, Cebon J, Frauman AG, Buchanan RRC. Association of good oncological response to therapy with the development of rheumatic immune-related adverse events following PD-1 inhibitor therapy. Int J Rheum Dis 2019; 22(2): 297–302
50. Teulings HE, Limpens J, Jansen SN, Zwinderman AH, Reitsma JB, Spuls PI, Luiten RM. Vitiligo-like depigmentation in patients with stage III-IV melanoma receiving immunotherapy and its association with survival: a systematic review and meta-analysis. J Clin Oncol 2015; 33(7): 773–781
51. Hua C, Boussemart L, Mateus C, Routier E, Boutros C, Cazenave H, Viollet R, Thomas M, Roy S, Benannoune N, Tomasic G, Soria JC, Champiat S, Texier M, Lanoy E, Robert C. Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab. JAMA Dermatol 2016; 152(1): 45–51
52. Freeman-Keller M, Kim Y,Cronin H, Richards A, Gibney G, Weber JS. Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. Clin Cancer Res 2016; 22(4): 886–894
53. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018; 378(2): 158–168
54. Xing K, Gu B, Zhang P, Wu X. Dexamethasone enhances programmed cell death 1 (PD-1) expression during T cell activation: an insight into the optimum application of glucocorticoids in anti-cancer therapy. BMC Immunol 2015; 16(1): 39
55. Draghi A, Borch TH, Radic HD, Chamberlain CA, Gokuldass A, Svane IM, Donia M. Differential effects of corticosteroids and anti-TNF on tumor-specific immune responses: implications for the management of irAEs. Int J Cancer 2019; 145(5): 1408–1413
56. Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, Wolchok JD, Clark JI, Sznol M, Logan TF, Richards J, Michener T, Balogh A, Heller KN, Hodi FS. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol 2012; 13(5): 459–465
57. Faje AT, Lawrence D, Flaherty K, Freedman C, Fadden R, Rubin K, Cohen J, Sullivan RJ. High-dose glucocorticoids for the treatment of ipilimumab-induced hypophysitis is associated with reduced survival in patients with melanoma. Cancer 2018; 124(18): 3706–

3714

58. Esfahani K, Miller WH Jr. Reversal of autoimmune toxicity and loss of tumor response by interleukin-17 blockade. N Engl J Med 2017; 376(20): 1989–1991
59. Weber JS, Hodi FS, Wolchok JD, Topalian SL, Schadendorf D, Larkin J, Sznol M, Long GV, Li H, Waxman IM, Jiang J, Robert C. Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. J Clin Oncol 2017; 35(7): 785–792
60. Arriola E, Wheater M, Karydis I, Thomas G, Ottensmeier C. Infliximab for IPILIMUMAB-related colitis—Letter. Clin Cancer Res 2015; 21(24): 5642–5643
61. Garant A, Guilbault C, Ekmekjian T, Greenwald Z, Murgoi P, Vuong T. Concomitant use of corticosteroids and immune checkpoint inhibitors in patients with hematologic or solid neoplasms: a systematic review. Crit Rev Oncol Hematol 2017; 120: 86–92
62. Hinrichs CS, Palmer DC, Rosenberg SA, Restifo NP. Glucocorticoids do not inhibit antitumor activity of activated $CD8^+$ T cells. J Immunother 2005; 28(6): 517–524
63. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, Chau I, Ernstoff MS, Gardner JM, Ginex P, Hallmeyer S, Holter Chakrabarty J, Leighl NB, Mammen JS, McDermott DF, Naing A, Nastoupil LJ, Phillips T, Porter LD, Puzanov I, Reichner CA, Santomasso BD, Seigel C, Spira A, Suarez-Almazor ME, Wang Y, Weber JS, Wolchok JD, Thompson JA; National Comprehensive Cancer Network. 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 2018; 36(17): 1714–1768
64. Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, Jordan K; ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (suppl_4): iv119–iv142
65. Khan SA, Pruitt SL, Xuan L, Gerber DE. Prevalence of autoimmune disease among patients with lung cancer: implications for immunotherapy treatment options. JAMA Oncol 2016; 2(11): 1507–1508
66. Johnson DB, Sullivan RJ, Ott PA, Carlino MS, Khushalani NI, Ye F, Guminski A, Puzanov I, Lawrence DP, Buchbinder EI, Mudigonda T, Spencer K, Bender C, Lee J, Kaufman HL, Menzies AM, Hassel JC, Mehnert JM, Sosman JA, Long GV, Clark JI. Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders. JAMA Oncol 2016; 2(2): 234–240
67. Menzies AM, Johnson DB, Ramanujam S, Atkinson VG, Wong ANM, Park JJ, McQuade JL, Shoushtari AN, Tsai KK, Eroglu Z, Klein O, Hassel JC, Sosman JA, Guminski A, Sullivan RJ, Ribas A, Carlino MS, Davies MA, Sandhu SK, Long GV. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. Ann Oncol 2017; 28 (2): 368–376
68. Abdel-Wahab N, Shah M, Lopez-Olivo MA, Suarez-Almazor ME. Use of immune checkpoint inhibitors in the treatment of patients with cancer and preexisting autoimmune disease: a systematic review. Ann Intern Med 2018; 168(2): 121–130
69. Cortellini A, Buti S, Santini D, Perrone F, Giusti R, Tiseo M, Bersanelli M, Michiara M, Grassadonia A, Brocco D, Tinari N, De Tursi M, Zoratto F, Veltri E, Marconcini R, Malorgio F, Garufi C, Russano M, Anesi C, Zeppola T, Filetti M, Marchetti P, Botticelli A, Antonini Cappellini GC, De Galitiis F, Vitale MG, Sabbatini R, Bracarda S, Berardi R, Rinaldi S, Tudini M, Silva RR, Pireddu A, Atzori F, Chiari R, Ricciuti B, Iacono D, Migliorino MR, Rossi A, Porzio G, Cannita K, Ciciarelli V, Fargnoli MC, Ascierto PA, Ficorella C. Clinical outcomes of patients with advanced cancer and pre-existing autoimmune diseases treated with anti-programmed death-1 immunotherapy: a real-world transverse study. Oncologist 2019; 24(6): e327–e337
70. Danlos FX, Voisin AL, Dyevre V, Michot JM, Routier E, Taillade L, Champiat S, Aspeslagh S, Haroche J, Albiges L, Massard C, Girard N, Dalle S, Besse B, Laghouati S, Soria JC, Mateus C, Robert C, Lanoy E, Marabelle A, Lambotte O. Safety and efficacy of anti-programmed death 1 antibodies in patients with cancer and pre-existing autoimmune or inflammatory disease. Eur J Cancer 2018; 91: 21–29
71. Johnson DB, Sullivan RJ, Menzies AM. Immune checkpoint inhibitors in challenging populations. Cancer 2017; 123(11): 1904–1911
72. Santini FC, Rizvi H, Plodkowski AJ, Ni A, Lacouture ME, Gambarin-Gelwan M, Wilkins O, Panora E, Halpenny DF, Long NM, Kris MG, Rudin CM, Chaft JE, Hellmann MD. Safety and efficacy of re-treating with immunotherapy after immune-related adverse events in patients with NSCLC. Cancer Immunol Res 2018; 6(9): 1093–1099
73. Simonaggio A, Michot JM, Voisin AL, Le Pavec J, Collins M, Lallart A, Cengizalp G, Vozy A, Laparra A, Varga A, Hollebecque A, Champiat S, Marabelle A, Massard C, Lambotte O. Evaluation of readministration of immune checkpoint inhibitors after immune-related adverse events in patients with cancer. JAMA Oncol 2019; 5 (9): 1310
74. Pollack MH, Betof A, Dearden H, Rapazzo K, Valentine I, Brohl AS, Ancell KK, Long GV, Menzies AM, Eroglu Z, Johnson DB, Shoushtari AN. Safety of resuming anti-PD-1 in patients with immune-related adverse events (irAEs) during combined anti-CTLA-4 and anti-PD1 in metastatic melanoma. Ann Oncol 2018; 29(1): 250–255