Research Article

Cancer Immunology Research

Comprehensive Meta-analysis of Key Immune-Related Adverse Events from CTLA-4 and PD-1/PD-L1 Inhibitors in Cancer Patients

Guillermo De Velasco[1,2], Youjin Je[3], Dominick Bossé[1], Mark M. Awad[1], Patrick A. Ott[1], Raphael B. Moreira[1], Fabio Schutz[4], Joaquim Bellmunt[1], Guru P. Sonpavde[5], F. Stephen Hodi[1], and Toni K. Choueiri[1]

Abstract

Immune-related adverse events (irAE) have been described with immune checkpoint inhibitors (ICI), but the incidence and relative risk (RR) of irAEs associated with these drugs remains unclear. We selected five key irAEs from treatments with approved cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), programmed cell death 1 (PD-1), and programmed death ligand 1 (PD-L1) inhibitors (ipilimumab, nivolumab, or pembrolizumab, and atezolizumab, respectively) to better characterize their safety profile. We performed a meta-analysis of randomized phase II/III immunotherapy trials, with non-ICI control arms, conducted between 1996 and 2016. We calculated the incidence and RR of selected all-grade and high-grade gastrointestinal, liver, skin, endocrine, and pulmonary irAEs across the trials using random-effect models. Twenty-one trials were included, totaling 11,454 patients, of whom 6,528 received an ICI (nivolumab, 1,534; pembrolizumab, 1,522; atezolizumab, 751; and ipilimumab, 2,721) and 4,926 had not. Compared with non-ICI arms, ICIs were associated with more all-grade colitis (RR 7.66, $P < 0.001$), aspartate aminotransferase (AST) elevation (RR 1.80; $P = 0.020$), rash (RR 2.50; $P = 0.001$), hypothyroidism (RR 6.81; $P < 0.001$), and pneumonitis (RR 4.14; $P = 0.012$). Rates of high-grade colitis (RR 5.85; $P < 0.001$) and AST elevation (RR 2.79; $P = 0.014$) were higher in the ICI arms. Ipilimumab was associated with a higher risk of all-grade rash ($P = 0.006$) and high-grade colitis ($P = 0.021$) compared with PD-1/PD-L1 ICIs. Incidence of fatal irAE was < 1%. This meta-analysis offers substantial evidence that ICIs are associated with a small but significant increase in risk of selected all-grade irAEs and high-grade gastrointestinal and liver toxicities. Although fatal irAEs remain rare, AEs should be recognized promptly as early interventions may alleviate future complications. *Cancer Immunol Res; 5(4); 312–8. ©2017 AACR.*

Introduction

Immune checkpoint inhibitors (ICI) have already been approved for use in melanoma, non–small cell lung cancer (NSCLC), renal cell carcinoma (RCC), bladder cancer, and squamous cell carcinoma of the head and neck (SCCHN; Supplementary Table S1), with likely more approvals coming for an increasing number of tumors types in the near future. Indeed, these novel immune-modulating molecules have resulted in major advances in the treatment of these tumors and they have shown promising activity against many other tumor types such as Merkel-cell carcinoma, Hodgkin lymphoma, and mismatch repair–deficient tumors (1–5).

Ipilimumab was the first inhibitor of cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) approved by the FDA, whereas nivolumab and pembrolizumab were the first two programmed cell-death 1 (PD-1) inhibitors to be approved (6). Atezolizumab is the first programmed death ligand 1 (PD-L1) inhibitor approved by the FDA (7). These drugs are also being assessed in many different solid and hematologic malignancies, including registration trials enrolling thousands of patients. Compared with cytotoxic or targeted agents, ICIs have a distinct toxicity profile (8). They can induce infiltration of immune cells into normal tissues, which leads to autoimmune-like toxicities different than traditional chemotherapy or targeted therapies (9, 10). Almost every organ may be affected with immune-related adverse events (irAE), including the skin, bowels, liver, kidneys, eyes, endocrine tissues, and even the central nervous system (11). Dermatological and gastrointestinal events are the most commonly reported irAEs (8, 10, 11), whereas less common toxicities include endocrine, hepatic, and neurological events (12, 13). A pooled analysis of nearly 1,500 patients with melanoma treated with ipilimumab showed that the incidence of irAEs could be as high as 65% (14, 15). Although infrequent, severe and even life-threatening irAEs such as immune-related pneumonitis and colitis may occur with these drugs (16, 17). In this report, we conducted a systematic review and meta-analysis to investigate the safety

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts. [2]Department of Medical Oncology, University Hospital 12 de Octubre, Madrid, Spain. [3]Department of Food and Nutrition, College of Human Ecology, Kyung Hee University, Seoul, Korea. [4]Department of Medical Oncology, Hospital São José, Beneficência Portuguesa de São Paulo, Brazil. [5]Division of Oncology and Hematology, University of Alabama, Birmingham, Alabama.

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Corresponding Author: Toni K. Choueiri, Dana-Farber Cancer Institute, 450 Brookline Avenue (DANA 1230), Boston, MA 02215. Phone: 617-632-5456; Fax: 617-632-2165; E-mail: toni_choueiri@dfci.harvard.edu

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profiles of ipilimumab, nivolumab, pembrolizumab, and atezolizumab, and identify the incidence and relative risk (RR) of five irAEs of interest.

Patients and Methods

Literature search and inclusion criteria

We identified all randomized clinical trials that compared ipilimumab (Yervoy), nivolumab (Opdivo), pembrolizumab (Keytruda), or atezolizumab (Tecentric) with a nonimmunotherapy control arm. An independent review of PubMed and Embase from January 1, 1996, to December 15, 2016, was conducted. Keywords included in the search were "ipilimumab," "nivolumab," "pembrolizumab," "atezolizumab," and studies were limited to randomized controlled trials in humans and published in English. Abstract proceedings and virtual meeting presentations containing the same terms from the American Society of Clinical Oncology and the European Society of Medical Oncology conferences held between January 2010 and December 15, 2016, were also used to identify relevant clinical trials. We reviewed each publication, and only the most recent or complete report of clinical trials was included when duplicate publications were identified. On December 15, 2016, the online updated manufacturers' package inserts of ipilimumab, nivolumab, pembrolizumab, and atezolizumab were also reviewed to identify relevant information not previously reported in published clinical trials. No placebo-controlled randomized trials including pembrolizumab, nivolumab, or atezolizumab were found. Selected all-grade and high-grade (grade 3 or higher) irAEs included gastrointestinal, liver, skin, endocrine, and pulmonary toxicities. Colitis was the most relevant gastrointestinal irAEs; rash the most relevant for dermatologic irAEs, increases in aspartate aminotransferase (AST) for hepatic irAEs, hypothyroidism for thyroid/endocrine irAEs, and pneumonitis for lung-related irAEs. Trials that met the following criteria were included in the meta-analysis: randomized phase II and III trials, prospective clinical trials in patients with cancer, and trials that had safety data available, including irAEs. Three reviewers (G. De Velasco, D. Bossé, T.K. Choueiri) independently evaluated studies for eligibility.

Data extraction and clinical end points

Data abstraction was conducted independently by two investigators (G. De Velasco, D. Bossé, T.K. Choueiri) according to the Quality of Reporting of Meta-Analyses (QUORUM) guidelines and any discrepancies between reviewers were resolved by consensus (G. De Velasco, D. Bossé, T.K. Choueiri). For each study, the following information was extracted: first author's last name, year of publication, phase of the trial, number of enrolled subjects, number of patients included in the safety analysis, treatment arms, number of patients in the ICI treatment and control groups, type of underlying malignancy, median age, overall survival, adverse events of interest, and the name of the ICI (ipilimumab, nivolumab, pembrolizumab, or atezolizumab).

Statistical analysis

All statistical analyses were performed using Stata/SE software, version 12.0 (Stata-Corp LP). For the calculation of incidence, the number of irAEs and the number of patients receiving ipilimumab, nivolumab, pembrolizumab, and atezolizumab were extracted from the safety profile. The proportion of patients with those adverse outcomes and 95% CIs were derived for each study. The control arm was used as comparative arm to calculate the RRs of irAEs in patients assigned to ipilimumab, nivolumab, pembrolizumab, or atezolizumab versus controls in the same trial. For trials reporting zero events in the ICI treatment or the control group, we applied a classic half-integer continuity correction to compute the RRs and variances.

To calculate the overall incidence and RRs of immune-related toxicities, we combined trial-specific estimates using random-effects models with the method of DerSimonian and Laird, which considers both within-study and between-study variations (18). Statistical heterogeneity among studies included in the meta-analysis was assessed using Cochrane Q statistic, and the inconsistency was quantified with the I^2 statistic, which is used to describe the percentage of total variation across studies that is due to heterogeneity rather than chance; a value of 0% indicates no observed heterogeneity, whereas values between 0% and 100% show increasing heterogeneity. The assumption of homogeneity was considered invalid for P values < 0.10. To explore the possible reasons for the heterogeneity, we conducted subgroup analyses by underlying malignancy or ICI, phase of clinical trial, age, and publication year, and we tested for variation in risk estimates by those variables through meta-regression analyses. Finally, potential publication bias was evaluated through Begg funnel plots to examine relative symmetry of individual study estimates around the overall estimate (19, 20). A two-tailed P value of < 0.05 was considered statistically significant.

Results

Characteristics of trials, patients, and interventions

Our search yielded a total of 1,617 potentially relevant studies with ipilimumab, nivolumab, pembrolizumab, or atezolizumab. After matching studies from different sources, we obtained 361 definitive studies after going through our selection process for the randomized controlled clinical trials (Fig. 1). Initially, 265 studies were excluded for at least one of the following reasons: reviews, letters, editorials, biomarkers only, cases retrospective studies, or commentaries. We screened 96 publications and 65 clinical trials were excluded (5 expanded-access studies with no control arm and 60 early-phase I/II or nonrandomized clinical trials). After reviewing the remaining 31 publications, 21 trials met the criteria for final inclusion in the meta-analysis (randomized phase II and III trials with a control arm that does not contain an ICI). Baseline characteristics of each trial are presented in Table 1. Eight trials were performed in patients with non–small cell lung cancer, six in melanoma, two in small cell lung cancer, two in prostate cancer and one in renal cell carcinoma, bladder cancer, and squamous cell cancer of the head and neck. Sixteen trials had two arms and five trials had three arms. A total of 11,454 patients were available for the meta-analysis: 6,528 patients were assigned to ICI arms (ipilimumab 2,721, nivolumab 1,534, pembrolizumab 1,522, and atezolizumab 751 patients), and 4,926 were assigned to placebo or control arms [placebo 1,069, chemotherapy 3,328, and biologic agents 529 (including everolimus and glycoprotein 100)]. All randomized controlled trials were sponsored by pharmaceutical companies and involved solid tumors. None of these studies had toxicity as a primary endpoint. The evaluation of the irAEs was based on the Common Terminology Criteria for Adverse Events version 3.0 or 4.0. The grading of rashes was the main variation between the two versions (Supplementary Table S2).

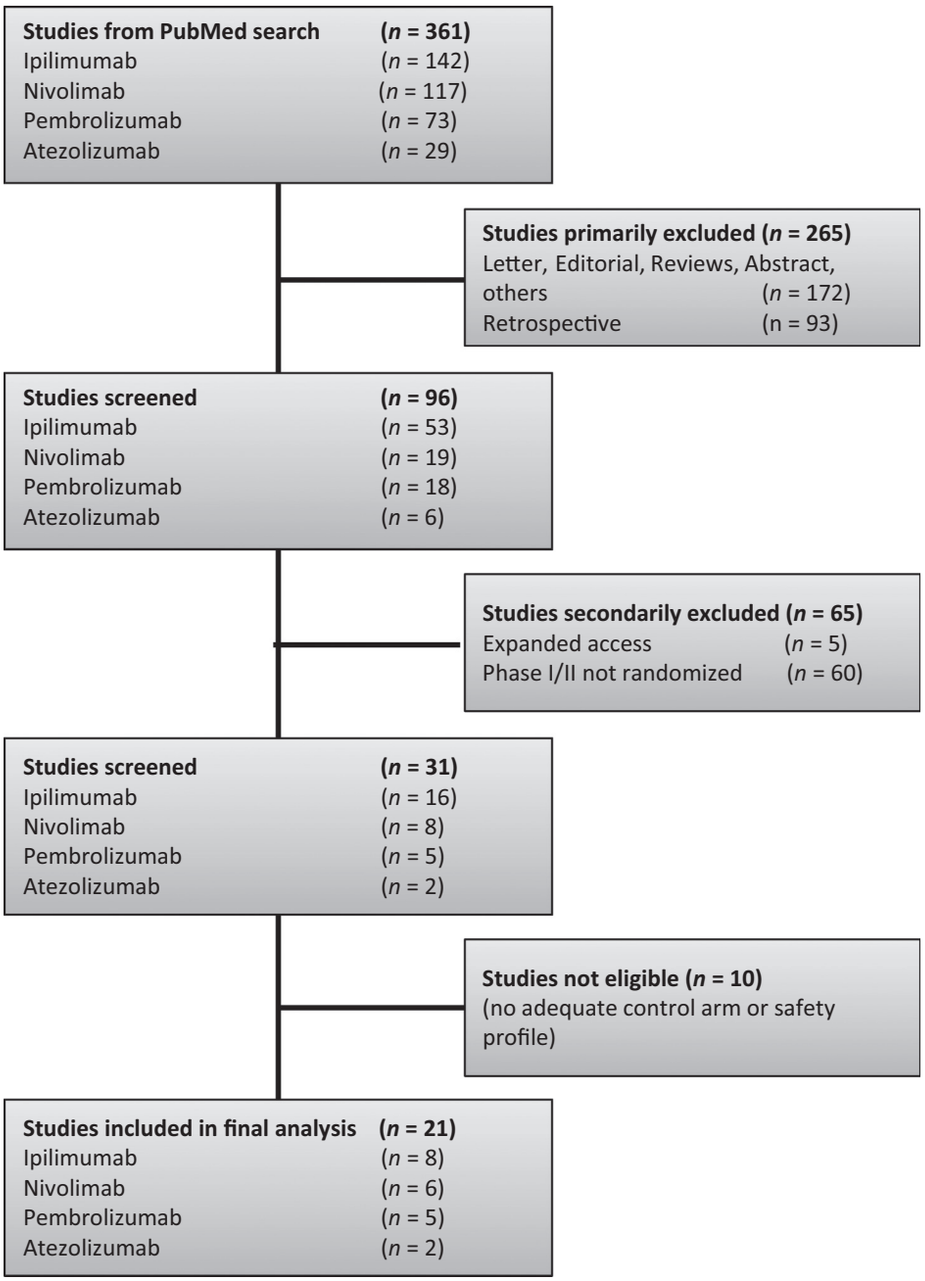

Figure 1.
Flow diagram of the systematic review.

Incidence and relative risk of all-grade irAEs of interest

In patients receiving ICI, all-grade colitis occurred in 206 of 5,422 (2.3%), AST elevation in 330 of 3,855 (6.5%), rash in 952 of 5,777 (13.9%), hypothyroidism in 244 of 4,622 (5.1%), and pneumonitis in 119 of 4,599 (2.6%; Table 2). Compared with patients in the non-ICI arms, those treated with an ICI were at a higher risk of immune-related colitis [RR 7.66; 95% confidence interval (CI), 4.58–12.8; $P < 0.001$], AST elevation (RR 1.80; 95% CI, 1.10–2.96; $P = 0.020$), rash (RR 2.50; 95% CI, 1.65–3.78; $P = 0.001$), hypothyroidism (RR 6.81; 95% CI, 4.20–11.0; $P < 0.001$), and pneumonitis (RR 4.14, 95% CI, 1.37–12.5; $P = 0.012$; Table 3).

Incidence and relative risk of high-grade irAEs of interest

In patients receiving ICI, high-grade colitis occurred in 119 of 5,442 (1.5%) patients, AST elevation in 94 of 3,855 (1.5%) patients, rash in 50 of 5,299 (1.1%) patients, hypothyroidism in 5 of 4,144 (0.3%), and pneumonitis in 42 of 4,599 (1.1%) patients receiving ICI (Table 2). Compared with patients in the non-ICI arms, those treated with an ICI were at a higher risk for high-grade grade colitis (RR 5.85; 95% CI, 2.66–12.8; $P < 0.001$), and increased AST (RR 2.79; 95% CI, 1.23–6.32; $P = 0.014$). The incidence of high-grade rash, hypothyroidism, or pneumonitis in patients who received ICIs was no different from patients in the non-ICI arms (Table 3). However, after excluding the CheckMate-

Table 1. List of clinical trials included in the meta-analysis

						Colitis		Increased AST		Rash		Hypothyroidism		Pneumonitis	
						Grade		Grade		Grade		Grade		Grade	
	Reference	Ph	Tumor Type	No.	Treatment arms	All	High	All	High	All	High	All	High	All	High
Ipilimumab															
1	Beer et al. 2016 (1)	3	Prostate	602	Ipilimumab	N/A	N/A	N/A	N/A	132	10	N/A	N/A	1	1
					Placebo	N/A	N/A	N/A	N/A	15	0	N/A	N/A	N/A	N/A
2	Reck et al. 2016 (2)	3	SCLC	1132	VP16 + Plt con Ipi	29	24	N/A	N/A	90	N/A	14	N/A	N/A	N/A
					VP16 + Plt + Placebo	N/A	N/A	N/A	N/A	14	N/A	N/A	N/A	N/A	N/A
3	Eggermont et al. 2016 (3)	3	Melanoma	951	Ipilimumab	75	36	78	20	162	6	42	1	N/A	N/A
					Placebo	6	1	24	0	52	0	4	0	N/A	N/A
4	Kwon et al. 2014 (4)	3	Prostate	799	Ipilimumab	27	18	22	9	68	2	9	2	5	1
					Placebo	3	0	13	4	16	0	1	0	0	0
5	Reck et al. 2013 (5)	2	SCLC	130	CP	N/A	N/A	14	0	1	0	N/A	N/A	N/A	N/A
					CP + Con Ipi	N/A	N/A	21	5	15	2	N/A	N/A	N/A	N/A
					CP + Seq Ipi	N/A	1	17	3	10	0	N/A	N/A	N/A	N/A
6	Lynch et al. 2012 (6)	2	NSCLC	204	CP	N/A	N/A	34	2	10	2	N/A	N/A	N/A	N/A
					CP + Con Ipi	N/A	N/A	27	2	28	3	N/A	N/A	N/A	N/A
					CP + Seq Ipi	N/A	2	33	2	13	3	N/A	N/A	N/A	N/A
7	Robert et al. 2011 (7)	3	Melanoma	502	Ipi + DTIC	11	5	66	43	55	3	4	0	N/A	N/A
					Dacarbazine	0	0	8	1	12	0	1	0	N/A	N/A
8	Hodi et al. 2010 (8)	3	Melanoma	676	Ipi + Gp100	20	12	4	1	67	5	6	1	N/A	N/A
					Ipilimumab	10	7	1	0	25	1	2	0	N/A	N/A
					Gp100	1	0	2	0	6	0	2	0	N/A	N/A
Nivolumab															
9	Ferris et al. 2016 (9)	3	Head and Neck	361	Nivolumab	0	0	2	0	18	0	9	0	5	2
					Chemotherapy	1	0	2	0	5	1	1	0	1	0
10	Robert et al. 2015 (10)	3	Melanoma	518	Nivolumab	2	1	2	1	31	1	9	0	3	0
					Dacarbazine	0	0	4	1	6	0	1	0	0	0
11	Weber et al. 2015 (11)	3	Melanoma	405	Nivolumab	5	2	12	1	35	1	15	0	5	0
					Chemotherapy	0	0	2	0	12	0	0	0	0	0
12	Brahmer et al. 2015 (12)	3	NSCLC	272	Nivolumab	1	1	2	0	5	0	5	0	6	1
					Docetaxel	0	0	1	0	8	2	0	0	0	0
13	Borghaei et al. 2015 (13)	3	NSCLC	582	Nivolumab	2	1	9	1	36	1	19	0	8	3
					Docetaxel	0	0	2	0	13	0	0	0	1	1
14	Motzer et al. 2015 (14)	3	RCC	821	Nivolumab	N/A	N/A	N/A	N/A	41	2	N/A	N/A	16	6
					Everolimus	N/A	N/A	N/A	N/A	79	3	N/A	N/A	58	11
Pembrolizumab															
15	Herbst et al. 2016 (15)	3	NSCLC	1034	Pembro 2 mg	4	3	10	2	29	1	28	0	16	7
					Pembro 10 mg	2	1	7	0	44	1	28	0	15	7
					Docetaxel	0	0	3	0	14	0	1	0	6	2
16	Langer et al. 2016 (16)	2	NSCLC	123	CPem + con/seq Pembrolizumab	N/A	N/A	11	1	1	1	9	0	3	1
					CPem	N/A	N/A	7	1	1	1	3	0	0	0
17	Reck et al. 2016 (17)	3	NSCLC	305	Pembrolizumab	3	2	N/A	N/A	6	6	14	0	9	4
					Chemotherapy	0	0	N/A	N/A	0	0	2	0	1	1
18	Ribas et al. 2015 (18)	2	Melanoma	540	Pembro 2 mg	2	0	N/A	N/A	21	0	9	0	3	0
					Pembro 10 mg	3	2	N/A	N/A	18	0	13	0	3	2
					Chemotherapy	1	1	N/A	N/A	8	0	0	0	0	0
19	Bellmunt et al. 2016 (19)	3	Bladder	542	Pembrolizumab	6	3[a]	N/A	N/A	2	1[a]	N/A	N/A	11	6[a]
					Chemotherapy	1	0	N/A	N/A	3	3	N/A	N/A	1	0
Atezolizumab															
20	Fehrenbacher et al. 2016 (20)	2	NSCLC	287	Atezolizumab	2	1	6	3	N/A	N/A	9	1[a]	4	1
					Docetaxel	N/A	N/A	N/A	N/A	N/A	N/A	0	0	N/A	N/A
21	Rittmeyer et al. 2016 (21)	3	NSCLC	1125	Atezolizumab	2	0	N/A	N/A	N/A	N/A	N/A	N/A	6	4
					Docetaxel	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: No.: number of patients; Tx: treatments; Mos: months; hypoT: hypothyroidism, CPem: carboplatin/Pemetrexed;PembroPembrolizmab; CP: carboplatin/paclitaxel; DTIC: Dacarbazine; gp100: Glycoprotein 100; VP16: etoposide; Plt: platinum salt Con: concurrent; Seq: sequential.
[a]Proportion of high-grade adverse events estimated from study's band diagram.

025, in which the comparator arm was everolimus, a drug known to cause pneumonitis, the risk of high-grade pneumonitis was significantly higher than the non-ICI group (RR 2.99; 95% CI, 1.37 to −6.54; $P = 0.006$). We found some heterogeneity for the RRs of all-grade AST elevation ($I^2 = 78.7\%$), rash ($I^2 = 86.1\%$), and pneumonitis ($I^2 = 78.9\%$), but not for the other toxicities. Overall, the Begg test detected no evidence of publication bias, except for colitis.

Subgroup analyses

Ipilimumab, compared with the PD-1/PD-L1 inhibitors, had a higher risk for all-grade immune-related rash [(RR 3.94; 95% CI, 3.02–5.14) vs. (RR 1.59; 95% CI, 0.90–2.82); P value for difference = 0.006)] and for high-grade colitis [(RR 22.5; 95% CI, 6.37–79.4) vs. (RR 2.47; 95% CI, 0.90–6.72); P value for difference = 0.021]. We did not find differences in the relative risk between PD-1/PD-L1 inhibitors versus CTLA-4 for all-grade or high-grade liver

Table 2. Incidence of all-grade and high-grade of immune-related toxicities of novel ICIs in cancer patients

Immune-related toxicities	No. trials	No. events	Incidence, % (95% CI)
All grades			
Colitis	16	206/5,442	2.3 (1.3–3.9)
AST	14	330/3,855	6.5 (3.3–12.4)
Rash	19	952/5,777	13.9 (10.6–18.0)
Hypothyroidism	15	244/4,622	5.1 (3.8–6.8)
Pneumonitis	15	119/4,599	2.6 (2.0–3.7)
High grade			
Colitis	16	119/5,442	1.5 (0.9–2.5)
AST	14	94/3,855	1.5 (0.7–3.4)
Rash	18	50/5,299	1.1 (0.7–1.7)
Hypothyroidism	14	5/4,144	0.3 (0.2–0.5)
Pneumonitis	15	42/4,599	1.1 (0.7–1.7)

Table 4. Comparison between PD-1/PD-L1 and CTLA-4 inhibitors

Immune-related toxicities	PD-1/PD-L1 inhibitors RR (95% CI)	CTLA-4 inhibitors RR (95% CI)	*P*
All grades			
Colitis	3.36 (1.36–8.33)	11.3 (6.05–21.1)	0.054
AST	1.71 (1.01–2.89)	1.92 (0.94–3.93)	0.745
Rash	1.59 (0.90–2.82)	3.94 (3.02–5.14)	**0.006**
Hypothyroidism	8.05 (4.26–15.2)	4.64 (1.42–15.2)	0.352
Pneumonitis	3.8 5(1.23–12.1)	11.1 (0.62–199.8)	0.562
High grade			
Colitis	2.47 (0.90–6.72)	22.5 (6.37–79.4)	**0.021**
AST	1.26 (0.38–4.16)	5.06 (1.26–20.3)	0.168
Rash	0.91 (0.40–2.10)	3.55 (1.37–9.19)	0.052
Hypothyroidism	0.85 (0.25–2.84)	2.02 (0.39–10.5)	0.421
Pneumonitis	1.49 (0.80–2.79)	3.02 (0.12–74.0)	0.798

toxicities, hypothyroidism, or pneumonitis (Table 4). In other subgroup analyses stratified by type of control-arm (chemotherapy vs. biological therapy vs. placebo), and type of tumor (melanoma vs. lung vs. other tumors), only a few subgroups with increased risk in irAEs were found. These analyses were limited by the small number of events in each subgroup (Supplementary Tables S3 and S4).

Fatal immune-related adverse events

Out of 6,528 patients treated with an ICI, 42 fatal irAEs were reported, totaling 0.64% of patients treated with ICIs, but up to 59 % of the total number of fatal AEs recorded in these clinical trials. Ipilimumab-induced colitis was the most common cause of fatal irAE.

Discussion

The incidence of immune-related adverse events in trials of immune checkpoint inhibitors can be challenging to discern because some adverse events, such as colitis, may be caused by a nonimmune reaction to drugs or to disease progression. Moreover, the report of irAE in the literature seems suboptimal, because no standardized method has been published specifying clinical criteria for irAEs versus nonimmune AEs (10). This prompted us to perform this meta-analysis evaluating the risk of selected key irAEs associated with single-agent administration of ipilimumab, nivolumab, pembrolizumab, or atezolizumab in cancer patients. In this comprehensive analysis, 11,454 patients from 21 randomized phase II and III trials were included. We focused on five adverse event categories and selected the most common irAE in each category in order to better understand and illustrate the spectrum of irAEs from ICIs. The incidence of irAEs is relatively low, but is clearly changing the patterns of care of patients treated with these novel therapies. This meta-analysis has shown that all five of the selected irAEs were more frequent with ICI than the comparator arms.

Immune-mediated hepatitis, which can initially present with abnormalities in the liver function tests, may also occur secondary to ICIs. Our analysis showed a slight rise in risk of all-grade and serious AST elevation. Additionally, the combination of ipilimumab and dacarbazine, a drug known to cause hepatic toxicity (8), was associated with higher risk of AST elevation than expected with either agent alone. This finding may be relevant, because of the growing interest in testing combinations of ICI with other drugs; hepatitis may therefore become an important challenge for trials using this strategy. Indeed, combinations of sunitinib or pazopanib with nivolumab in RCC and ipilimumab with BRAF inhibitors in melanoma have already been shown to be significantly hepatotoxic and have led to drug discontinuation (40, 41). The incidence of hypothyroidism and skin rash increased 7- and 2-fold, respectively, in patients treated with ICI compared with patients treated in the comparator arms. These infrequent irAEs may be perceived as minor AEs; however, careful assessment should be performed considering the potentially life-threatening complications of severe hypothyroidism or serious skin toxicities. Furthermore, the combinations of different ICIs, or of an ICI with other drugs such as tyrosine kinase inhibitors, may exponentially increase these risks and their severity, as seen with hepatitis (42). Pneumonitis, which most commonly manifests as radiological ground glass opacities, was selected based on the potential risk of severity previously described (43). Noninfectious pneumonitis is

Table 3. Pooled relative risk (RR) of all-grade and high-grade of immune-related toxicities of ICIs in cancer patients

Immune-related toxicities	No. trials	No. events/sample size		Effect estimate		Heterogeneity
		ICI	Control	RR (95% CI)	*P*	*P* I^2(%)
All grades						
Colitis	13	173/4,213	18/2,970	7.66 (4.58–12.8)	<0.001	0.645 (0.0)
AST	13	324/3,713	151/2,548	1.80 (1.10–2.96)	0.020	<0.001 (78.7)
Rash	19	952/5,777	266/4,213	2.50 (1.65–3.78)	0.001	<0.001 (86.1)
Hypothyroidism	14	230/4,144	15/2,895	6.81 (4.20–11.0)	<0.001	0.452 (0.0)
Pneumonitis	12	108/3,449	69/2,572	4.14 (1.37–12.5)	0.012	<0.001 (78.9)
High grade						
Colitis	13	98/4,213	4/2,970	5.85 (2.66–12.8)	<0.001	0.598 (0.0)
AST	13	55/3,713	10/2,548	2.79 (1.23–6.32)	0.014	0.173 (26.9)
Rash	18	59/5,299	12/3,737	1.65 (0.88–3.08)	0.117	0.585 (0.0)
Hypothyroidism	14	6/4,144	0/2,895	1.15 (0.44–3.05)	0.777	0.999 (0.0)
Pneumonitis	12	39/3,349	15/2,572	1.53 (0.83–2.83)	0.172	0.558 (0.0)

a recognized specific adverse event associated with several drugs, such as rapalogs (everolimus or temsirolimus; ref. 44). It is also possible that in some situations, the control arm (e.g., everolimus) can also cause pneumonitis and could have diluted the overall relative risk of pneumonitis associated with ICIs. Nevertheless, immune-related pneumonitis can be one of the most common treatment-related events leading to treatment discontinuation (31). Despite the fact that several severe irAEs can occur in patients treated with anti–CTLA-4 and anti–PD-1/PD-L1 agents, treatment-related death remains a rare event. In our review, we found that fewer than 1% of all patients had ICI-related fatal events across all trials.

This meta-analysis has several limitations. First, coexisting conditions and classification of side effects as immune-related can be challenging (45). Also, we could not retrieve patient level data, and it therefore remains unknown whether cumulative, or combinations of several, immune-related toxicities may have played a role. Nevertheless, previous reports suggest that trial-level and patient-level meta-analyses reach comparable results (46). Many issues with ICI safety remain unresolved. Patients with discontinuation due to toxicity may have higher rate of response, but it is unclear whether the dosage of ICIs should be increased for patients without toxicity. Another intriguing question is whether the balance between safety and efficacy profile will be superior with immunotherapy combinations. For example, nivolumab combined with ipilimumab could improve progression-free survival, compared with ipilimumab alone, in patients with melanoma (47), but led to a rate of high-grade irAEs of 55%, compared with 27% or 16% for nivolumab or ipilimumab monotherapy, respectively. The development of biomarkers to improve patient selection may enhance the risk/benefit profile in patients with melanoma. For example, in melanoma patients whose tumors had PD-L1 expression < 5% by immunohistochemistry, combination therapy with nivolumab and ipilimumab significantly improved progression-free survival compared with nivolumab monotherapy. However, in patients whose tumors had PD-L1 expression in at least 5% of the cells, nivolumab alone had a favorable risk/benefit ratio, leading to less toxicity and similar progression-free survival than the combination arm (47).

This meta-analysis draws attention to a shift in toxicity patterns that oncologists will face in the coming years. Overall, the use of ICI is associated with an increased risk of developing all-grade irAEs in each category analyzed. These irAEs are generally well tolerated and increasingly recognized, but can occasionally be fatal, such as intestinal perforation secondary to colitis or high-grade hepatitis. Despite the increased relative risks of irAEs, these drugs are already achieving significant benefit in terms of quality of life and overall survival in several tumor types. The timely recognition and appropriate management of irAEs therefore becomes a priority.

Disclosure of Potential Conflicts of Interest

G. De Velasco is a consultant/advisory board member for Pfizer and Janssen. P.A. Ott is a consultant/advisory board member for BMS and Roche/Genentech. F.A. B. Schutz reports receiving speakers bureau honoraria from BMS, Pfizer, and Novartis and is a consultant/advisory board member for Novartis and Pfizer. G. Sonpavde reports receiving commercial research grants from Onyx, Bayer, Boehringer-Ingelheim, Celgene, Merck, Sanofi, and Pfizer; reports receiving speakers bureau honoraria from Clinical Care Options and Uptodate; is a consultant/advisory board member for Bayer, Sanofi, Argos, Agensys, Pfizer, Novartis, Eisai, Janssen, Amgen, AstraZeneca, Merck, and Genentech. F.S. Hodi reports receiving a commercial research grant from Bristol-Myers Squibb to institution, has ownership interest (including patents) in Bristol-Myers Squibb to institution per institutional policy, and is a consultant/advisory board member for Merck, Novartis, Genentech, and EMD Serono. T.K. Choueiri is a consultant/advisory board member for Merck, Bristol-Myers Squibb, Roche, and AstraZeneca. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: G. De Velasco, R.B. Moreira, F. Schutz, T.K. Choueiri
Development of methodology: G. De Velasco, T.K. Choueiri
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): G. De Velasco, D. Bossé, P.A. Ott, F.S. Hodi, T.K. Choueiri
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): G. De Velasco, Y. Je, D. Bossé, M.M. Awad, F. Schutz, J. Bellmunt, G.P. Sonpavde, F.S. Hodi, T.K. Choueiri
Writing, review, and/or revision of the manuscript: G. De Velasco, Y. Je, D. Bossé, M.M. Awad, P.A. Ott, R.B. Moreira, F. Schutz, J. Bellmunt, G.P. Sonpavde, F.S. Hodi, T.K. Choueiri
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): G. De Velasco, D. Bossé, T.K. Choueiri
Study supervision: T.K. Choueiri

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