Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors

Khoja, L.; Day, D.; Wei-wu Chen, T.; Siu, L.l.; Hansen, A.r.

DOI:
10.1093/annonc/mdx286

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28: 2377–2385, 2017
doi:10.1093/annonc/mdx286
Published online 8 August 2017

REVIEW

Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review

L. Khoja[1,2†], D. Day[3,4,5†], T. Wei-Wu Chen[6,7,8], L. L. Siu[3,4] & A. R. Hansen[3,4*]

[1]Clinical Development Unit, Early Clinical Development, AstraZeneca UK plc, Melbourn Science Park, Melbourn, Hertfordshire; [2]Medical Oncology, Addenbrookes Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge Biomedical Campus, Cambridge, UK; [3]Drug Development Program, Division of Medical Oncology and Haematology, Princess Margaret Cancer Centre, Toronto; [4]Department of Medicine, University of Toronto, Toronto; [5]Ontario Institute for Cancer Research (OICR), Toronto, Canada; [6]Department of Oncology, National Taiwan University Hospital, Taipei; [7]National Taiwan University Cancer Center, Taipei; [8]Graduate Institute of Oncology, National Taiwan University College of Medicine, Taipei, Taiwan

Correspondence to: Dr Aaron R. Hansen, Division of Medical Oncology & Haematology, Princess Margaret Cancer Centre, University Health Network, 7-623, 700 University Avenue, Toronto, ON, Canada M5G2M9. Tel: +1-416-946-4501; Fax: +1-416-946-4563; E-mail: Aaron.Hansen@uhn.ca.

†The first two authors are joint first authors.

Background: Immune checkpoint inhibitor (ICI) monoclonal antibodies (mAbs) targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1) or its ligand (PD-L1) produce unique toxicity profiles. The objective of this review was to identify patterns and incidence of immune-related adverse events (irAE) based on tumour type and ICI class.

Methods: Medline, EMBASE and COCHRANE databases were searched to identify prospective monotherapy trials of ICIs from 2003 to November 2015. Paired reviewers selected studies for inclusion and extracted data. Odds ratio (OR), χ^2 tests and multivariable regression models were used to analyse for effect size and associations.

Results: We identified 48 trials (6938 patients), including 26 CTLA-4, 17 PD-1, 2 PD-L1 trials, and 3 studies tested both CTLA-4 and PD-1. Grade 3/4 irAE were more common with CTLA-4 mAbs compared with PD-1 (31% versus 10%). All grades colitis (OR 8.7, 95% CI 5.8–12.9), hypophysitis (OR 6.5, 95% CI 3.0–14.3) and rash (OR 2.0, 95% CI 1.8–2.3) were more frequent with CTLA-4 mAbs; whereas pneumonitis (OR 6.4, 95% CI 3.2–12.7), hypothyroidism (OR 4.3, 95% CI 2.9–6.3), arthralgia (OR 3.5, 95% CI 2.6–4.8) and vitiligo (OR 3.5, 95% CI 2.3–5.3) were more common with PD-1 mAbs. Comparison of irAE from the three most studied tumour types in PD-1 mAbs trials [melanoma ($n = 2048$), non-small-cell lung cancer ($n = 1030$) and renal cell carcinoma ($n = 573$)] showed melanoma patients had a higher frequency of gastrointestinal and skin irAE and lower frequency of pneumonitis.

Discussion: CTLA-4 and PD-1 mAbs have distinct irAE profiles. Different immune microenvironments may drive histology-specific irAE patterns. Other tumour-dependent irAE profiles may be identified as data emerge from ICI trials.

Key words: immune-related adverse events, immune checkpoint inhibitors

Introduction

Immune surveillance involves detection and elimination of cancer cells by the immune system [1]. A hallmark of cancer is a failure of surveillance that leads to tolerance, equilibrium and escape with the establishment of malignant disease. Examples of mechanisms of adaptive immune resistance include downregulation of major histocompatibility complex antigen expression, secretion of immunosuppressive cytokines and negative regulation of cytotoxic CD8+ T cells via checkpoint inhibition [2].

Impressive single agent activity of various immune checkpoint inhibitors (ICIs) has resulted in regulatory approval of several agents in a variety of solid tumour indications [3–9]. To enhance antitumour immune responses, combination strategies that include ICI with chemotherapy, targeted molecules and other immune-based therapies are being explored. Successful combination strategies will depend not only on antitumour immune response and survival outcomes, but also on the toxicity profile and tolerability.

Immune-related adverse events (irAE) from ICI, differ from toxicities caused by cytotoxic or molecularly targeted agents. The time to toxicity may be delayed and not follow a cyclical pattern as seen with conventional cytotoxics. Mechanisms of toxicity remain to be defined and may well be heterogeneous between patients even with the same agent. The over-reactive immune response may be driven by the removal of tolerance by ICI unmasking low-level self-reactive T cells, macrophage-mediated toxicity or production of antibodies from activated B cells [2]. These irAE are wide ranging in terms of organs affected and severity. Dermatologic, endocrine, neurologic, gastrointestinal, respiratory and musculoskeletal toxicities may occur alone or in constellation. The majority are self-limiting or resolve with immunosuppressants such as corticosteroids. Persistent irAE that do not resolve with corticosteroids require tumour necrosis factor α receptor antagonists such as infliximab, in the case of colitis or mycophenolate in the case of refractory hepatitis, an inhibitor of purine synthesis in T and B cells. Only a small minority of irAE do not respond to these immune modulators [10].

We hypothesize that the patterns, range and severity of irAE may differ between different ICI classes. A better understanding of irAE would enable better patient management of irAE. It would also inform the design of future ICI trials particularly where combinations of agents are being explored and where tolerability is key to their success. We conducted a systematic review of prospective monotherapy trials of ICI. The objective was to identify and contrast patterns and incidence of irAE based on ICI class and tumour type.

Materials and methods

Data sources and search strategy

A literature search was carried out using Medline, EMBASE and COCHRANE databases to identify prospective clinical trials of ICIs with single agent treatment arms from 2003 to 2015. Keywords included neoplasm, clinical trials, immune checkpoint, cytotoxic T-lymphocyte antigen (CTLA-4), programmed cell death protein-1 (PD-1), its ligand PD-L1 and specific ICI drug names. The search was conducted in November 2015.

Study selection

We defined inclusion and exclusion criteria a priori. Two sets of reviewers (LK and AH or LK and DD) evaluated the titles and abstracts of publications identified by the search strategy, and any publication thought to be potentially relevant was retrieved in full. The same set of two reviewers then assessed full publications for eligibility. Only prospective clinical trials in solid tumours with single agent treatment arms and those published in English were included. Reviewers were not blinded to study authors or outcomes. The decision to include a study for review was made by consensus between the reviewers (LK, AH and DD). The plan was that disagreements would be resolved by the third author, but none occurred.

Data extraction

Data were extracted by paired reviewers (LK and AH or LK and DD). Disagreements were resolved by consensus. Data extracted included study size, tumour type, phase of study, ICI class/agent and year of publication. All treatment-related AEs and AEs of special interest deemed to be possible immune-related toxicities were considered to be irAE. The incidence of all grade and grade $\geq$3 AE was collected. AEs that were not described as treatment related or possibly treatment related were excluded. Data were extracted from the main text and supplementary. Where combination studies were examined, data from the single agent arms only were extracted.

Study objectives

The primary objective was to determine the frequency of reported all grade and grade $\geq$3 irAE from ICI. Secondary aims included a comparison of irAE across ICI classes and tumour types. Associations between irAE and other study or treatment-related factors were also explored.

Statistical analysis

Baseline categorical variables were summarized using frequency and percentage, and continuous variables were summarized using mean or median. For each irAE, percentages were reported and used in all analyses to account for differences in trial size. Odds ratio (OR) with 95% confidence intervals (CI) were used to quantify the impact of different tumour types, ICI drugs, or drug doses to the incidence and severity of each irAE. The *P*-values were calculated using the χ^2 test and presented in contingency tables. A multivariate logistic regression model was used for analysis of the association between irAE and clinical variables. These variables assessed for confounding included tumour type, ICI drug and drug dose. To capture the detail irAE in different doses of ICI in each study, trials with multiple doses of ICIs were separated into multiple arms in the multivariate analysis model. A *P*-value <0.05 was considered statistically significant. No adjustments were made for multiple significance testing. All analyses were carried out by Microsoft Excel (2016) or SPSS 19 (Chicago, IL).

Results

Trial characteristics

The literature search identified a total of 5589 publications (Figure 1). Upon review 5473 publications were excluded leaving 116 ICI trials. This was supplemented by hand searches of meeting proceedings and references in published articles (6 studies). Of these 122 publications a total of 74 were excluded due to secondary reporting ($n=33$), combination studies ($n=36$), retreatment study with ICI ($n=1$), neoadjuvant or adjuvant studies ($n=2$) or incomplete reporting of irAE (2). Thus, the final total number of studies included in this review was 48 (supplementary Table S1, available at *Annals of Oncology* online).

The most studied tumour type was melanoma in 25 (52%) studies. Fifty-four percent of trials evaluated an anti-CTLA-4

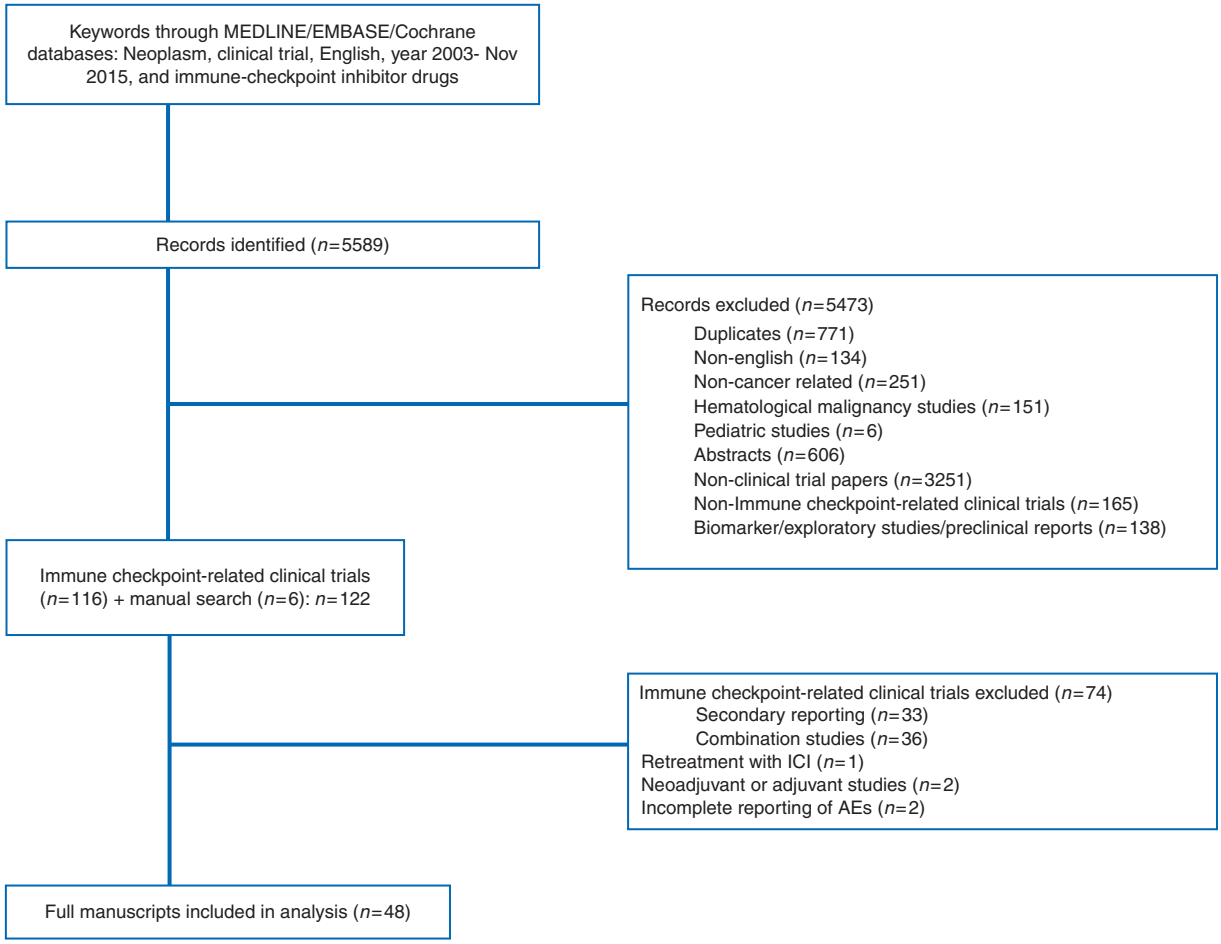

Figure 1. Consort diagram showing the selection process of studies included in the literature review.

agent [9, 11–35], 35% an anti-PD-1 agent [3, 4, 6–8, 36–47] and 4% an anti-PD-L1 ICI [48, 49]. Randomized studies that had a treatment arm that used single agent ICI comprised 6% of trials included [50–52]. Phase II studies predominated (40%, $n = 19$) with only 19% ($n = 9$) being phase III. Eighty-seven percent were conducted between 2009 and 2015. A total of 6938 patients were treated in 48 trials but 6869 were assessable for safety. Table 1 details the characteristics of the trials.

Incidence of all grade and grade ≥3 irAE. Examining irAE only, the most commonly reported irAE that occurred for all ICI were endocrine (thyroid disorders such as hypothyroidism and hyperthyroidism followed by pituitary and adrenal dysfunction), gastrointestinal (diarrhoea, colitis, nausea), lung (pneumonitis), skin (rash, pruritus and vitiligo) and musculoskeletal (arthralgia and myalgia). Constitutional symptoms of fatigue, pyrexia and anorexia were also common. Supplementary Table S2, available at *Annals of Oncology* online, reports the percentages of these common toxicities per class of ICI agent.

Incidence of irAE according to ICI class. Grade ≥3 irAE were more common with CTLA-4 compared with PD-1 ICI (31% versus 10%; OR 4.0, 95% CI 3.5–4.6). All grades colitis (OR 8.7, 95% CI 5.8–12.9), hypophysitis (OR 6.5, 95% CI 3.0–14.3) and rash (OR 2.0, 95% CI 1.8–2.3) were more frequent with CTLA-4 ICI; whereas pneumonitis (OR 6.4, 95% CI 3.2–12.7), hypothyroidism (OR 4.3, 95% CI 2.9–6.3), arthralgia (OR 3.5, 95% CI 2.6–4.8) and vitiligo (OR 3.5, 95% CI 2.3–5.3) were more common with PD-1 monoclonal antibodies (Figure 2).

Incidence of irAE according to histology. Comparison of irAE from the three most studied tumour types in PD-1 ICI trials [melanoma ($n = 2048$), non-small-cell lung cancer (NSCLC, $n = 1030$) and renal cell carcinoma (RCC, $n = 573$)] showed that melanoma patients had a higher frequency of gastrointestinal and skin irAE; and lower frequency of pneumonitis compared with NSCLC. Arthritis and myalgia were more common in melanoma patients compared with RCC where pneumonitis and dyspnoea were more prevalent. These results are in Table 2 and Figures 3 and 4. CTLA-4 mAb trials were typically in melanoma or mixed tumour types; hence, a similar analysis comparing histology-specific irAE profiles was not feasible.

Differences in incidence of irAE according to ICI dose level. Where possible, the rates of commonly reported toxicities for each dose level of an individual ICI agent were evaluated and compared (supplementary Table S3, available at *Annals of Oncology* online). Although a proportional increase in the frequency of irAE was observed with an increase in dose level, the only irAE that demonstrated a statistically significant association with dose was

Table 1. Characteristics of the 48 immune checkpoint inhibitor clinical trials

Study characteristic	Trials (*N*=48)	
	No.	%
ICI target(s)		
CTLA-4	26	54
PD-1/PD-L1	17/2	35/4
CTLA-4/PD-1[a]	3	6
Tumour site(s)		
Melanoma	24	50
Lung	4	8
Kidney	3	6
Prostate	2	4
mesothelioma	2	4
Mixed tumour types	7	15
Others (bladder, colorectal, gastro-oesophageal, liver, ovarian, pancreas)	6	13
Phase of clinical trials		
Phase I	14	29
Phase I/II	4	8
Phase II	21	44
Phase III	9	19
CTCAE version used for AE-reporting		
CTCAE 2.0	4	8
CTCAE 3.0	19	40
CTCAE 4.0	19	40
Unknown	6	13
Randomized study		
Yes	16	23
No	32	77
Sources of trial funding		
Industry	38	79
Non-industry	8	17
Unknown	2	4
Year of publication		
2003–2008	6	13
2009–2015	42	87
Region in which trial was conducted		
Multi-national	20	40
North America	21	46
Europe	5	10
Japan	2	4
Trial patient number recruited per single agent arm		
Median	70	
Range	9–555	

[a]Studies including both anti-CTLA-4 and anti-PD-1 agents, as single agents or combinations. Only single agent treatment arms were included in this analysis.

pneumonitis with nivolumab treatment; 10 versus 3 mg (HR 2.76, 95% CI 1.23–6.18). These comparisons are reported in supplementary Table S4, available at *Annals of Oncology* online.

Multivariable analysis. A multivariate logistic regression model for the risk of colitis or pneumonitis occurrences was derived using tumour type (melanoma versus non-melanoma), ICI class (CTLA4 versus PD-1) and dose [equivalent or lower than recommended phase II dose (RP2D) versus higher than RP2D dose]. Only ICI class was significantly associated with a risk of irAE: CTLA-4 agents had increased risk for the development of colitis compared with PD-1 agents (OR 3.12, 95% CI 1.06–9.24, $P = 0.04$) and lower risk of pneumonitis occurrence when compared with PD-1 agents (OR 0.03, 95% CI, 0.01–0.15, $P < 0.001$). Results of the multivariable analysis are outlined in Table 3.

Incidence of irAE leading to dose discontinuation and deaths. Dose discontinuation due to irAE was not consistently reported nor described in the included clinical trials. When reported, discontinuation rates ranged between 3% and 12% in anti-PD-1 trials and between 3% and 25% in anti-CTLA-4 trials. The most common irAE leading to discontinuation was diarrhoea/colitis. Supplementary Table S5, available at *Annals of Oncology* online, reports irAE leading to death. AEs leading to death were exceedingly rare for anti-PD-1 agents (pembrolizumab, 0.1%; nivolumab 0.3%) and most often secondary to pneumonitis. In the case of anti-CTLA-4 clinical trials, death were more likely secondary to gastrointestinal events including diarrhoea, colitis and colonic perforation (9/29, 31% of grade 5 events).

Discussion

Our study has demonstrated several important new aspects of irAE that have not been reported before. We have shown that different tumour histologies (melanoma, renal cell and NSCLC) have a different irAE profile when treated with PD-1 inhibitors. While intriguing, such a finding should not be a surprise given that antitumour immune responses differ across patients with different tumour types treated with the same ICI. Currently the reasons for this observation are not clear. The tumour microenvironment (TME), immune infiltrate, adaptive immune response and neoantigen formation may be influenced by histology and is thus one potential explanation for different toxicities [53–55]. It is not known if the site of metastasis also influences the irAE pattern, because this level of detail was not reported in the reviewed studies. Furthermore, comorbidities such as chronic obstructive airways disease and prior therapies including lung irradiation in patients with NSCLC may have influenced the higher rates of pneumonitis in these patients when treated with PD-1 inhibitors when compared with patients with melanoma. This does not explain the higher incidence of pneumonitis also observed in patients with renal cell cancer. This observation raises the interesting possibility that such differential effects may be seen in other tumour types and across different ICI classes.

Anti-PD-1/PD-L1 mAbs gained FDA approval over the past year in both cisplatin-refractory head and neck cancers and urothelial carcinomas. Interestingly, first line approval of pembrolizumab in NSCLC is limited to PD-L1 positivity defined by immunohistochemical staining of at least 50% of cells and non-ALK, non-EGFR mutant patients [56]. Translational research efforts in these cancers and in different treatment settings may elucidate differences in the TME, the effect of tumour heterogeneity both on the TME and the immune response [57], and the effect of other treatment modalities on the TME. All of these factors may affect subsequent toxicity. The identification of specific toxicity profiles related to different treatment settings will require concerted efforts and large pooled

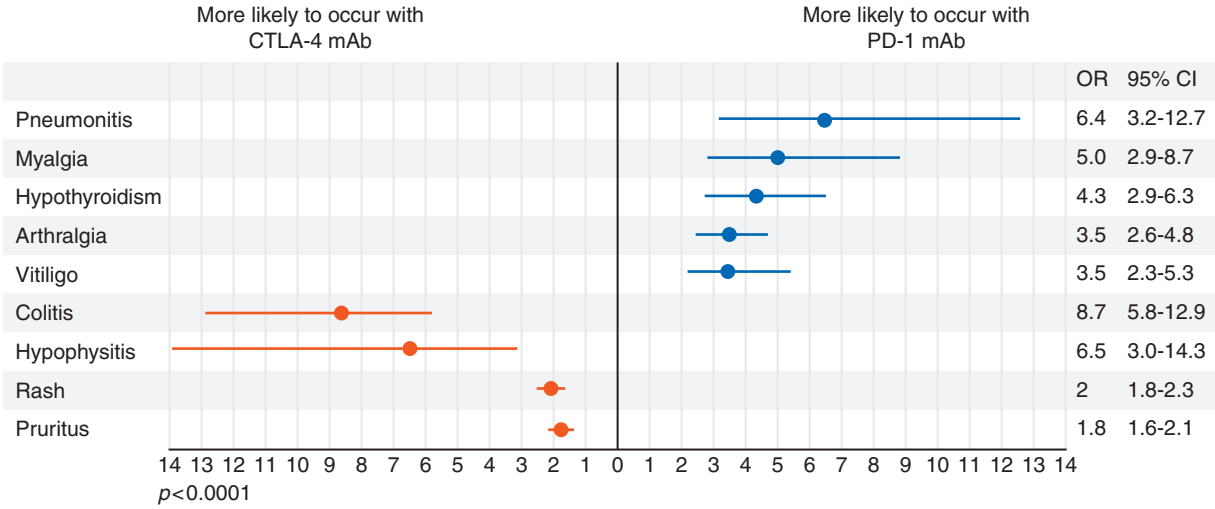

Figure 2. The odds ratio (OR) of different immune-related adverse events (all grades) comparing PD-1/PD-L1 versus CTLA-4 immune checkpoint inhibitors.

Table 2. Comparison of the incidence of irAE between tumour types for patients receiving anti PD-1 agent

irAE	Melanoma versus NSCLC OR (95% CI)	*P* value	Melanoma versus RCC OR (95% CI)	*P* value
Colitis	4.2 (1.3–14.0)	0.01	NA (no event for RCC)	
Diarrhoea	1.9 (1.5–2.5)	<0.001	1.3 (1.1–1.8)	0.04
Pruritus	2.4 (1.9–3.1)	<0.001	1.5 (1.2–2.0)	0.003
Rash	1.8 (1.4–2.3)	<0.001	1.6 (1.2–2.1)	0.002
Pneumonitis	0.4 (0.3–0.7)	<0.001	0.3 (0.2–0.6)	<0.001

datasets for analysis. An added layer of complexity to the interaction between TME and tumour cells is the individual patient's immune profile. To explore this interaction immunopharmacogenomics combines analysis of the immune response with an individual's pharmacologic responses based on genetic characteristics, somatic mutations and gene expression profiles. The analysis of T-cell and B-cell clonality within a patient's tumour, the relationship to response and toxicity along with other factors such as the microbiome and crucially the study of autoimmunity will ultimately aide personalized immune-oncology therapy [58]. As an example, single nucleotide polymorphisms in the PD-1 gene have been reported to be associated with susceptibility to rheumatoid arthritis [59, 60] and thus may predispose these patients to immune mediated arthralgia.

Overall, our results did not show a dose-dependent increase in irAE severity or percentage. The majority of irAE included in our analysis were from recent trials and it may be that investigators are more aware of and aggressive in their management of irAE. Thus, earlier detection and wider use of steroids may have affected the rate of grade 3/4 irAE. It should be noted that a recently reported phase 3 trial comparing 3 versus 10 mg/kg ipilimumab in metastatic melanoma did show an ~50% increase in the rates of grade 3–5 irAE with the higher dose and an increased death rate secondary to toxicity [61]. Trials to date (including randomized trials) with various doses of anti-PD-1 antibodies have not shown this difference for these agents [3, 4, 7, 52]. We also analysed specific commonly occurring irAE, in particular colitis and pneumonitis to determine whether any factors could predict the occurrence of these side-effects. These irAE can be fatal and thus identifying high-risk patients would be informative. However, apart from PD-1 therapy being associated with pneumonitis, our multivariable analysis did not reveal any predictors of pneumonitis or colitis.

In addition, our review has confirmed observations previously made. Trials with ICI agents have a wide variety of irAE with the endocrine, skin and gastrointestinal systems being most commonly affected [62, 63]. The irAE pattern is different across ICI class [62, 63]. This could be driven by different immune cell activation that can occur with ICI of different class. Furthermore, tissue-related factors may also contribute to irAE, for example CTLA-4 expression is found in the pituitary accounting for the greater incidence of hypophysitis with CTLA-4 mAbs [64]. The greater incidence of pneumonitis with therapies targeting the anti-PD-1 axis may be due to activation of macrophages but the pattern behind other differences is not clear [65]. Interestingly, initial protocols of ICI trials precluded patients who had experienced grade ≥3 toxicity with a previous ICI because of the concern that patients would be at higher risk of irAE on the subsequent ICI. However, the experience of patients off trial has shown that patients can switch (due to toxicity) from one ICI to another without further irAE [66]. Patterns of toxicity with particular ICI class/agents in relation to duration of treatment have been examined [62, 67–69]. For example, skin toxicity tends to occur early with both CTLA-4 and anti-PD-1 mAbs. Moreover, it does appear that the likelihood of toxicity falls but does not disappear, the longer a patient has been treated. We could not examine the multivariate effect of median duration of treatment on toxicity, as this was not universally reported. Moreover, due to the small number of PD-L1 studies it was not possible to do an adequate comparison between toxicity profiles of anti-PD-1 and anti-PD-L1 agents. Given the reported patterns of expression of

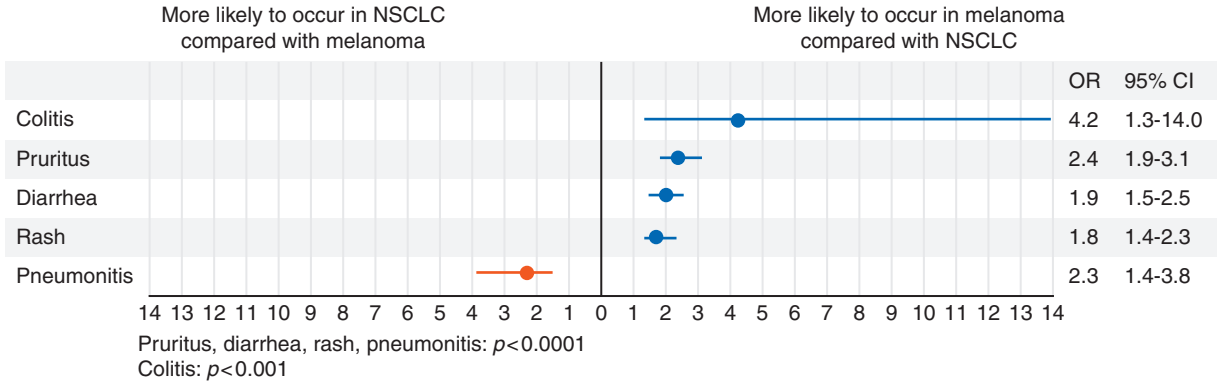

Figure 3. The odds ratio (OR) of different immune-related adverse events (all grades) comparing melanoma and non-small cell lung cancer (NSCLC) anti-PD-1 immune checkpoint inhibitor studies.

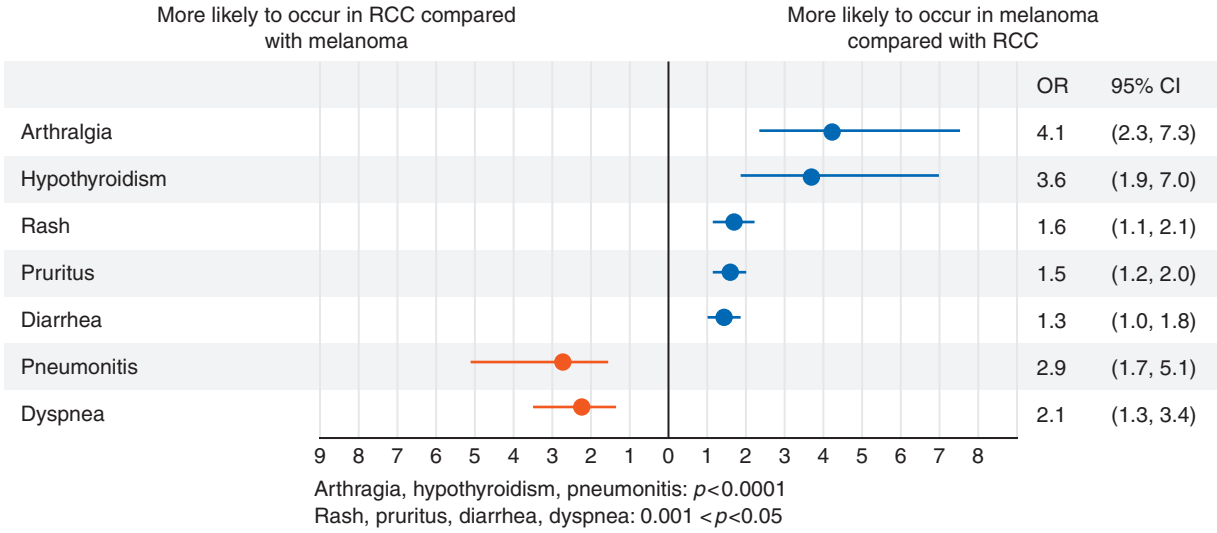

Figure 4. The odds ratio (OR) of different immune-related adverse events (all grades) comparing melanoma and renal cell carcinoma (RCC) anti-PD-1 immune checkpoint inhibitor studies.

Table 3. Risk factors correlated with pneumonitis and colitis incidence in multivariate model

	Colitis OR (95% CI)	Pneumonitis OR (95% CI)
Drug type (CTLA-4 versus PD-1/PD-L1)	3.12 (1.06–9.24) $P = 0.04$	0.03 (0.007–0.148) $P < 0.001$
Tumour type (Melanoma versus non-melanoma)	0.85 (0.28–2.57) $P = 0.78$	0.51 (0.11–2.41) $P = 0.40$
Higher than RP2D versus equivalent or lower than RP2D	1.74(0.51–5.94) $P = 0.38$	2.79 (0.52–15.04) $P = 0.23$

these targets, it could be hypothesized that anti-PD-L1 agents could be associated with less toxicity because of PD-L2 sparing, which preserves normal immune homeostasis.

Other published meta-analyses on irAE with ICI have examined patterns and incidence of pneumonitis specifically. Our findings are consistent with these reports. For example, in one report [70] of 6360 patients, the incidence of pneumonitis was increased in NSCLC and RCC with an overall incidence of 2.9% for all grades and 1.5% for grade 3 or above. In another study of 4496 patients [71], the incidence of all grade pneumonitis was increased in RCC compared with melanoma, although not for events of grade 3 and above. When comparing melanoma and NSCLC, the incidence was higher in NSCLC for both all grade and grade 3 or above events. In this study, the overall incidence of pneumonitis was 2.7% for all grades and 0.8% of grade 3 or above across all histologies.

Deaths due to irAE are not common; however, it is difficult to determine how frequently irAE lead to discontinuation of treatment. Some toxicities such as skin-related rash or itch resolve completely with appropriate management whilst others such as endocrine disorders require replacement treatment long term. Specific management guidelines exist for ICI agents, although such recommendations have not been tested in a prospective randomized setting and represent consensus expert opinion [10]. Corticosteroids remain the initial immunosuppressant of choice and are administered either intravenously or orally depending on the severity of the irAE. On improvement or resolution of the

irAE, the steroids are slowly tapered over weeks to limit relapse of the side-effect. ICI dosing is also delayed or skipped during the occurrence of an irAE or while patients are receiving steroid therapy above an equivalent dose of prednisone 10 mg daily. Re-treating patients with the same ICI after resolution of an irAE should account for the system affected and the severity of the event. Patients with skin irAE or endocrinopathies on stable doses of hormone replacement may be re-treated safely. However, re-challenging patients with life threatening irAE, such pneumonitis or colitis, probably should be avoided for safety reasons. As combinations of ICI agents with immune or non-immune therapies are increasingly being tested in the clinic, it is anticipated that severe, unusual or unexpected toxicities could occur, and detailed reporting in the literature is crucial to help understand and manage them.

Our review included studies over a 12-year period and has several limitations. We did not have individual patient data to analyse and thus our review is subject to the quality of reporting of irAE. This has previously been shown to be often missing important details about toxicities [72]. Moreover trials vary in reporting all AEs to reporting only those that occur above a certain percentage ranging between $\geq$1% and 5–10%. Experience gained in defining and managing these toxicities during earlier trials has led to earlier recognition and better management of irAE in subsequent trials and thus potentially has decreased the frequency of severe events. The diagnosis of colitis may also differ between protocols or treatment centres where biopsy is required by some physicians. While our analysis involved just under 7000 patients, caution should be taken in relation to extrapolating these results to other ICI or tumour types given the limited number of studies included. Previously, it has been described that the severity and frequency of toxicities are usually worse in a real world population when compared with the clinical trial patient sample [73]. Hence, we may have underestimated the true differences of irAE profiles between ICI class or tumour histology. Different versions of CTCAE may have been used across studies although this is unlikely to have had a significant impact on our findings given that latter versions tended to include more descriptors and with better harmonization with Medical Dictionary for Regulatory Activities (MedDRA) terminology. There is for example no major difference between the grading for pneumonitis and colitis in version 2 compared with version 4. A further limitation in the field as a whole is the definition of an irAE. There is currently no standardized methodology to determine whether an AE is an irAE or an AE of other aetiology. Whilst particular toxicities have emerged through trial experience as being associated with ICI, such as colitis with CTLA-4 mAbs, others such as arthritis are yet to be defined clearly [74]. We reported side-effects as irAE if they were reported as such in the study or if they were reported as a toxicity of special interest. Typically, the diagnostic tests used to define irAE were not provided by the studies. Thus we cannot confirm if for example, inflammatory arthritis met specific histological/cytological and radiographic definitions [74]. Actual frequencies of irAE would be affected by failure to recognize symptoms that were irAE (under reporting) or if symptoms were incorrectly defined as an irAE (over reporting).

This comprehensive review has described several important new insights and confirmed previous observations about irAE. In light of this study, we should be mindful that different tumour types may have different irAE patterns when treated with the same ICI and this may be more evident when these agents are utilized in real world patients. Clearly, a more thorough understanding of the mechanisms of irAE is needed, which may lead to the identification of biomarkers to predict the occurrence of toxicity in patients or predict those who have irAE that are unlikely to respond to corticosteroids. These markers could have the potential to impact irAE management. In addition, efforts should be made to identify clinical factors such as prior treatment or concomitant comorbidities that could be associated with a higher risk of irAE. Coupled with better reporting of irAE from clinical trials, quality of life data must also be captured ideally by a tool that has been tailored to patients receiving ICI therapy; the endeavour to create such a tool is currently being undertaken by our group. A better understanding of irAE can inform patient management and enhance the evaluation of ICI treatments.

Funding

None declared.

Disclosure

There are no relevant disclosures from any of the authors relating to this work. For transparency LK is currently an employee of Astrazeneca (AZ) plc but this work is independent of AZ.

References

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144: 646–674.
2. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity 2013; 39: 1–10.
3. Garon EB, Rizvi NA, Hui R et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015; 372: 2018–2028.
4. Robert C, Ribas A, Wolchok JD et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet 2014; 384: 1109–1117.
5. Robert C, Schachter J, Long GV et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015; 372: 2521–2532.
6. Weber JS, D'Angelo SP, Minor D et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015; 16: 375–384.
7. Hamid O, Robert C, Daud A et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med 2013; 369: 134–144.
8. Robert C, Long GV, Brady B et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015; 372: 320–330.
9. Hodi FS, O'Day SJ, McDermott DF et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363: 711–723.
10. Gangadhar TC, Vonderheide RH. Mitigating the toxic effects of anticancer immunotherapy. Nat Rev Clin Oncol 2014; 11: 91–99.
11. Calabro L, Morra A, Fonsatti E et al. Tremelimumab for patients with chemotherapy-resistant advanced malignant mesothelioma: an open-label, single-arm, phase 2 trial. Lancet Oncol 2013; 14: 1104–1111.
12. Calabro L, Morra A, Fonsatti E et al. Efficacy and safety of an intensified schedule of tremelimumab for chemotherapy-resistant malignant mesothelioma: an open-label, single-arm, phase 2 study. Lancet Respir Med 2015; 3: 301–309.
13. Camacho LH, Antonia S, Sosman J et al. Phase I/II trial of tremelimumab in patients with metastatic melanoma. J Clin Oncol 2009; 27: 1075–1081.
14. Chung KY, Gore I, Fong L 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: 3485–3490.
15. Hersh EM, O'Day SJ, Powderly J et al. A phase II multicenter study of ipilimumab with or without dacarbazine in chemotherapy-naive patients with advanced melanoma. Invest New Drugs 2011; 29: 489–498.
16. Hodi FS, Mihm MC, Soiffer RJ et al. Biologic activity of cytotoxic T lymphocyte-associated antigen 4 antibody blockade in previously vaccinated metastatic melanoma and ovarian carcinoma patients. Proc Natl Acad Sci USA 2003; 100: 4712–4717.
17. Joshua AM, Monzon JG, Mihalcioiu C et al. A phase 2 study of tremelimumab in patients with advanced uveal melanoma. Melanoma Res 2015; 25: 342–347.
18. Kirkwood JM, Lorigan P, Hersey P et al. Phase II trial of tremelimumab (CP-675,206) in patients with advanced refractory or relapsed melanoma. Clin Cancer Res 2010; 16: 1042–1048.
19. Maker AV, Yang JC, Sherry RM et al. Intrapatient dose escalation of anti-CTLA-4 antibody in patients with metastatic melanoma. J Immunother 2006; 29: 455–463.
20. Margolin K, Ernstoff MS, Hamid O et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol 2012; 13: 459–465.
21. O'Day SJ, Maio M, Chiarion-Sileni V 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: 1712–1717.
22. Ralph C, Elkord E, Burt DJ 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: 1662–1672.
23. Ribas A, Camacho LH, Lopez-Berestein G et al. Antitumor activity in melanoma and anti-self responses in a phase I trial with the anti-cytotoxic T lymphocyte-associated antigen 4 monoclonal antibody CP-675,206. J Clin Oncol 2005; 23: 8968–8977.
24. Ribas A, Chesney JA, Gordon MS 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.
25. Ribas A, Kefford R, Marshall MA et al. Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. J Clin Oncol 2013; 31: 616–622.
26. Royal RE, Levy C, Turner K et al. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother 2010; 33: 828–833.
27. Sangro B, Gomez-Martin C, de la Mata M et al. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. J Hepatol 2013; 59: 81–88.
28. Slovin SF, Higano CS, Hamid O 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: 1813–1821.
29. Small EJ, Tchekmedyian NS, Rini BI et al. A pilot trial of CTLA-4 blockade with human anti-CTLA-4 in patients with hormone-refractory prostate cancer. Clin Cancer Res 2007; 13: 1810–1815.
30. Weber J, Hamid O, Amin A 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.
31. Weber JS, O'Day S, Urba W et al. Phase I/II study of ipilimumab for patients with metastatic melanoma. J Clin Oncol 2008; 26: 5950–5956.
32. Wolchok JD, Neyns B, Linette G et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol 2010; 11: 155–164.
33. Yamazaki N, Kiyohara Y, Uhara H et al. Phase II study of ipilimumab monotherapy in Japanese patients with advanced melanoma. Cancer Chemother Pharmacol 2015; 76: 997–1004.
34. Yang JC, Hughes M, Kammula U et al. Ipilimumab (anti-CTLA4 antibody) causes regression of metastatic renal cell cancer associated with enteritis and hypophysitis. J Immunother 2007; 30: 825–830.
35. Zimmer L, Vaubel J, Mohr P et al. Phase II DeCOG-study of ipilimumab in pretreated and treatment-naive patients with metastatic uveal melanoma. PLoS ONE 2015; 10: e0118564.
36. Borghaei H, Paz-Ares L, Horn L et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015; 373: 1627–1639.
37. Brahmer J, Reckamp KL, Baas P et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015; 373: 123–135.
38. Brahmer JR, Drake CG, Wollner I 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: 3167–3175.
39. Hamanishi J, Mandai M, Ikeda 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: 4015–4022.
40. Le DT, Uram JN, Wang H et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015; 372: 2509–2520.
41. Motzer RJ, Escudier B, McDermott DF et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015; 373: 1803–1813.
42. Motzer RJ, Rini BI, McDermott DF et al. Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial. J Clin Oncol 2015; 33: 1430–1437.
43. Patnaik A, Kang SP, Rasco D 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: 4286–4293.
44. Ribas A, Puzanov I, Dummer R et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol 2015; 16: 908–918.
45. Rizvi NA, Mazieres J, Planchard D et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol 2015; 16: 257–265.
46. Topalian SL, Hodi FS, Brahmer JR et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012; 366: 2443–2454.
47. Weber JS, Kudchadkar RR, Yu B et al. Safety, efficacy, and biomarkers of nivolumab with vaccine in ipilimumab-refractory or -naive melanoma. J Clin Oncol 2013; 31: 4311–4318.
48. Brahmer JR, Tykodi SS, Chow LQ et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012; 366: 2455–2465.
49. Powles T, Eder JP, Fine GD et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 2014; 515: 558–562.
50. Larkin J, Chiarion-Sileni V, Gonzalez R et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015; 373: 23–34.
51. Postow MA, Chesney J, Pavlick AC et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015; 372: 2006–2017.
52. Robert C, Schachter J, Long GV et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015; 372: 2521–32.
53. Tumeh PC, Harview CL, Yearley JH et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature 2014; 515: 568–571.
54. Tumeh PC, Rosenblum M, Handley N et al. Abstract 2857: metastatic site and response to pembrolizumab (anti-PD1 antibody) in melanoma. Cancer Res 2015; 75: 2857.
55. Khoja L, Kibiro M, Metser U et al. Patterns of response to anti-PD-1 treatment: an exploratory comparison of four radiological response criteria and associations with overall survival in metastatic melanoma patients. Br J Cancer 2016; 115: 1186–1192.
56. Reck M, Rodriguez-Abreu D, Robinson AG et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016; 375: 1823–1833.
57. McGranahan N, Furness AJ, Rosenthal R et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science 2016; 351: 1463–1469.

58. June CH, Warshauer JT, Bluestone JA. Is autoimmunity the Achilles' heel of cancer immunotherapy? Nat Med 2017; 23: 540–547.
59. Prokunina L, Padyukov L, Bennet A et al. Association of the PD-1.3A allele of the PDCD1 gene in patients with rheumatoid arthritis negative for rheumatoid factor and the shared epitope. Arthritis Rheum 2004; 50: 1770–1773.
60. Kong EK, Prokunina-Olsson L, Wong WH et al. A new haplotype of PDCD1 is associated with rheumatoid arthritis in Hong Kong Chinese. Arthritis Rheum 2005; 52: 1058–1062.
61. Ascierto PA, Del Vecchio M, Robert C et al. Overall survival (OS) and safety results from a phase 3 trial of ipilimumab (IPI) at 3 mg/kg vs 10 mg/kg in patients with metastatic melanoma (MEL). Ann Oncol 2016; 27: 379–400.
62. Tarhini A. Immune-mediated adverse events associated with ipilimumab ctla-4 blockade therapy: the underlying mechanisms and clinical management. Scientifica (Cairo). 2013; 2013: 857519.
63. Freeman-Keller M, Kim Y, Cronin H et al. Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. Clin Cancer Res 2016; 22: 886–894.
64. Iwama S, De Remigis A, Callahan MK et al. Pituitary expression of CTLA-4 mediates hypophysitis secondary to administration of CTLA-4 blocking antibody. Sci Transl Med 2014; 6: 230ra245.
65. Mitchem JB, Brennan DJ, Knolhoff BL et al. Targeting tumor-infiltrating macrophages decreases tumor-initiating cells, relieves immunosuppression, and improves chemotherapeutic responses. Cancer Res 2013; 73: 1128–1141.
66. Aya F, Fernandez-Martinez A, Gaba L et al. Pembrolizumab in a BRAF-mutant metastatic melanoma patient following a severe immune-related adverse event with ipilimumab. Immunotherapy 2016; 8: 687–692.
67. Weber JS, Hodi FS, Wolchok JD et al. Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. J Clin Oncol 2017; 35: 785–792.
68. Weber JS, Dummer R, de Pril V et al. 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: 1675–1682.
69. Naidoo J, Wang X, Woo KM et al. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. J Clin Oncol 2017; 35: 709–717.
70. Wu J, Hong D, Zhang X et al. PD-1 inhibitors increase the incidence and risk of pneumonitis in cancer patients in a dose-independent manner: a meta-analysis. Sci Rep. 2017; 7: 44173.
71. Nishino M, Giobbie-Hurder A, Hatabu H et al. Incidence of programmed cell death 1 inhibitor-related pneumonitis in patients with advanced cancer: a systematic review and meta-analysis. JAMA Oncol 2016; 2: 1607–1616.
72. Chen TW, Razak AR, Bedard PL et al. A systematic review of immune-related adverse event reporting in clinical trials of immune checkpoint inhibitors. Ann Oncol 2015; 26: 1824–1829.
73. Templeton AJ, Vera-Badillo FE, Wang L et al. Translating clinical trials to clinical practice: outcomes of men with metastatic castration resistant prostate cancer treated with docetaxel and prednisone in and out of clinical trials. Ann Oncol 2013; 24: 2972–2977.
74. Cappelli LC, Gutierrez AK, Baer AN et al. Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab. Ann Rheum Dis 2017; 76: 43–50.