REVIEW

Immune-related adverse events following administration of anti-cytotoxic T-lymphocyteassociated protein-4 drugs: a comprehensive systematic review and meta-analysis

This article was published in the following Dove Press journal: Drug Design, Development and Therapy

Objective: Administration of drugs targeting anti-cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) is often associated with serious immune-related adverse events (irAEs). Here, we performed a comprehensive analysis of organ-specific irAEs and treatment-related hematologic abnormalities and musculoskeletal disorders resulting from anti-CTLA-4 treatment.

Materials and methods: PubMed, the Cochrane library, Web of Science, and ClinicalTrials.gov were searched for studies between January 1990 and March 2018 reporting AEs associated with anti-CTLA-4 therapies.

Results: A total of 11 clinical trials with 7,088 patients were included; of these, data were accessible for 10 on ClinicalTrials.gov. Compared with control therapies (placebo, chemotherapy, radiation therapy, or vaccine), anti-CTLA-4 therapies (ipilimumab and tremelimumab) were associated with an increased risk of serious irAEs, predominantly dermatologic (rash: odds ratio [OR] 3.39, P<0.01), gastrointestinal (diarrhea and colitis: OR 6.57 and 14.01, respectively; both P<0.001), endocrine (hypophysitis, hypothyroidism, adrenal insufficiency, and hypopituitarism: OR 4.22, 3.72, 3.77, and 4.73, respectively; all P<0.05), and hepatic (hepatitis, elevated alanine aminotransferase, and elevated aspartate aminotransferase: OR 4.44, 3.28, and 3.12, respectively; all P<0.05). The most common serious organ-specific irAEs were gastrointestinal (diarrhea 9.8% and colitis 5.3%). Although the incidence of selected events was higher in anti-CTLA-4-treated patients, no significant differences were found between anti-CTLA-4 and the control therapies in treatment-related hematologic abnormalities or severe musculoskeletal disorders.

Conclusion: Anti-CTLA-4 therapies are associated with an increased risk of serious organspecific irAEs, most frequently involving the gastrointestinal system; however, no increased risk of hematologic abnormalities or severe musculoskeletal disorders was detected compared with other therapies. These results underscore the need for clinical awareness and prompt and effective management of multi-organ irAEs related to anti-CTLA-4 drugs.

Keywords: immune-related adverse events, anti-CTLA-4 drugs, ipilimumab, tremelimumab

Hang Xu^{1,*} Ping Tan^{1,*} Xiaonan Zheng^{2,*} Yu Huang¹ Tianhai Lin¹ Qiang Wei¹ Jianzhong Ai¹ Lu Yang¹

¹Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu 610041, People's Republic of China; ²West China Medical School, Sichuan University, Chengdu 610041, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jianzhong Ai; Lu Yang Department of Urology, Institute of Urology, West China Hospital, Sichuan University, No. 37 Guoxue Xiang, Chengdu 610041, People's Republic of China Tel +86 152 0821 2056; +86 135 4123 5213 Email ajz1986@126.com; wycleflue@163.com



Introduction

Recent years have seen increasing interest in immunotherapy-based immune checkpoint blockade for various advanced or metastatic solid tumors, such as prostate cancer,¹ melanoma,² lung cancer,³ and mesothelioma.⁴ Cytotoxic T lymphocyteassociated antigen 4 (CTLA-4) is expressed exclusively on the surface of T cells and

© 2019 Xu et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 42. and 5 of our Terms (http://www.dovepress.com/terms.php). inhibits their activation and function by binding to the ligand B7.^{5,6} As such, CTLA-4 is a crucial negative regulator of the anti-tumor immune response and a key target of immune checkpoint therapy. Several anti-CTLA-4 monoclonal antibodies (mAbs) have been developed that block the inhibitory pathway, thereby restoring or enhancing T cell functions in the anti-tumor response.

Currently, the two most widely used anti-CTLA-4 drugs in clinical practice are the fully human mAbs ipilimumab and tremelimumab. Both mAbs have shown benefit for several cancers in a number of clinical trials.^{7,8} Nevertheless, despite the beneficial effects of immune checkpoint inhibitors in promoting the anti-tumor response, their mechanism of action in enhancing T cell activity⁹ also increases the risk of immune-related adverse events (irAEs), which often affect multiple organs.⁸ The most common anti-CTLA-4-associated organ-specific irAEs involve the skin, gastrointestinal tract, liver, and endocrine and nervous systems. In addition, treatment-related hematologic abnormalities, including thrombocytopenia, anemia, and neutropenia, are commonly seen in patients treated with anti-CTLA-4 mAbs and may be related to their immune activities.¹⁰ Musculoskeletal disorders, which can seriously impact the patient's quality of life, have also been observed following treatment with immune checkpoint inhibitors. Their incidence has been investigated for drugs that disrupt the interaction between programmed cell death-1 and its ligand (PD-1–PDL-1);¹¹ however, little is known about the incidence of musculoskeletal disorders in patients administered anti-CTLA-4 drugs.

Several meta-analyses have analyzed irAEs of cancer patients undergoing treatment with CTLA-4 inhibitors,^{12–14} but most of these studies have focused mainly on ipilimumab and examined only a limited number of irAEs. Moreover, a more complete review of the incidence of AEs is justified by the increasing clinical use of anti-CTLA-4 drugs and the potentially severe outcomes if irAEs are not recognized and managed in a timely manner. Here, we performed a systematic review and meta-analysis to evaluate irAEs related to anti-CTLA-4 drugs, with most data collected from ClinicalTrials.gov.

Materials and methods

Search strategy

We searched three databases (PubMed, Cochrane library and Web of Science) from January 1990 to march 2018 to identify all qualified trials. The following items: "anti-

cvtotoxic T-lymphocyte-associated protein-4", "anti-CTLA -4", "Ipilimumab", and "tremelimumab" were adopted in Cochrane library and Web of Science with the restriction to language (English) and publication type (clinical trial). As for PubMed searching, the following search strategy was used "((((((clinical trial[Title/Abstract]) OR randomized controlled trial[Title/Abstract]) OR randomized trial[Title/ Abstract]) OR clinical study[Title/Abstract]) OR trial[Title/ Abstract])) AND ((((((. (anti-cytotoxic T lymphocyteassociated antigen 4[Title/Abstract]) OR anti CTLA4 [Title/Abstract]) OR anti CTLA-4[Title/Abstract]) OR OR ipilimumab[Title/Abstract]) tremelimumab[Title/ Abstract])))" EndNote, a bibliography managing software, was used to integrate our search results and find duplicates.

Study selection

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines,¹⁵ we applied the Population, Intervention, Comparator, Outcome, and Study design (PICOS) approach to identify eligible studies. Trials were selected if they were randomized and controlled in nature (S), compared anti-CTLA-4 drugs with control therapies (I, C) in cancer patients (P), and provided information on AEs (O). Nonrandomized controlled trials, including case reports, commentaries, reviews, and quality of life studies, were excluded. Studies were also excluded if the intervention arm was a combination of mAbs, if the control arm was one or more mAb, or the enrolled population had previously been treated with mAbs. After duplicates were removed, two authors (H.X. and P.T.) independently screened the titles and abstracts, and the full text of the selected studies was further reviewed. Any disagreements were resolved by consulting a third reviewer (L.Y.).

Data extraction and outcomes

Data extraction was performed independently by two authors using a pre-designed extraction form. Any discrepancies were resolved by discussion. The following items were extracted from each study by two authors (H.X. and P.T.) independently: author, year, NCT number, trial phase, cancer type, sample size, intervention drugs and doses, control therapies, median follow-up duration in the experiment group, the primary outcome and the description of irAEs. Our primary outcome was the incidence of organspecific irAEs including dermatologic (pruritus, rash,), gastrointestinal (diarrhea, colitis), endocrine (hypophysitis, hyperthyroidism, hypothyroidism, adrenal insufficiency, hypopituitarism), hepatic (hepatitis, elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels), and other (pneumonitis, pancreatitis, Guillain-Barre syndrome) adverse events. Our secondary outcome was the treatment-related hematologic abnormalities (anemia, neutropenia, thrombocytopenia) and musculoskeletal disorders (arthralgia, arthritis, back pain, bone pain, musculoskeletal pain, myalgia). ClinicalTrials.gov provided the main sources of adverse events data (search deadline: 20 March 2018). The information on adverse events from published literature was also extracted only when the information was not exhibited in ClinicalTrials.gov (the ClinicalTrials.gov had the priority over the published literature given its complete AEs information). Serious and other AEs were defined as grades ≥ 3 or grade 1-2 in published articles according to The Common Terminology of Clinical Adverse Events (CTCAE) categorization. We deemed an AE did not happen if an adverse event was not reported in both two sources.

Quality assessment

The Cochrane Risk of Bias Tool¹⁶ was applied to assess the quality of each included trial using the following six items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting and other sources of bias. Discrepancies were resolved by discussion.

Data synthesis and analysis

When possible, a meta-analysis was performed, and the pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated. A fixed effects model or random effects model (using the inverse variance method) was adopted for the meta-analysis according to the heterogeneity. Heterogeneity was assessed using Cochran Q and I² statistics (if P<0.1, heterogeneity was considered present and the random effects model was used). A two-sided P-value of less than 0.05 was deemed statistically significant. If a study involved more than one intervention arm (eg, the trials conducted by Reck et al,¹⁷ Lynch et al,¹⁸ and Hodi et al⁸), we separately compared each intervention arm with the control arm. Subgroup analyses were conducted according to the control therapies. Publication bias was detected using the Egger's test. All statistical analyses were performed using STATA 12.0 (Stata Corp, College Station, TX, USA).

Results

Basic characteristics of included trials

The process of study selection is shown in Figure S1. Table 1 summarizes the basic characteristics of the included trials. All 11 studies^{7,8,17–25} included were multicenter, randomized, controlled trials and included a total of 7,088 patients (intervention 3,985 vs control 3,103). Four trials were conducted in melanoma,^{7,8,24,25} two in metastatic non-small cell lung cancer,^{18,20} two in small cell lung cancer,^{17,22} two in metastatic castration-resistant prostate cancer,^{21,23} and one in mesothelioma.¹⁹ Ipilimumab and tremelimumab were used in nine and two trials, respectively. Doses of 10 mg/kg and 15 mg/kg of tremelimumab were administered in Maio et al¹⁹ and Ribas et al,²⁴ respectively, and a 3 mg/kg dose of ipilimumab was administered in Hodi et al;8 the remaining 8 studies administered 10 mg/kg dose of ipilimumab or tremelimumab. The trials conducted by Rech et al¹⁷ and Lynch et al¹⁸ assessed two regimens of ipilimumab in the experimental group: ipilimumab + paclitaxel/carboplatin followed by placebo + paclitaxel/carboplatin; and placebo + paclitaxel/carboplatin followed by ipilimumab + paclitaxel/carboplatin. The trial conducted by Hodi et al⁸ included three arms: ipilimumab + gp100 (melanoma peptide vaccine), ipilimumab alone, and gp100 alone. The control arms consisted of a single chemotherapy drug in one trial, two chemotherapy drugs in four trials, radiotherapy in one trial, vaccine (gp100) in one trial, and placebo in three trials.

The median follow-up duration was 21 months (range 9.9–63.6 months), and the primary end point in all trials was survival. Data on AEs were available on ClinicalTrials.gov for 10 of the 11 studies (except Ribas et al²⁴); only two trials did not describe irAEs. The risk of bias in the included trials is shown in Table 2. One of the trials was an open-label, randomized, comparative study and we considered it at high risk of bias for assessing random sequence generation and allocation concealment.

Organ-specific irAEs

Table 3 summarizes the incidence of organ-specific irAEs related to anti-CTLA-4 drugs, and Table 4 shows the pooled ORs of irAEs compared with the control therapies.

Dermatologic AEs

Pruritus and rash affected 1022 (25.6%) and 1058 (26.5%) patients, respectively, and were reported in all 11 trials at all grades. The incidence of all grades of pruritus (OR 4.35, 95% CI 3.74–5.07) and rash (OR 4.03, 95% CI 3.22–5.04) was significantly higher for

Trials	NCT		Cancer type	Size (Intervention/ Control)				(intervention)	outcome	of irAEs
Maio 2017 ¹⁹	01843374	2	Mesothelioma	569 (380/189)	Tremelimumab	10 mg/kg	Placebo	AN	SO	No
Govindan 2017 ²⁰	01285609	e	NSCLC	948 (475/473)	Ipilimumab +	10 mg/kg	Chemotherapy	12.5 months	SO	Yes
					Chemotherapy		+ Placebo			
Beer 2017 ²¹	01057810	e	mCRPC	600 (399/199)	Ipilimumab	10 mg/kg	Placebo	AA	SO	Yes
Reck 2016 ²²	01450761	e	SCLC	954 (562/561)	Ipilimumab +	10 mg/kg	Chemotherapy	10.5 months	SO	Yes
					Chemotherapy		+ Placebo			
Eggermont 2016 ⁷	00636168	m	Melanoma	945 (471/474)	Ipilimumab	10 mg/kg	Placebo	63.6 months	RFS	Yes
kwon 2014 ²³	00861614	e	mCRPC	799 (393/396)	Ipilimumab +	10 mg/kg	Radiotherapy +	9 -9 months	SO	Yes
					Radiotherapy		placebo			
Ribas 2013 ²⁴	00257205	m	Melanoma	644 (325/319)	Tremelimumab	15 mg/kg	Chemotherapy	31 months	SO	٩
Reck 2012 ¹⁷	00527735	2	SCLC	86 (42/44)	Ipilimumab	10 mg/kg	Chemotherapy	NA	irPFS	Yes
					(Phased) $^{\#}$		+ Placebo			
				86 (42/44)	lpilimumab [#]	10 mg/kg	Chemotherapy			
					(Concurrent)		+ Placebo			
Lynch 2012 ¹⁸	00527735	2	NSCLC	132 (67/65)	lpilimumab [#]	10 mg/kg	Chemotherapy	AA	irPFS	Yes
					(Phased)		+ Placebo			
				136 (71/65)	Ipilimumab [#]	10 mg/kg	Chemotherapy			
					(Concurrent)		+ Placebo			
Robert 2011 ²⁵	00324155	ß	Melanoma	498 (247/251)	Ipilimumab +	10 mg/kg	Chemotherapy	AA	SO	Yes
					Chemotherapy		+ Placebo			
Hodi 2010 ⁸	00094653	e	Melanoma	512 (380/132)	Ipilimumab +	3 mg/kg	gp100	21 months	os	Yes
					gp 100					
				263 (131/132)	Ipilimumab	3 mg/kg	gp100	27.8 months		

 Table I Characteristics of included trials

Study	Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data*	Selective reporting*	Other sources of bias
Maio ¹⁹	2017	Low	Low	Low	Low	High	High	Low
Govindan ²⁰	2017	Low	Low	Low	Low	High	High	Low
Beer ²¹	2017	Low	Low	Low	Low	High	High	Low
Reck ²²	2016	Low	Low	Low	Low	High	High	Low
Eggermont ⁷	2016	Low	Low	Low	Low	High	High	Low
kwon ²³	2014	Low	Low	Low	Low	High	High	Low
Ribas ²⁴	2013	Low	Low	High	High	High	High	Low
Reck ¹⁷	2012	Low	Unclear	Low	Low	High	High	Low
Lynch ¹⁸	2012	Low	Unclear	Low	Low	High	High	Low
Robert ²⁵	2011	Low	Unclear	Low	Low	High	High	Low
Hodi ⁸	2010	Low	Unclear	Low	Low	High	High	Low

Table 2 Risk of bias of included trials

Note: *Applies to adverse events.

 Table 3 Incidence of organ-specific immune-related adverse events related to anti-CTLA-4 drugs. Values are percentages (95% confidence intervals)

Drugs	Ipilimumab (n	=3280)	Tremelimuma	b (n=705)	Total (n=3985))
IrAEs*	All [#]	Serious [†]	All	Serious	All	Serious
Dermatologic						
Pruritus	25.0 (23.5–26.5)	0.1 (0.0-0.3)	28.8 (25.5–32.3)	0.4 (0.1–1.2)	25.6 (24.3–27.0)	0.2 (0.1–0.4)
Rash	26.6 (25.1–28.2)	0.7 (0.4–1.1)	26.2 (23.0–29.7)	1.4 (0.7–2.6)	26.5 (25.2–28.0)	0.8 (0.6–1.2)
Gastrointestinal						
Diarrhea	46.2 (44.5–47.9)	8.4 (7.4–9.4)	55.3 (51.6-59.0)	16.5 (13.8–19.4)	47.8 (46.2–49.4)	9.8 (8.9–10.8)
Colitis	6.6 (5.8–7.5)	5.3 (4.6–6.1)	5.2 (3.7–9.2)	5.2 (3.7–9.2)	6.4 (5.6–7.2)	5.3 (4.6-6.0)
Endocrine						
Hypophysitis	3.9 (3.3-4.6)	2.0 (1.6–2.6)	0.4 (0.1–1.2)	0.4 (0.1–1.2)	3.3 (2.8–3.9)	1.7 (1.3–2.2)
Hypothyroidism	2.5 (2.0–3.1)	0.3 (0.2–0.6)	2.7 (1.6–4.2)	0.6 (0.2–1.4)	2.5 (2.0–3.0)	0.4 (0.2–0.6)
Hyperthyroidism	0.3 (0.1–0.5)	0.3 (0.1–0.5)	0.0 (0.0–0.5)	0.0 (0.0–0.5)	0.2 (0.1–0.4)	0.2 (0.1–0.4)
Adrenal insufficiency	0.6 (0.3–0.9)	0.6 (0.3–0.9)	0.9 (0.3–1.8)	0.7 (0.2–1.6)	0.6 (0.4–0.9)	0.6 (0.4–0.9)
Hypopituitarism	0.8 (0.5–1.2)	0.8 (0.5–1.2)	0.1 (0.0–0.8)	0.1 (0.0–0.8)	0.7 (0.4–1.0)	0.7 (0.4–1.0)
Hepatic						•
Hepatitis	0.5 (0.3–0.8)	0.5 (0.3–0.8)	0.3 (0.0-1.0)	0.3 (0.0-1.0)	0.5 (0.3–0.7)	0.5 (0.3–0.7)
ALT increased	12.3 (11.2–13.4)	2.6 (2.1–3.2)	0.0 (0.0–0.5)	0.0 (0.0-0.5)	10.1 (9.2–11.1)	2.1 (1.7–2.6)
AST increased	11.0 (10.0–12.1)	2.5 (2.0–3.1)	0.0 (0.0–0.5)	0.0 (0.0–0.5)	9.1 (8.2–10.0)	2.0 (1.6–2.5)
Other						
Pneumonitis	1.2 (0.8–1.6)	0.8 (0.5–1.2)	0.3 (0.0-1.0)	0.3 (0.0-1.0)	1.0 (0.7–1.4)	0.7 (0.5–1.0)
Pancreatitis	0.1 (0.0-0.3)	0.1 (0.0-0.3)	0.7 (0.2–1.6)	0.7 (0.2–1.6)	0.2 (0.1–1.4)	0.2 (0.1–0.4)
Guillain-Barre syndrome	0.2 (0.0-0.4)	0.2 (0.0-0.4)	0.1 (0.0-0.8)	0.1 (0.0–0.8)	0.2 (0.1–0.3)	0.2 (0.1–0.3)

Notes: *IrAEs, immune-related adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase. $^{#}$ Includes both serious and other adverse events if data were extracted from ClinicalTrials.gov; includes all Common Terminology of Clinical Adverse Events (CTCAE) grades if data were extracted from the publication. † Serious adverse events if data were extracted from ClinicalTrials.gov; CTCAE grades ≥ 3 if data were extracted from the publication.

Table 4 Pooled odds ratio of adverse events for anti-CTLA-4 drugs compared with control therapies

	All [#]			Serious [†]		
IrAEs*	OR	95%CI	Р	OR	95%CI	Р
Dermatologic						
Pruritus	4.35	3.74–5.07	<0.0001	3.64	0.89–14.91	0.072
Rash	4.03	3.22–5.04	<0.0001	3.39	1.52–7.59	0.003
Gastrointestinal						
Diarrhea	2.88	2.35-3.78	<0.0001	6.57	4.09-10.58	<0.000
Colitis	14.62	8.61–24.83	<0.0001	14.01	7.34–26.77	<0.000
Endocrine		•			•	•
Hypophysitis	5.30	1.71–16.46	0.004	4.22	1.72–10.34	0.002
Hypothyroidism	7.86	4.10-15.04	<0.0001	3.72	1.18–11.75	0.025
Hyperthyroidism	3.78	0.94-15.17	0.061	3.78	0.94–15.17	0.061
Adrenal insufficiency	3.88	1.46-10.36	0.007	3.77	1.41-10.06	0.008
Hypopituitarism	4.73	1.73–12.95	0.003	4.73	1.73–12.95	0.003
Hepatic			•		,	
Hepatitis	4.44	1.51-13.04	0.007	4.44	1.51-13.04	0.007
ALT increased	3.28	1.79–6.02	<0.0001	11.37	4.45-29.10	<0.000
AST increased	3.12	1.92–5.09	<0.0001	4.9	1.41–17.07	0.013
Other		•			•	•
Pneumonitis	1.64	0.91–2.94	0.098	1.27	0.66–2.44	0.477
Pancreatitis	1.51	0.49-4.60	0.472	1.51	0.49-4.60	0.472
Guillain-Barre syndrome	2.00	0.54–7.40	0.299	2.00	0.54–7.40	0.299
Treatment-related AEs		•			•	•
Hematologic						
Anemia	1.11	0.83-1.49	0.484	0.95	0.68–1.34	0.782
Neutropenia	1.05	0.66-1.68	0.826	0.72	0.37-1.42	0.349
Thrombocytopenia	0.84	0.47–1.52	0.569	0.57	0.34–0.96	0.035
Musculoskeletal problems						
Arthritis	1.30	0.25-6.77	0.755	1.30	0.25–6.77	0.755
Arthralgia	1.02	0.86-1.20	0.851	0.84	0.27–2.61	0.769
Back pain	0.77	0.65-0.90	0.001	0.65	0.36-1.15	0.137
Musculoskeletal pain	0.72	0.58-0.90	0.003	0.7	0.24–2.01	0.503
Bone pain	0.76	0.58-0.99	0.044	0.73	0.30-1.78	0.488
Myalgia	1.33	1.00-1.77	0.05	0.71	0.07–6.83	0.765

Notes: *IrAEs, immune-related adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; OR, odds ratio; CI, confidence interval. #Includes both serious and other adverse events if data were extracted from ClinicalTrials.gov; includes all Common Terminology of Clinical Adverse Events (CTCAE) grades if data were extracted from the publication. $^{+}$ Serious adverse events if data were extracted from ClinicalTrials.gov; CTCAE grades \geq 3 if data were extracted from the publication.

the anti-CTLA-4 treatment groups than the corresponding control groups (Figure 1), as was the incidence of severe rash (OR 3.39, P=0.003). There was no significant difference between the experimental and control groups with respect to the incidence of severe pruritus (OR 3.64, P=0.072) (Table 4).

Gastrointestinal AEs

Diarrhea and colitis were reported in 11 and 9 studies, and affected a total of 1905 (47.8%) and 254 (6.4%) patients, respectively (all grades). Compared with the control group, the anti-CTLA-4-treated patients had higher overall risks of diarrhea (OR 2.88, 95% CI 2.35–3.78) and colitis

Study ID			OR (95% CI)	Events, Intervention	Events, Control	% Weigh
Placebo						
Eggermont (2016)			4.37 (3.20, 5.98)	203/471	70/474	23.53
Maio (2017)		•	4.31 (2.43, 7.66)	103/380	15/189	6.98
Beer (2017)			3.78 (2.29, 6.23)		21/199	9.20
Subtotal (I–squared = 0.0%, <i>P</i> =0.885)		\diamond	4.22 (3.31, 5.36)		106/862	39.70
Chemotherapy						
Robert (2011)			4.45 (2.66, 7.45)	74/247	22/251	8.65
Reck (ipilimumab, phased) (2012)		*	5.73 (1.16, 28.33)	9/42	2/44	0.90
Reck (ipilimumab, concurrent) (2012)			6.56 (1.34, 32.06)	10/42	2/44	0.91
Lynch (ipilimumab, Phased) (2012)		•	1.78 (0.50, 6.39)	7/67	4/65	1.40
Lynch (ipilimumab, concurrent) (2012)			3.75 (1.16, 12.05)	14/71	4/65	1.68
Ribas (2013)		•	8.42 (4.83, 14.66)	100/325	16/319	7.45
Reck (2016)			6.31 (3.59, 11.08)	83/562	15/561	7.24
Govindan (2017)			3.30 (2.09, 5.21)	79/475	27/473	10.98
Subtotal (I-squared = 31.3%, P=0.178)		\diamond	4.80 (3.77, 6.12)	376/1831	92/1822	39.22
Radiotherapy		_				
Kwon (2014)			5.72 (3.52, 9.31)	99/393	22/396	9.70
Subtotal (I-squared = .%, P=.)		$\langle \rangle$	5.72 (3.52, 9.31)	99/393	22/396	9.70
gp 100		_				
Hodi (ipilimumab + gp100) (2010)			2.21 (1.21, 4.06)	79/380	14/132	6.24
Hodi (ipilimumab alone) (2010)			3.57 (1.83, 6.97)		14/132	5.14
Subtotal (I-squared = 7.6%, P=0.298)		\sim	2.75 (1.75, 4.31)	118/511	28/264	11.37
Heterogeneity between groups: P=0.114						
Overall (I-squared = 25.6%, <i>P</i> =0.179)		\$	4.35 (3.74, 5.07)	1022/3985	248/3344	100.00
l 0.0312	1	i	32.1			

Rash

Study			Events,	Events,	%
ID		OR (95% CI)	Intervention	Control	Weight
Placebo					
Eggermont (2016)		3.21 (2.37, 4.35)	186/471	80/474	12.48
Maio (2017)		3.55 (1.92, 6.57)	79/380	13/189	7.27
Beer (2017)		4.80 (2.95, 7.81)	149/399	22/199	9.15
Subtotal (I-squared = 0.0%, P=0.393)	\diamond	3.59 (2.83, 4.55)	414/1250	115/862	28.89
Chemotherapy					
Robert (2011)		4.81 (2.73, 8.50)	64/247	17/251	7.90
Reck (ipilimumab, phased) (2012)	*	5.47 (1.42, 21.09)	12/42	3/44	2.34
Reck (ipilimumab, concurrent) (2012)		→ 9.29 (2.47, 34.94)	17/42	3/44	2.42
Lynch (ipilimumab, Phased) (2012)		1.45 (0.52, 4.08)	10/67	7/65	3.63
Lynch (ipilimumab, concurrent) (2012)	i	4.50 (1.79, 11.34)	25/71	7/65	4.30
Ribas (2013)		 8.60 (5.01, 14.77) 	106/325	17/319	8.31
Reck (2016)		5.39 (3.51, 8.28)	124/562	28/561	10.14
Govindan (2017)		2.32 (1.58, 3.39)	93/475	45/473	11.00
Subtotal (I-squared = 69.8%, <i>P</i> =0.002)		4.42 (2.85, 6.83)	451/1831	127/1822	50.04
Radiotherapy					
Kwon (2014)		3.57 (2.27, 5.62)	84/393	28/396	9.71
Subtotal (I-squared = .%, P=.)		3.57 (2.27, 5.62)	84/393	28/396	9.71
gp 100					
Hodi (ipilimumab + gp100) (2010)		3.64 (1.77, 7.49)	80/380	9/132	6.03
Hodi (ipilimumab alone) (2010)		3.89 (1.76, 8.58)	29/131	9/132	5.33
Subtotal (I-squared = 0.0%, <i>P</i> =0.907)		3.75 (2.20, 6.39)	109/511	18/264	11.36
Overall (I–squared = 50.1%, <i>P</i> =0.017)	↓ ♦	4.03 (3.22, 5.04)	1058/3985	288/3344	100.00
NOTE: weights are from random effects analysis					
l 0.0286	и 1	1 34.9			

Figure I Forest plot of the overall risk of pruritus and rash related to anti-CTLA-4 drugs.

(OR 14.62, 95% CI 8.61–24.83) (Figure 2). The same trends were observed for serious diarrhea (OR 6.57, 95% CI 4.09–10.58) and serious colitis (OR 14.01, 95% CI 7.34–26.77) (Table 4).

Endocrine AEs

Hypophysitis, hyperthyroidism, hypothyroidism, adrenal insufficiency, and hypopituitarism of any grade were observed in 131 (3.3%), 100 (2.5%), 9 (0.2%), 25 (0.6%), and 27 (0.7%),

Colitis			
Study		Events, Events	
ID	OR (95% CI)	Intervention Contro	I Weigh
Placebo			
Eggermont (2016)	20.23 (8.77, 46.66)	97/471 6/474	40.1
Maio (2017)	26.05 (1.58, 430.68)	24/380 0/189	3.56
Beer (2017)	7.72 (1.82, 32.69)	29/399 2/199	13.4
subtotal (I-squard =0.0%, P=0.498)	16.38 (8.13, 33.00)	150/1250 8/862	57.2
Chemotherapy			
Robert (2011)	17.85 (1.02, 310.99)	8/247 0/251	3.44
Reck (ipilimumab, phased) (2012)	3.22 (0.13, 81.19)	1/42 0/44	2.69
Lynch (ipilimumab, phased) (2012)	5.00 (0.24, 106.17)	2/67 0/65	3.01
Ribas (2013)	27.60 (1.63, 466.36)	13/325 0/319	3.51
Reck (2016) -	24.98 (3.37, 185.31)		6.99
Govindan (2017)	7.15 (1.62, 31.64)	14/475 2/473	12.6
Reck (ipilimumab, concurrent) (2012)	(Excluded)	0/42 0/44	0.00
Lynch (ipilimumab, concurrent) (2012)	I (Excluded)	0/71 0/65	0.00
subtotal (I-squard =0.0%, <i>P</i> =0.807)	10.83 (4.26, 27.49)	62/1831 3/1822	
Padiatharany			
Radiotherapy Known(2014)	4 5.77 (2.76, 758.28)	21/393 0/396	3.56
subtotal (I-squard =.%, P= .)	45.77 (2.76, 758.28)		3.56
gp100		14/290 0/122	2 5 1
Hodi (ipilimumab + gp100) (2010)			3.51
Hodi (ipilimumab alone) (2010)	15.96 (0.90, 282.44)		3.40
subtotal (I-squard =0.0%, P=0.838) Placebo	12.89 (1.72, 96.68)	21/211 0/264	6.91
Heterogeneity between groups: P=0.765			
Overall (I-squard =0.0%, <i>P</i> =0.937)	14.62 (8.61, 24.83)	254/3985 11/334	4 100.
00133	1		
.00132	Г 758		
.00132 Diarrhea	1 758		
	E	Events, Events	
Study	E	Events, Events	
Study ID	E		
Diarrhea	E		l Weig
Diarrhea Study ID Placebo	e OR (95% Cl) ir	tervention Contro	l Weig 4 9.14
Diarrhea Study ID Placebo Eggermont (2016) Maio (2017)	CR (95% CI) Ir 	264/471 146/47	l Weig 4 9.14 7.83
Diarrhea Study ID Placebo Eggermont (2016)	E OR (95% CI) ir 	264/471 146/47 237/380 36/189	4 9.14 7.83 8.17
Diarrhea Study D Placebo Eggermont (2016) Maio (2017) Beer (2017) Beer (2017) subtotal (I-squard =0.0%, <i>P</i> =0.498)	E OR (95% CI) Ir 2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74)	264/471 146/47 237/380 36/186 237/399 48/199	4 9.14 7.83 8.17
Diarrhea Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) Beer (2017) subtotal (I-squard =0.0%, <i>P</i> =0.498) Chemotherapy	CR (95% Cl) In 2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54)	Attervention Control 264/471 146/47 237/380 36/189 237/399 48/199 738/1250 230/86	4 9.14 7.83 8.17 2 25.1
Diarrhea Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) Subtotal (I-squard =0.0%, <i>P</i> =0.498) Chemotherapy Robert (2011)	E OR (95% Cl) Ir 2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54) 2.04 (1.39, 2.99)	attervention Control 264/471 146/47 237/380 36/182 237/399 48/192 738/1250 230/86 99/247 62/251	4 9.14 7.83 8.17 2 25.1 8.15
Diarrhea Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) subtotal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012)	2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54) 2.04 (1.39, 2.99) 2.77 (1.03, 7.43)	Attrivention Control 264/471 146/47 237/380 36/186 237/399 48/199 738/1250 230/86 99/247 62/251 16/42 8/44	4 9.14 7.83 8.17 2 25.1 8.15 3.73
Diarrhea Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) Beer (2017) subtotal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, concurrent) (2012)	2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54) 2.04 (1.39, 2.99) 2.77 (1.03, 7.43) 2.37 (0.84, 6.70)	tervention Control 264/471 146/47 237/380 36/188 237/399 48/199 738/1250 230/86 99/247 62/251 16/42 8/44 13/42 7/44	4 9.14 7.83 8.17 2 25.1 8.15 3.73 3.48
Diarrhea Study ID Placebo Eggermont (2016) Maio (2017) Beder (2017) subtotal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, phased) (2012)	2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54) 2.04 (1.39, 2.99) 2.77 (1.03, 7.43) 2.37 (0.84, 6.70) 1.55 (0.75, 3.24)	tervention Control 264/471 146/47 237/380 36/188 237/399 48/199 738/1250 230/86 99/247 62/251 16/42 8/44 13/42 7/44 25/67 18/65	4 9.14 7.83 8.17 2 25.1 8.15 3.73 3.48 5.21
Diarrhea Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) Subtotal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012)	CR (95% CI) In 2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54) 2.04 (1.39, 2.99) 2.77 (1.03, 7.43) 2.37 (0.84, 6.70) 1.55 (0.75, 3.24) 2.37 (1.11, 5.07)	Addition Control 264/471 146/47 237/380 36/188 237/380 36/189 237/380 36/189 738/1250 230/86 99/247 62/251 16/42 8/44 13/42 7/44 25/67 18/65 28/71 14/65	4 9.14 7.83 8.17 2 25.1 8.15 3.73 3.48 5.21 5.04
Diarrhea Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) subtotal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Ribas (2013)	2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54) 2.04 (1.39, 2.99) 2.77 (1.03, 7.43) 2.37 (0.84, 6.70) 1.55 (0.75, 3.24)	tervention Control 264/471 146/47 237/380 36/188 237/399 48/199 738/1250 230/86 99/247 62/251 16/42 8/44 13/42 7/44 25/67 18/65	4 9.14 7.83 8.17 2 25.1 8.15 3.73 3.48 5.21 5.04
Diarrhea Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) subtotal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Ribas (2013)	CR (95% CI) In 2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54) 2.04 (1.39, 2.99) 2.77 (1.03, 7.43) 2.37 (0.84, 6.70) 1.55 (0.75, 3.24) 2.37 (1.11, 5.07)	Addition Control 264/471 146/47 237/380 36/188 237/380 36/189 237/380 36/189 738/1250 230/86 99/247 62/251 16/42 8/44 13/42 7/44 25/67 18/65 28/71 14/65	 Wei 9.14 7.83 8.17 2 25.1 8.15 3.73 3.48 5.21 5.04 8.34
Diarrhea Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) Beer (2017) subtotal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Lynch (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Reck (2016)	CR (95% CI) In 2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54) 2.04 (1.39, 2.99) 2.77 (1.03, 7.43) 2.37 (0.84, 6.70) 1.55 (0.75, 3.24) 2.37 (1.11, 5.07) 4.18 (2.91, 6.00)	tervention Control 264/471 146/47 237/380 36/188 237/390 48/199 738/1250 230/86 99/247 62/251 16/42 8/44 13/42 7/44 25/67 18/65 28/71 14/65	 Wei 4 9.14 7.83 8.17 2 25.1 8.15 3.48 5.21 5.04 8.34 1 9.18
Diarrhea Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) Beer (2017) subtotal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Reck (2016) Reck (2016) Govindan (2017)	2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54) 2.04 (1.39, 2.99) 2.77 (1.03, 7.43) 2.37 (0.84, 6.70) 1.55 (0.75, 3.24) 2.37 (1.11, 5.07) 4.18 (2.91, 6.00) 1.86 (1.44, 2.42)	tervention Control 264/471 146/47 237/380 36/185 237/399 48/195 738/1250 230/86 99/247 62/251 16/42 8/44 13/42 7/44 25/67 18/65 153/325 56/315 201/562 129/56 18/2/475 99/473	 Wei 4 9.14 7.83 8.17 2 25.1 8.15 3.73 3.48 5.21 5.04 8.34 1 9.18 8.97
Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) subttal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Reck (2016) Govindan (2017) subtotal (I-squard =0.0%, P= 0.042)	2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54) 2.04 (1.39, 2.99) 2.77 (1.03, 7.43) 2.37 (0.84, 6.70) 1.55 (0.75, 3.24) 2.37 (1.11, 5.07) 4.18 (2.91, 6.00) 1.86 (1.44, 2.42) 2.35 (1.76, 3.13)	tervention Control 264/471 146/47 237/380 36/185 237/399 48/195 738/1250 230/86 99/247 62/251 16/42 8/44 13/42 7/44 25/67 18/65 153/325 56/315 201/562 129/56 18/2/475 99/473	 Weight 4 9.14 7.83 8.17 2 25.1 8.15 3.73 3.48 5.21 5.04 8.34 1 9.18 8.97
Diarrhea Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) Beer (2017) Subtotal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Ribas (2013) Reck (2016) Govindan (2017) Subtotal (I-squard =0.0%, P= 0.042) Radiotherapy	2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54) 2.04 (1.39, 2.99) 2.77 (1.03, 7.43) 2.37 (0.84, 6.70) 1.55 (0.75, 3.24) 2.37 (1.11, 5.07) 4.18 (2.91, 6.00) 1.86 (1.44, 2.42) 2.35 (1.76, 3.13) 2.36 (1.85, 3.00)	tervention Control 264/471 146/47 237/380 36/183 237/390 48/199 738/1250 230/86 99/247 62/251 16/42 8/44 13/42 7/44 25/67 18/65 153/325 56/315 201/562 129/56 182/475 99/473 717/1831 393/18	 Wei, 4 9.14 7.83 8.17 2 25.1 8.15 3.73 3.48 5.21 5.04 8.34 1 9.18 8.97 22 52.1
Diarrhea Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) Beer (2017) Subtotal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Reck (2016) Govindan (2017)	2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54) 2.04 (1.39, 2.99) 2.77 (1.03, 7.43) 2.37 (0.84, 6.70) 1.55 (0.75, 3.24) 2.37 (1.11, 5.07) 4.18 (2.91, 6.00) 1.86 (1.44, 2.42) 2.35 (1.76, 3.13)	tervention Control 264/471 146/47 237/380 36/185 237/399 48/195 738/1250 230/86 99/247 62/251 16/42 8/44 13/42 7/44 25/67 18/65 153/325 56/315 201/562 129/56 18/2/475 99/473	4 9.14 7.83 8.17 2 25.1 8.15 3.73 3.48 5.21 5.04 8.34 1 9.18 8.97 22 52.1 6 8.83
Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) subtotal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Reck (ipilimumab, concurrent) (2012) Reck (2016) Govindan (2017) subtotal (I-squard =0.0%, P= 0.042) Radiotherapy Known(2014) subtotal (I-squard =.%, P= .)	2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54) 2.04 (1.39, 2.99) 2.77 (1.03, 7.43) 2.37 (0.84, 6.70) 1.55 (0.75, 3.24) 2.37 (1.11, 5.07) 4.18 (2.91, 6.00) 1.86 (1.44, 2.42) 2.35 (1.76, 3.13) 2.36 (1.85, 3.00) 4.90 (3.61, 6.65)	tervention Control 264/471 146/47 237/380 36/185 237/380 36/185 237/399 48/196 738/1250 230/86 99/247 62/251 16/42 8/44 13/42 7/44 25/67 18/65 153/255 56/315 201/562 129/56 18/475 99/477 717/1831 393/18 245/393 100/38	4 9.14 7.83 8.17 2 25.1 8.15 3.73 3.48 5.21 5.04 8.34 1 9.18 8.34 1 9.18 8.37 4 8.34 1 9.18 8.34 6 8.83
Study JD Placebo Eggermont (2016) Maio (2017) Beer (2017) subtotal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Reids (2016) Govindan (2017) subtotal (I-squard =0.0%, P= 0.042) Radiotherapy Known(2014) subtotal (I-squard =%, P= .) gp100	2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54) 2.04 (1.39, 2.99) 2.77 (1.03, 7.43) 2.37 (0.84, 6.70) 1.55 (0.75, 3.24) 2.37 (1.11, 5.07) 4.18 (2.91, 6.00) 1.86 (1.44, 2.42) 2.35 (1.76, 3.13) 2.36 (1.85, 3.00) 4.90 (3.61, 6.65) 4.90 (3.61, 6.65)	tervention Control 264/471 146/47 237/380 36/188 237/399 48/199 738/1250 230/86 99/247 62/251 16/42 8/44 13/42 7/44 25/67 18/65 28/71 14/65 153/325 56/318 201/562 129/56 182/475 99/477 717/1831 393/18 245/393 100/38 245/393 100/38	4 9.14 7.83 8.17 2 25.1 8.15 3.73 3.48 5.21 5.04 8.34 1 9.18 8.97 22 52.1 6 8.83
Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) subtotal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, phased) (2012) Kuch (ipilimumab, concurrent) (2012) Reck (2016) Govindan (2017) subtotal (I-squard =0.0%, P= 0.042) Radiotherapy Known(2014) subtotal (I-squard =.%, P= .) gp100 Hodi (ipilimumab + gp100) (2010)	2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54) 2.04 (1.39, 2.99) 2.77 (1.03, 7.43) 2.37 (0.84, 6.70) 1.55 (0.75, 3.24) 2.37 (1.11, 5.07) 4.18 (2.91, 6.00) 1.86 (1.44, 2.42) 2.35 (1.76, 3.13) 2.36 (1.85, 3.00) 4.90 (3.61, 6.65) 4.90 (3.61, 6.65) 2.90 (1.80, 4.67) 1	tervention Control 264/471 146/47 237/380 36/189 237/399 48/199 738/1250 230/86 99/247 62/251 16/42 8/44 13/42 7/44 25/67 18/65 28/71 14/65 153/325 56/316 201/562 129/56 18/2/475 99/47 717/1831 393/16 245/393 100/32 245/393 26/132	 Weij 4 9.14 7.83 8.17 2 25.1 8.15 3.73 3.48 5.21 5.04 8.34 1 9.18 8.87 22 52.1 6 8.83 7.32
Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) subtotal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Khosa (2013) Reck (2016) Govindan (2017) subtotal (I-squard =0.0%, P= 0.042) Radiotherapy Known(2014) subtotal (I-squard =.%, P= .) gp100 Hodi (ipilimumab alone) (2010) Hodi (ipilimumab alone) (2010)	2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54) 2.04 (1.39, 2.99) 2.77 (1.03, 7.43) 2.37 (0.84, 6.70) 1.55 (0.75, 3.24) 2.37 (1.11, 5.07) 4.18 (2.91, 6.00) 1.86 (1.44, 2.42) 2.35 (1.76, 3.13) 2.36 (1.85, 3.00) 4.90 (3.61, 6.65) 4.90 (3.61, 6.65) 4.90 (3.61, 6.65) 4.90 (3.61, 6.65) 4.90 (3.61, 6.65) 4.90 (1.80, 4.67) 1 2.28 (1.31, 3.99) 4	tervention Control 264/471 146/47 237/380 36/185 237/380 36/185 237/399 48/195 738/1250 230/86 99/247 62/251 16/42 8/44 13/42 7/44 25/67 18/65 153/255 56/315 201/562 129/56 18/2/475 99/477 717/1831 393/16 245/393 100/35 245/393 100/35 558/380 26/132 17/131 26/132	 Weij 4 9.14 7.83 8.15 3.73 3.48 5.21 5.04 8.34 1 9.18 8.97 22 52.1 6 8.83 6 8.83 7.32 6.59
Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) subtotal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Reak (2016) Govindan (2017) subtotal (I-squard =0.0%, P= 0.042) Radiotherapy Known(2014)	2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54) 2.04 (1.39, 2.99) 2.77 (1.03, 7.43) 2.37 (0.84, 6.70) 1.55 (0.75, 3.24) 2.37 (1.11, 5.07) 4.18 (2.91, 6.00) 1.86 (1.44, 2.42) 2.35 (1.76, 3.13) 2.36 (1.85, 3.00) 4.90 (3.61, 6.65) 4.90 (3.61, 6.65) 4.90 (3.61, 6.65) 4.90 (3.61, 6.65) 4.90 (3.61, 6.65) 4.90 (1.80, 4.67) 1 2.28 (1.31, 3.99) 4	tervention Control 264/471 146/47 237/380 36/189 237/399 48/199 738/1250 230/86 99/247 62/251 16/42 8/44 13/42 7/44 25/67 18/65 28/71 14/65 153/325 56/316 201/562 129/56 18/2/475 99/47 717/1831 393/16 245/393 100/32 245/393 26/132	 Weig 4 9.14 7.83 8.17 2 25.1 8.15 3.73 3.48 5.21 5.04 8.34 8.37 1 9.18 8.97 22 52.1 6 8.83 6 8.83 7.32 6.59
Diarrhea Study JD Placebo Eggermont (2016) Maio (2017) Beer (2017) subtotal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Rubas (2013) Reck (2016) Govindan (2017) subtotal (I-squard =0.0%, P= 0.042) Radiotherapy Known(2014) subtotal (I-squard =.%, P= .) gp100 Hodi (ipilimumab alone) (2010) Hodi (ipilimumab alone) (2010)	2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54) 2.04 (1.39, 2.99) 2.77 (1.03, 7.43) 2.37 (0.84, 6.70) 1.55 (0.75, 3.24) 2.37 (1.11, 5.07) 4.18 (2.91, 6.00) 1.86 (1.44, 2.42) 2.35 (1.76, 3.13) 2.36 (1.85, 3.00) 4.90 (3.61, 6.65) 4.90 (3.61, 6.65)	tervention Control 264/471 146/47 237/380 36/188 237/399 48/199 738/1250 230/86 99/247 62/251 16/42 8/44 13/42 7/44 25/67 18/65 1201/562 129/56 182/475 99/473 217/1831 393/18 245/393 100/35 58/380 26/132 58/380 26/132 57/131 26/132	 Weij 4 9.14 7.83 8.15 3.73 3.48 5.21 5.04 8.34 1 9.18 8.97 22 52.1 6 8.83 6 8.83 7.32 6.59
Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) subtotal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Rack (2016) Govindan (2017) subtotal (I-squard =0.0%, P= 0.042) Radiotherapy Known(2014) subtotal (I-squard =.%, P= .) gp100 Hodi (ipilimumab alone) (2010) Hodi (ipilimumab alone) (2010) Hodi (ipilimumab alone) (2010)	2.87 (2.19, 3.74) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54) 2.04 (1.39, 2.99) 2.77 (1.03, 7.43) 2.37 (0.84, 6.70) 1.55 (0.75, 3.24) 2.37 (1.11, 5.07) 4.18 (2.91, 6.00) 1.86 (1.44, 2.42) 2.35 (1.76, 3.13) 2.36 (1.85, 3.00) 4.90 (3.61, 6.65) 4.90 (3.61, 6.65)	tervention Control 264/471 146/47 237/380 36/188 237/399 48/199 738/1250 230/86 99/247 62/251 16/42 8/44 13/42 7/44 25/67 18/65 1201/562 129/56 182/475 99/473 217/1831 393/18 245/393 100/35 58/380 26/132 58/380 26/132 57/131 26/132	 Wei 9.14 7.83 8.17 2 25.1 8.16 3.77 3.42 5.24 5.24 5.24 5.24 6.883 6.883 7.32 6.58 13.5

Figure 2 Forest plot of the overall risk of colitis and diarrhea related to anti-CTLA-4 drugs.

respectively, of patients treated with anti-CTLA-4 drugs. Meta-analysis showed that patients in the intervention arms

had higher risks of hypophysitis (OR 5.30, 95% CI 1.71-16.46), hypothyroidism (OR 7.86, 95% CI 4.10-15.04),

adrenal insufficiency (OR 3.88, 95% CI 1.46–10.36), and hypopituitarism (OR 4.73, 95% CI 1.73–12.95), but not hyperthyroidism (OR 3.78, 95% CI 0.94–15.17), compared with the control therapies (Figures 3, 4, and S2). The same trends were observed when the rates of severe AEs were analyzed (Table 4).

Hepatic AEs

A total of 8, 9, and 9 studies evaluated the incidence of hepatitis, alanine aminotransferase (ALT) levels, and aspartate aminotransferase (AST) levels, respectively, and were found to affect 19 (0.5%), 402 (10.1%), and 361 (9.1%) patients, respectively, in the anti-CTLA-4 intervention groups. Meta-analysis showed that the risks of all three hepatic AEs were higher for the anti-CTLA-4 compared with control groups (hepatitis: OR 4.44, 95% CI 1.51–13.04; ALT: OR 3.28, 95% CI 1.79–6.02; AST: OR 3.12, 95% CI 1.92–5.09) (Figures 5 and S3). The same trend held when severe hepatic AEs were analyzed (Table 4).

Other irAEs

We also analyzed the incidence of pneumonitis, pancreatitis and Guillain–Barre syndrome in our study. Most of them were severe and the rates were low (<1%) in the intervention arms (18 [0.7%], 8 [0.2%], and 6 [0.2%] for severe pneumonitis, pancreatitis, and Guillain–Barre syndrome). No significant differences were observed between the two arms (pneumonitis: OR 1.64 95% CI 0.91–2.94; pancreatitis: OR 1.51 95% CI 0.49–4.60; Guillain–Barre syndrome: OR 2.00 95% CI 0.54–7.04) (Figure 6 and S4).

Treatment-related AEs

In addition to the organ-specific irAEs, we also examined the incidence of treatment-related AEs including hematologic abnormalities and musculoskeletal disorders (seen in Table 5). The pooled odds ratios are exhibited in Table 4.

Hematologic abnormalities

Anemia, neutropenia, and thrombocytopenia were assessed in nine studies. A total of 717 (18.0%), 451 (11.3%), and 206 (5.2%) patients occurred these three AEs when receiving anti-CTLA-4 drugs, respectively. Our meta-analyses demonstrated no significant difference existed between the two arms with regard to anemia (OR 1.11 95% CI 0.83–1.49), neutropenia (OR 1.05 95% CI 0.66–1.68), and thrombocytopenia (OR 0.84 95% CI 0.47–1.52). When looking at severe hematologic AEs, patients treated with anti-CTLA-4 drugs were less likely to suffer thrombocytopenia (OR 0.57 95% CI 0.34–0.96) (Table 4).

Musculoskeletal disorders

Six musculoskeletal disorders including arthritis, arthralgia, back pain, musculoskeletal pain, bone pain, and myalgia were analyzed in our study. The numbers and rates were 3 (0.1%), 374 (9.4%), 363 (9.1%), 183 (4.6%), 110 (2.8%), and 115 (3.5%) for each musculoskeletal problem related to anti-CTLA-4 drugs, respectively (Table 5). Meta-analysis showed that patients were less likely to experience back pain, musculoskeletal pain, and bone pain (OR 0.77, 0.72, 0.76; all P<0.05) and more likely to experience myalgia (OR 1.33, P=0.05) compared to the control group. There was no significant difference regarding the severe musculoskeletal disorders (arthritis: OR 1.30 95% CI 0.25-6.77; arthralgia: OR 0.84 95% CI 0.27-2.61; back pain: OR 0.65 95% CI 0.36-1.15; musculoskeletal pain: OR 0.70 95% CI 0.24-2.01; bone pain: OR 0.73 95% CI 0.30-1.78; myalgia: OR 0.71 95% CI 0.07-6.83) (Table 4).

Discussion

The aim of this study was to provide further understanding of the incidence of irAEs related to anti-CTLA-4 drugs with the ultimate goal of assisting clinicians in treating patients with this drug class. We analyzed 11 randomized controlled trials that included a total of nearly 4000 patients treated with ipilimumab or tremelimumab and provided precise data of the common and important AEs involving multiple organs. To our knowledge, this is the most comprehensive meta-analysis of the incidence and risk of organ-specific irAEs following anti-CTLA-4 therapy in cancer patients, and additionally, we believe this is the first meta-analysis to comprehensively evaluate the incidence of anti-CTLA-4 treatment-related hematologic abnormalities and musculoskeletal disorders compared with control treatments.

Among the strengths of our study is the inclusion of AE data mainly collected from ClinicalTrials.gov (10 of 11 trials). Several meta-analyses have previously investigated anti-CTLA-4-related AEs,^{12–14} but most of them focused mainly on ipilimumab and evaluated a limited number of irAEs. Compared with these studies, we included ipilimumab and tremelimumab and analyzed more trials and more irAEs, which is a strength but could also be a source of inconsistency between the studies. Unlike the study conducted by Velasco et al,¹³ we found an increased risk of all-grade AST elevation and high-grade hypothyroidism with CTLA-4 inhibitors

Adrenal insufficiency

D OR (05%, C1) Meterwink Control N Pleads Segments (2010) 13.25 (0.74, 25.69) 0.471 0.474 1 See (2017)		F	Events, E	Events,	%
Egement (2016) Marc (2017) Ber (2018) Ber (2017) Ber (2017) B	Study ID				Wei
Egymon (2016) Marc (2017) Barc (2017) Barc (2017) Barc (2017) Barc (2017) Barc (2017) Barc (2017) Barc (2017) Barc (2013) Barc (2014) Barc (2015) Barc (2015) Bar	Placebo				
main (a) (1)		13.25 (0.74, 235.89) 6	6/471	0/474	11.6
Base (D27) 6.58 (D27,17,27) 6.58 (D27,17,28) 1.68 (D27,17,28) 6.58					10.4
biotocal (1-squared = 0.0%, P=0.737) 6.22 (1.41, 33.77) 14/1250 0.882 2 Demotherapy 8.4 (0.44, 166.41) 4.025 0.019 1 Stackad (1-squared = 0.0%, P=0.137) 6.22 (1.41, 33.77) 14/1250 0.882 2 Stackad (1-squared = 0.0%, P=0.184) 3.00 (0.12, 7.04.43) 2.47 (0.45, 166.41) 4.025 0.047 1 0.058 0 0.047 1 0.047 1 0.047 1 0.047 1 0.047 1 0.048 1 0.047 1 0.048 1 0.047 1 0.058 0 0.047 1 0.048 1 0.047 1 0.058 0 0.047 1 0.058 0 0.047 1 0.048 1 0.048 1 0.048 1 0.048 1 0.048 1 0.047 1 0.048 1 0.047 1 0.058 0 0.047 1 0.058 0 0.047 1 0.058 0 0.047 1 0.058 0 0.047 1 0.058 0 <t< td=""><td></td><td></td><td></td><td></td><td>11.5</td></t<>					11.5
Demolbarapy Bites (2015) Bites (2017) Bites (2017) Bit					33.6
Blase (2015) 8.4 (4.08, 16.8 1) 4.025 0014 Seck (2016) 3.00 (1.2, 7.3.6) 1.625 0014 0.047 Seck (2017) 5.00 (1.2, 7.3.6) 1.625 0.021 0.042	Subtotal (I-squared = 0.0% , $P=0.737$)	6.22 (1.14, 33.77)	14/1250	0/002	33.0
Back (2015) Back (2015) Back (2017) Back					
Several (2017) Sever (2017)	Ribas (2013)	8.94 (0.48, 166.81) 4	4/325	0/319	11.2
Statert (2011) (Excluded) 0.427 0.251 C State (plinnumb, bread() (2012) (Excluded) 0.42 0.44 C State (plinnumb, bread() (2012) (Excluded) 0.42 0.44 C State (plinnumb, bread() (2012) (Excluded) 0.71 0.85 C State (plinnumb, bread() (2012) (Excluded) 0.71 0.85 C State (plinnumb, bread() (2010) (Excluded) 0.71 0.224 1 Dockate (Unit) (Excluded) 0.71 0.28 1 State (Diff) (Excluded) 0.71 0.28 1 State (Diff) (Excluded) 0.71 0.78 1 State (Diff)	Reck (2016)		1/562	0/561	9.38
Back (Bimmuch, Dataced) (2012) Back (Bimmuch, Dataced) (2012) Back (Bimmuch, Dataced) (2012) Back (Bimmuch, Dataced) (2012) Back (Binmuch, Dataced) (2012) Back (Binmuch, Dataced) (2010) Back (Binmuch, Dataced) (2012) Back (Binmuch, Dataced) (2012)	Govindan (2017)	5.00 (0.24, 104.43) 2	2/475	0/473	10.4
Back (pilimunab. concurrent) (2012) yrnch (pilimunab. concurrent) (2012) statistic (L-squared = 0.0%, P=0.884) Back (bit (L-squared = 0.0%, P=0.884) Statistic (L-squared = 0.0%, P=0.455) Statistic (L-squared = 0.0%, P=0.456) Statistic (L-squared = 0.0%, P=0.765) Statistic (L-squared = 0.0%, P=0.785) Statistic (L-squared = 0.0%, P=0.246) Statistic (L-squared = 0.0%, P=0.246) Statistic (L-squared = 2.0.1%, P=0.246) Statisti (L-squared = 2.0.1%, P=0.246)	Robert (2011)	(Excluded) 0	0/247	0/251	0.0
Bask (Binnumab, concurrent) (2012) ymh (Binnumab, Based) (2012) babota (L-squared = 0.0%, P-0.884) Balothempy web (2014) babota (L-squared = -%, P-x.) pr 100 todi (Binnumab accourse) (2010) babota (L-squared = -%, P-x.) pr 100 todi (Binnumab accourse) (2010) babota (L-squared = -%, P-x.) pr 100 todi (Binnumab - gr100) (2010) babota (L-squared = -%, P-x.) pr 100 todi (Binnumab - gr100) (2010) babota (L-squared = -%, P-x.) pr 100 todi (Binnumab - gr100) (2010) babota (L-squared = -0.%, P-0.645) babota (L-squared = -0.%, P-0.645) babota (L-squared = -0.%, P-0.755 based Babota (L-squared = -0.%, P-0.249) babota (L-squared = -0.%, P-0.248) babota (L	Reck (ipilimumab, phased) (2012)				0.0
ynch (pilamunab, Phased) (2012) ynch (pilamunab, Phased) (2012) babdotal (I-squared = 0,0%, P=0,884) babdotal (I-squared = 0,0%, P=0,884) babdotal (I-squared = 0,0%, P=0,045) teterogenety between groups: P=0.765 bverall (I-squared = 0,0%, P=0.045) teterogenety between groups: P=0.765 bverall (I-squared = 0,0%, P=0.045) teterogenety between groups: P=0.765 bverall (I-squared = 0,0%, P=0.045) teterogenety between groups: P=0.765 bverall (I-squared = 0,0%, P=0.046) junction de state sta					0.0
ynch (pilmumab, concurrent) (2012) (Excluded) 0/71 0/65 0 Staktotal (I-equared = 0.0%, P=0.884) S.29 (0.91, 30.76) 7/1831 0/182 2 Radiotherapy S.29 (0.91, 30.76) 7/1831 0/182 2 Staktotal (I-equared = .%, P=.) 2.02 (0.16, 22.37) 2/393 1/396 1 pp 106 1.05 (0.04, 25.57) 1/390 0/132 5 Staktod (I-equared = 0.0%, P=0.646) 3.05 (0.17, 7.5.66) 1/171 0/124 1 Ondergometry between groups: P=0.7765 3.88 (1.46, 10.36) 25/3985 1/3344 1 Outcattod (I-equared = 0.0%, P=0.646) 3.65 (0.17, 7.5.66) 1/171 0/142 2 Stardy O O C (06% CI) Intervention P O 0.0424 1 236 2 1/191 0/141 1/					0.0
Sadobal (I-squared = 0.0%, P=0.864) Sadobarspy Kewn (2014) Sadobarspy Kewn (2014) Sadobal (I-squared = 0.0%, P=0.765 Subtral (I-squared = 28.1%, P=0.249) Subtral (I-squared = 28.1%, P=0.249) Subtral (I-squared = 28.1%, P=0.249) Subtral (I-squared = 28.1%, P=0.249) Subtral (I-squared = 0.0%, P=0.965) Subtral (I-squared = 0.0%, P=0.462) Subtral (I-squared = 0.0%,					0.0
Backinbrarayy 202 (0.18, 22.37) 2793 1796 1 Subtotal (L-squared = .%, P=.) 2.02 (0.18, 22.37) 2793 1796 1 pp 100 1.05 (0.04, 25.87) 17380 0.132 6 Subtotal (L-squared = .0%, P=0.045) 1.05 (0.04, 25.87) 17380 0.132 6 Subtotal (L-squared = .0%, P=0.045) 1.05 (0.04, 25.87) 17380 0.132 6 Verall (L-squared = .0%, P=0.045) 3.88 (1.46, 10.36) 25/3885 1/3344 1 0.0424 236 236 1.05 (0.04, 25.87) 1/340 1/141 3/47 1 0.0424 236 236 1.05 (0.04, 25.87) 1/380 0.18 / 7.29 2/11 0.28 / 8 0.0424 236 236 1.01 / 9.14 / 1.34 / 10.4					31.0
Swan (2014) 2.02 (0.18, 22.37) 2393 1396 1 pi 100 1.05 (0.04, 25.87) 17380 0132 6 skabtotal (i-squared = 0.0%, P=0.645) 1.05 (0.04, 25.87) 17380 0132 6 skabtotal (i-squared = 0.0%, P=0.645) 1.79 (0.18, 17.26) 2/511 0.264 1 skabtotal (i-squared = 0.0%, P=0.645) 3.88 (146, 10.36) 25/3885 1/334 1 skabtotal (i-squared = 0.0%, P=0.645) 1.79 (0.18, 17.26) 2/151 0.264 1 skabtotal (i-squared = 0.0%, P=0.645) 1.79 (0.18, 17.26) 2/511 0.264 1 1.79 (0.18, 17.26) 2/511 0.264 1 1.79 (0.18, 17.26) 2/511 0.264 1 1.79 (0.18, 17.26) 2/511 0.264 1 1.79 (0.18, 17.26) 2/511 0.264 1 1.79 (0.18, 17.26) 1.79 (0.18, 17.26) 1.79 (0.18, 17.26) 1.79 (0.18, 07.26) 1.79 (0.18, 07.26) 1.79 (0.18, 07.26) 1.79 (0.18, 07.26) 1.79 (0.18, 07.26) 1.79 (0.18, 07.26) 1.79 (0.18, 07.26) 1.79 (0.18, 07.26) 1.79 (0.18, 07.26) 1.79 (0.18, 07.26) 1.79 (0.18, 07.26) 1.79 (0.18, 07.26) 1.79 (0.18, 07.26) 1.79 (0.18, 07.26)					
Study between groups: P-0.765 Dverall (L-squared = 0.0%, P-0.646) Hypophysitis Dverall (L-squared = 0.0%, P-0.74) 388 (1.46, 10.36) 25/3865 1/3344 1 0.0424 226 Hypophysitis Dverall (L-squared = 0.0%, P-0.278) Dverall (L-squared = 0.0%, P-0.289) Dverall (L-squared = 0.0%, P-0.482) Dverall (L-squared = 0.0%, P-0.482) Dverall (L-squared = 0.0%, P-0.482) D			2/303	1/2022	16.6
p 100 1.05 (0.04, 25.87) 1/380 0/132 6 todi (pilinumab alone) (2010) 3.05 (0.12, 75.46) 1/131 0/132 6 subtodi (-squared = 0.0%, P=0.055) 1/79 (0.18, 17.26) 26/19 1/79 (0.18, 17.26) 26/19 subtodi (-squared = 0.0%, P=0.974) 3.88 (1.46, 10.36) 26/3965 1/3344 1 subtodi (-squared = 0.0%, P=0.974) 3.88 (1.46, 10.36) 26/3965 1/3344 1 subtodi (-squared = 0.0%, P=0.974) 3.88 (1.46, 10.36) 26/3965 1/3344 1 subtodi (-squared = 0.0%, P=0.974) 0.0424 236 1 1/26 (0.76, 216.5)					
iodi (jolimunab e gor100) (2010) .1.05 (0.04, 25.87) 17.880 01.32 E iodi (jolimunab conc) (2010) .3.05 (0.12, 75.46) 11.31 01.32 E iodi (jolimunab conc) (2010) .3.05 (0.12, 75.46) 11.31 01.32 E iodi (jolimunab conc) (2010) .3.88 (1.46, 10.36) 25/3985 17.34.4 1 iodi (jolimunab conc) (2010) .3.88 (1.46, 10.36) 25/3985 17.34.4 1 iodi (jolimunab conc) (2010) .3.88 (1.46, 10.36) 25/3985 17.34.4 1 iodi (jolimunab conc) (2010) .3.88 (1.46, 10.36) 25/3985 17.34.4 1 iodi (jolimunab conc) (2010) .3.88 (1.46, 10.36) 25/3985 17.34.4 1 iodi (jolimunab conc) (2016)	Subtotal (I-squared = .%, P=.)	2.02 (0.18, 22.37) 2	2/393	1/396	16.6
Hod (pillmumab alone) (2010) Subtral (I-squared = 0.0%, P=0.45) Heterogeneity between groups: P=0.765 Dverall (I-squared = 0.0%, P=0.974) 1.79 (0.18, 17.26) 25/3985 1/3344 1 0.0424 236 Hypophysitis Study D Placebo Eggermont (2016) Halo (2017) Beck (2016) Subtral (I-squared = 28.1%, P=0.249) Chemotherapy Yench (pillmumab, bnased) (2012) Reck (2016) Subtral (I-squared = 2.8.1%, P=0.249) Chemotherapy Yench (pillmumab, bnased) (2012) Reck (2017) Reck (
Subtoal (I-squared = 0.0%, P=0.845) teterogenelity between groups: P=0.765 Sverall (I-squared = 0.0%, P=0.974) 0.0424 1 0.0424 1 0.0425 101 (0.14, 7.19) 2.79 (0.11, 69.46) 1.01 (0.45, 30.3) 4.62 (0.11, 69.83) 3.080 0.1189 9 0.0427 1.01 (0.45, 30.3) 4.62 (0.11, 69.84) 1.01 (0.45, 30.3) 4.62 (0.11, 69.84) 1.01 (0.45, 30.3) 4.62 (0.11, 69.84) 1.01 (0.45, 30.3) 4.62 (0.11, 69.84) 1.01 (0.45, 30.3) 4.62 (0.11, 69.84) 4.01 (0.45, 30.33) 4.02 (0.24, 10.44) (Excluded) 0.042 (Excluded) 0.042 (E	Hodi (ipilimumab + gp100) (2010)	1.05 (0.04, 25.87) 1	1/380	0/132	9.3
Subtoal (I-squared = 0.0%, P=0.645) teterogeneity between groups: P=0.765 Sverall (I-squared = 0.0%, P=0.974) 0.0424 1 236 Hypophysitis Study D OR (95% CI) Events, Events, 9 Intervention Control V Placebo Eggermont (2016) Ada (2017) Seek (plinumab, concurrent) (2012) Tek (plinumab, phased) (2012) Tek (plinumab, phased) (2012) Tek (plinumab, oncurrent) (2012) Tex (plinumab, oncurrent) (2014) Tex (plinumab + pp100) (2010) Tex (Hodi (ipilimumab alone) (2010)	3.05 (0.12, 75.46) 1	1/131	0/132	9.34
Devrail (I-squared = 0.0%, P=0.974) 3.88 (1.46, 10.36) 25/3985 1/3344 1 0.0424 236 Hypophysitis Study OR (95% CI) Events, Events, 9 1 236 Parents, 236 Parents, 236 Not (2016) Adv (14.00, 141.34) 104/471 3/474 1 Jato (2016) Adv (2016) Stato (2017) Stato (2017) Stato (2017) Stato (2012) Stato (2014) Stato (2014) Stato (2014) Stato (2014) <td>Subtotal (I–squared = 0.0%, <i>P</i>=0.645)</td> <td>1.79 (0.18, 17.26) 2</td> <td>2/511</td> <td>0/264</td> <td>18.</td>	Subtotal (I–squared = 0.0%, <i>P</i> =0.645)	1.79 (0.18, 17.26) 2	2/511	0/264	18.
Devrail (I-squared = 0.0%, P=0.974) 3.88 (1.46, 10.36) 25/3985 1/3344 1 0.0424 236 Hypophysitis Study OR (95% CI) Events, Events, 9 1 236 Parents, 236 Parents, 236 Not (2016) Adv (14.00, 141.34) 104/471 3/474 1 Jato (2016) Adv (2016) Stato (2017) Stato (2017) Stato (2017) Stato (2012) Stato (2014) Stato (2014) Stato (2014) Stato (2014) <td>Heterogeneity between groups: P=0.765</td> <td></td> <td></td> <td></td> <td></td>	Heterogeneity between groups: P=0.765				
Hypophysitis Stady CR (9% C1) Events, 0 Events, 0 Events, 0 Events, 0 Events, 0 Events, 0 Control 0 V Alacebo 44.94 (14.00,114.3) 10.47.1 1,47.4 1 1,351 (0.18,68.38) 3300 0/199 9 Alacebo 12.87 (0.76,218.51) 12.99 0/199 9 2,45 (5.15,93.38) 119/1250 3.662		3.88 (1.46, 10.36) 2	25/3985	1/3344	100
Bindly Events,	I 0.0424	1 236			
Eggermont (2016) 44.49 (14.00, 141.34) 104/471 3/474 1 Maio (2017) 3.51 (0.18, 68.38) 3/380 0/189 9 Subtolal (I-squared = 28.1%, P=0.249) 12.87 (0.76, 218.51) 12/399 0/199 9 Subtola (I-squared = 28.1%, P=0.249) 21.45 (5.15, 89.35) 119/1250 3/862 3 Chemotherapy 2.79 (0.11, 69.64) 1/71 0/65 8 Ack (2016) 4.01 (0.45, 36.03) 4/562 1/561 1 Sovindan (2017) 5.00 (0.24, 104.43) 2/475 0/473 8 Ack (2016) Keck (pilimumab, concurrent) (2012) (Excluded) 0/42 0/44 0 Sovindan (2017) (Excluded) 0/42 0/44 0 0/42 0/44 0 Sovindan (2017) (Excluded) 0/42 0/44 0 0/42 0/44 0 Sovindan (2012) (Excluded) 0/42 0/44 0 0/42 0/44 0 Subtotal (I-squared = 0.0%, P=0.966) 3.90 (0.82, 18.53) 7/1831 1/1822 3 Subtotal (I-squared = .%, P=.) 1.01 (0.14	-				
Eggermont (2016) 44.49 (14.00, 141.34) 104/471 3/474 1 Maio (2017) 3.51 (0.18, 68.38) 3/380 0/189 9 Subtolal (I-squared = 28.1%, P=0.249) 12.87 (0.76, 218.51) 12/399 0/199 9 Subtola (I-squared = 28.1%, P=0.249) 21.45 (5.15, 89.35) 119/1250 3/862 3 Chemotherapy 2.79 (0.11, 69.64) 1/71 0/65 8 Ack (2016) 4.01 (0.45, 36.03) 4/562 1/561 1 Sovindan (2017) 5.00 (0.24, 104.43) 2/475 0/473 8 Ack (2016) Keck (pilimumab, concurrent) (2012) (Excluded) 0/42 0/44 0 Sovindan (2017) (Excluded) 0/42 0/44 0 0/42 0/44 0 Sovindan (2017) (Excluded) 0/42 0/44 0 0/42 0/44 0 Sovindan (2012) (Excluded) 0/42 0/44 0 0/42 0/44 0 Subtotal (I-squared = 0.0%, P=0.966) 3.90 (0.82, 18.53) 7/1831 1/1822 3 Subtotal (I-squared = .%, P=.) 1.01 (0.14					
signification (cord) 3.51 (0.18, 68.38) 3/380 0/189 9 Seer (2017) 12.87 (0.76, 218.51) 12/399 0/199 9 Subtotal (I-squared = 28.1%, P=0.249) 21.45 (5.15, 89.35) 119/1250 3/862 3 Chemotherapy 2.79 (0.11, 69.64) 1/71 0/65 8 4.01 (0.45, 36.03) 4/662 1/651 1 Sovindan (2017) Xobert (2011) Exck (pilimumab, phased) (2012) (Excluded) 0/247 0/443 0 Rock (pilimumab, phased) (2012) Reck (pilimumab, phased) (2012) (Excluded) 0/67 0/65 0 Radiothrapy (U-squared = 0.0%, P=0.966) 3.90 (0.82, 18.53) 7/1831 1/1822 3 Subtotal (I-squared = .%, P=.) 1.01 (0.14, 7.19) 2/393 2/396 1 subtotal (I-squared = .%, P=.) 1.01 (0.14, 7.19) 2/393 2/396 1 subtotal (I-squared = .%, P=.) 1.05 (0.04, 25.87) 1/380 0/132 8 subtotal (I-squared = .%, P=.) 2.41 (0.26, 21.95) 3/511 0/132 8 Subtotal (I-squared = .00%, P=0.482) 2.41 (0.26, 21.95) 3/511 <		44.49 (14.00, 141.34)	104/471	3/474	19.7
https://doi.org/10.11/10.114 12.87 (0.76, 218.51) 12/399 0/199 9 Subtotal (I-squared = 28.1%, P=0.249) 21.45 (5.15, 89.35) 119/1250 3/862 3 Chemotherapy 2.79 (0.11, 69.64) 1/71 0/65 8 vynch (ipilimumab, concurrent) (2012) 2.79 (0.11, 69.64) 1/71 0/65 8 Sovindan (2017) 5.00 (0.24, 104.43) 2/475 0/473 8 Sovindan (2017) 5.00 (0.24, 104.43) 2/475 0/473 8 Keck (ipilimumab, phased) (2012) (Excluded) 0/42 0/44 0 Vench (ipilimumab, concurrent) (2012) (Excluded) 0/42 0/44 0 Vench (ipilimumab, Phased) (2012) (Excluded) 0/67 0/65 0 Subtotal (I-squared = 0.0%, P=0.966) 3.90 (0.82, 18.53) 7/1831 1/1822 3 Radiotherapy 1.01 (0.14, 7.19) 2/393 2/396 1 yp 100 1.01 (0.14, 7.19) 2/393 2/396 1 yp 100 1.01 (0.14, 7.19) 2/393 2/396 1 yp 100 1.01 (0.14, 7.19) 2/393					9.18
Subtatal (I-squared = 28.1%, P=0.249) 21.45 (5.15, 89.35) 119/1250 3/862 3 21.45 (5.15, 89.35) 119/1250 3/862 3 2.79 (0.11, 69.64) 1771 0/65 8 4.01 (0.45, 36.03) 4/562 1/561 1 5.00 (0.24, 104.43) 2/475 0/473 8 4.01 (0.45, 36.03) 4/562 1/561 1 5.00 (0.24, 104.43) 2/475 0/473 8 (Excluded) 0/247 0/251 0 (Excluded) 0/42 0/44 0 (Excluded) 0/42 0/44 0 (Excluded) 0/47 0/65 0 (Excluded) 0/47 0/44 0 (Excluded) 0/47 0/44 0 (Excluded) 0/47 0/42 0/44 0 (Excluded) 0/47 0/42 0/44 0 (Excluded) 0/47 0/65 0 (Excluded) 0/42 0/44 0 (Excluded) 0/42 0/44 0 (Excluded) 0/47 0/44			3/380		
Chemotherapy synch (ipilimumab, concurrent) (2012) Reck (2016) Sovindar (2017) Robert (2011) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, phased) (2012) Vgnch (ipilimumab + gp100) (2010) Vgnch (ipilimumab + gp100) (2010) Vgnch (ipilimumab alone) (2010)	Лаіо (2017)				
synch (ipilinumab, concurrent) (2012) 2.79 (0.11, 69.64) 1/71 0/65 8 Sack (2016) 3.01 (0.45, 36.03) 4/562 1/561 1 Sourdan (2017) 5.00 (0.24, 104.43) 2/475 0/473 8 Keck (ipilinumab, phased) (2012) Keck (ipilinumab, concurrent) (2012) (Excluded) 0/42 0/44 0 Subtotal (I-squared = 0.0%, P=0.966) 3.90 (0.82, 18.53) 7/1831 1/1822 3 Subtotal (I-squared = .%, P=.) 1.01 (0.14, 7.19) 2/393 2/396 1 p1 100 1.05 (0.04, 25.87) 1/380 0/132 8 Subtotal (I-squared = .%, P=.) 1.05 (0.04, 25.87) 1/380 0/132 8 Subtotal (I-squared = 0.0%, P=0.482) 2/131 0/132 8 5.12 (0.24, 107.59) 2/131 0/132 8	Лаіо (2017) Зеег (2017)	12.87 (0.76, 218.51)	12/399	0/199	9.73
Leck (2016) 4.01 (0.45, 36.03) 4/562 1/561 1 Sovindan (2017) 5.00 (0.24, 104.43) 2/475 0/473 8 Keck (ipilimumab, phased) (2012) (Excluded) 0/247 0/221 0 Keck (ipilimumab, concurrent) (2012) (Excluded) 0/42 0/44 0 ynch (ipilimumab, concurrent) (2012) (Excluded) 0/67 0/65 0 ynch (ipilimumab, Phased) (2012) (Excluded) 0/67 0/65 0 ynch (ipilimumab, Phased) (2012) (Excluded) 0/325 0/319 0 ynch (ipilimumab, Pased) (2012) (Excluded) 0/67 0/65 0 ynch (ipilimumab, Pased) (2012) (Excluded) 0/325 0/319 0 ynch (ipilimumab + Pased) 0.0%, P=0.966) 3.90 (0.82, 18.53) 7/1831 1/1822 3 kadiotherapy 1.01 (0.14, 7.19) 2/393 2/396 1 1 1.01 (0.14, 7.19) 2/393 2/396 1 p 100 1.05 (0.04, 25.87) 1/380 0/132 8 1.01 (0.14, 7.19) 2/393 2/396 1 koid (ipilim	Maio (2017) Seer (2017)	12.87 (0.76, 218.51)	12/399	0/199	
Sovindan (2017) 5.00 (0.24, 104.43) 2/475 0/473 8 Kabert (2011) (Excluded) 0/247 0/251 0 Reck (ipilimumab, phased) (2012) (Excluded) 0/42 0/44 0 Reck (ipilimumab, phased) (2012) (Excluded) 0/42 0/44 0 which (ipilimumab, phased) (2012) (Excluded) 0/42 0/44 0 which (ipilimumab, phased) (2012) (Excluded) 0/42 0/44 0 which (ipilimumab, phased) (2012) (Excluded) 0/47 0/65 0 Subtotal (I-squared = 0.0%, P=0.966) 3.90 (0.82, 18.53) 7/1831 1/1822 3 Radiotherapy 1.01 (0.14, 7.19) 2/393 2/396 1 won (2014) 1.01 (0.14, 7.19) 2/393 2/396 1 subtotal (I-squared = .%, P=.) 1.05 (0.04, 25.87) 1/380 0/132 8 doid (ipilimumab alone) (2010) 5.12 (0.24, 107.59) 2/131 0/132 8 subtotal (I-squared = 0.0%, P=0.482) 2.41 (0.26, 21.95) 3/511 0/264 1 <td>Лаіо (2017) Beer (2017) Subtotal (I–squared = 28.1%, <i>P</i>=0.249)</td> <td>12.87 (0.76, 218.51)</td> <td>12/399</td> <td>0/199</td> <td></td>	Лаіо (2017) Beer (2017) Subtotal (I–squared = 28.1%, <i>P</i> =0.249)	12.87 (0.76, 218.51)	12/399	0/199	
kobert (2011) (Excluded) 0/247 0/251 0 keck (ipilimumab, phased) (2012) (Excluded) 0/42 0/44 0 ynch (ipilimumab, concurrent) (2012) (Excluded) 0/42 0/44 0 ynch (ipilimumab, concurrent) (2012) (Excluded) 0/42 0/44 0 ynch (ipilimumab, concurrent) (2012) (Excluded) 0/65 0 ynch (ipilimumab, concurrent) (2012) (Excluded) 0/625 0/319 0 skadiotherapy (xon (2014) 1.01 (0.14, 7.19) 2/393 2/396 1 ynot (opilimumab + gp100) (2010) 1.05 (0.04, 25.87) 1/380 0/132 8 skubtal (I-squared = 0.0%, P=0.482) 2.41 (0.26, 21.95) 3/511 0/132 8	Λaio (2017) Beer (2017) Subtotal (I–squared = 28.1%, <i>Ρ</i> =0.249) Shemotherapy	12.87 (0.76, 218.51) 21.45 (5.15, 89.35)	12/399 119/1250	0/199 3/862	9.73 38.6 8.26
Robert (2011) (Excluded) 0/247 0/251 0 Reck (ipilimumab, phased) (2012) (Excluded) 0/42 0/44 0 ynch (ipilimumab, concurrent) (2012) (Excluded) 0/42 0/44 0 ynch (ipilimumab, concurrent) (2012) (Excluded) 0/42 0/44 0 ynch (ipilimumab, Phased) (2012) (Excluded) 0/65 0 Stabiotal (I-squared = 0.0%, P=0.966) 3.90 (0.82, 18.53) 7/1831 1/1822 3 Radiotherapy (xon (2014) 1.01 (0.14, 7.19) 2/393 2/396 1 yubtotal (I-squared = .%, P=.) 1.05 (0.04, 25.87) 1/380 0/132 8 iodi (ipilimumab alone) (2010) 5.12 (0.24, 107.59) 2/131 0/132 8 yubtotal (I-squared = 0.0%, P=0.482) 2.41 (0.26, 21.95) 3/511 0/132 8	Aaio (2017) Seer (2017) Subtotal (I–squared = 28.1%, <i>P</i> =0.249) Chemotherapy ynch (ipilimumab, concurrent) (2012)	12.87 (0.76, 218.51) 21.45 (5.15, 89.35) 2.79 (0.11, 69.64)	12/399 119/1250 1/71	0/199 3/862 0/65	38.6
keck (pilinumab, phased) (2012) (Excluded) 0/42 0/44 0 keck (pilinumab, concurrent) (2012) (Excluded) 0/42 0/44 0 ynch (pilinumab, Phased) (2012) (Excluded) 0/42 0/44 0 kibas (2013) (Excluded) 0/67 0/65 0 vubtotal (I-squared = 0.0%, P=0.966) 3.90 (0.82, 18.53) 7/1831 1/1822 3 kadiotherapy 1.01 (0.14, 7.19) 2/393 2/396 1 yubtotal (I-squared = .%, P=.) 1.01 (0.14, 7.19) 2/393 2/396 1 p 100 1.05 (0.04, 25.87) 1/380 0/132 8 kodi (ipilimumab alone) (2010) 5.12 (0.24, 107.59) 2/131 0/132 8 vubtotal (I-squared = 0.0%, P=0.482) 2.41 (0.26, 21.95) 3/511 0/264 1	Aaio (2017) teer (2017) subtotal (I–squared = 28.1%, <i>P</i> =0.249) Shemotherapy ynch (ipilimumab, concurrent) (2012) — Reck (2016)	12.87 (0.76, 218.51) 21.45 (5.15, 89.35) 2.79 (0.11, 69.64) 4.01 (0.45, 36.03)	12/399 119/1250 1/71 4/562	0/199 3/862 0/65 1/561	38.6 8.26
Leck (pilimumab, concurrent) (2012) (Excluded) 0/42 0/44 0 ynch (ipilimumab, concurrent) (2012) (Excluded) 0/67 0/65 0 ynch (ipilimumab, Phased) (2012) (Excluded) 0/67 0/65 0 ylubtotal (I-squared = 0.0%, P=0.966) 3.90 (0.82, 18.53) 7/1831 1/1822 3 ktadiotherapy 1.01 (0.14, 7.19) 2/393 2/396 1 ybutotal (I-squared = .%, P=.) 1.01 (0.14, 7.19) 2/393 2/396 1 p 100 1.05 (0.04, 25.87) 1/380 0/132 8 kodi (ipilimumab alone) (2010) 5.12 (0.24, 107.59) 2/131 0/132 8 kubtotal (I-squared = 0.0%, P=0.482) 2.41 (0.26, 21.95) 3/511 0/264 1	Maio (2017) leer (2017) lubtotal (I–squared = 28.1%, <i>P</i> =0.249) Chemotherapy ynch (ipilimumab, concurrent) (2012) Reck (2016) Sovindan (2017)	12.87 (0.76, 218.51) 21.45 (5.15, 89.35) 2.79 (0.11, 69.64) 4.01 (0.45, 36.03) 5.00 (0.24, 104.43)	12/399 119/1250 1/71 4/562 2/475	0/199 3/862 0/65 1/561 0/473	38.6 8.26 12.8 8.91
ynch (ipilimumab, Phased) (2012) (Excluded) 0/67 0/65 0 (Excluded) 0/325 0/319 0 (Excluded) 0	Maio (2017) leer (2017) lubtotal (I–squared = 28.1%, <i>P</i> =0.249) Schemotherapy ynch (ipilimumab, concurrent) (2012) Reck (2016) Sovindan (2017) Robert (2011)	2.79 (0.11, 69.64) 2.79 (0.11, 69.64) 4.01 (0.45, 36.03) 5.00 (0.24, 104.43) 2 (Excluded)	12/399 119/1250 1/71 4/562 2/475 0/247	0/199 3/862 0/65 1/561 0/473 0/251	38.0 8.20 12.8 8.9 0.00
When (2013) (Excluded) 0/325 0/319 0 Subtotal (I-squared = 0.0%, P=0.966) 3.90 (0.82, 18.53) 7/1831 1/1822 3 Radiotherapy 1.01 (0.14, 7.19) 2/393 2/396 1 Subtotal (I-squared = .%, P=.) 1.01 (0.14, 7.19) 2/393 2/396 1 ip 100 1.05 (0.04, 25.87) 1/380 0/132 8 iodi (ipilimumab alone) (2010) 5.12 (0.24, 107.59) 2/131 0/132 8 subtotal (I-squared = 0.0%, P=0.482) 2.41 (0.26, 21.95) 3/511 0/264 1	Aaio (2017) Beer (2017) Subtotal (I–squared = 28.1%, P=0.249) Chemotherapy ynch (ipilimumab, concurrent) (2012) – Reck (2016) Sovindan (2017) Sobert (2011) Reck (ipilimumab, phased) (2012)	2.79 (0.11, 69.64) 4.01 (0.45, 36.03) (Excluded) (Excluded)	12/399 119/1250 1/71 4/562 2/475 0/247 0/42	0/199 3/862 0/65 1/561 0/473 0/251 0/24	38.0 8.20 12.8 8.9 0.00
Subtral (I-squared = 0.0%, P=0.966) Radiotherapy Kwon (2014) 1.01 (0.14, 7.19) 2/393 2/396 1 1.01 (0.14, 7.19) 2/393 2/396 1 2.10 (0.04, 25.87) 1/380 0/132 8 2.11 (0.26, 21.95) 3/511 0/264 1 1.01 (0.14, 7.19) 2/393 2/396 1 1.02 (0.04, 25.87) 1/380 0/132 8 2.11 (0.26, 21.95) 3/511 0/264 1 1.01 (0.14, 7.19) 2/393 2/396 1 1.02 (0.14, 7.19) 2/393 2/396 1	Aaio (2017) Jeer (2017) Subtotal (I–squared = 28.1%, <i>P</i> =0.249) Chemotherapy ynch (ipilimumab, concurrent) (2012) Veck (2016) Sovindan (2017) Robert (2011) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, concurrent) (2012)	2.79 (0.11, 69.64) 4.01 (0.45, 36.03) (Excluded) ((Excluded) ((Excluded) (12/399 119/1250 1/71 4/562 2/475 0/247 0/42 0/42	0/199 3/862 0/65 1/561 0/473 0/251 0/44 0/44	38.0 8.20 12.8 8.9 0.00 0.00
tadiotherapy 1.01 (0.14, 7.19) 2/393 2/396 1 subtotal (I-squared = .%, P=.) 1.01 (0.14, 7.19) 2/393 2/396 1 p 100 1.05 (0.04, 25.87) 1/380 0/132 8 lodi (ipilimumab + gp100) (2010) 1.05 (0.04, 25.87) 1/380 0/132 8 lodi (ipilimumab alone) (2010) 5.12 (0.24, 107.59) 2/131 0/132 8 subtotal (I-squared = 0.0%, P=0.482) 2.41 (0.26, 21.95) 3/511 0/264 1	Maio (2017) leer (2017) lubtotal (I–squared = 28.1%, P=0.249) Chemotherapy ynch (ipilimumab, concurrent) (2012) leck (2016) Sovindan (2017) Robert (2011) Robert (2011) Rock (ipilimumab, phased) (2012) Rock (ipilimumab, concurrent) (2012) ynch (ipilimumab, Phased) (2012)	2.79 (0.11, 69.64) 2.79 (0.11, 69.64) 4.01 (0.45, 36.03) (Excluded) ((Excluded) (12/399 119/1250 1/71 4/562 2/475 0/247 0/42 0/42 0/67	0/199 3/862 0/65 1/561 0/473 0/251 0/44 0/44 0/65	38.0 8.20 12.8 8.9 0.00 0.00 0.00
Swon (2014) 1.01 (0.14, 7.19) 2/393 2/396 1 Jubtotal (I-squared = .%, P=.) 1.01 (0.14, 7.19) 2/393 2/396 1 p 100 1.05 (0.04, 25.87) 1/380 0/132 8 lodi (ipilimumab + gp100) (2010) 5.12 (0.24, 107.59) 2/131 0/132 8 louid (ipilimumab alone) (2010) 2.41 (0.26, 21.95) 3/511 0/264 1	Maio (2017) Heer (2017) Subtotal (I–squared = 28.1%, P=0.249) Schemotherapy ynch (ipilimumab, concurrent) (2012) Heck (2016) Sovindan (2017) Robert (2011) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, Phased) (2012) Ribas (2013)	2.79 (0.11, 69.64) 2.79 (0.11, 69.64) 4.01 (0.45, 36.03) (Excluded) ((Excluded) (((Excluded) ((((((((((((((12/399 119/1250 1/71 4/562 2/475 0/247 0/42 0/42 0/42 0/67 0/325	0/199 3/862 0/65 1/561 0/473 0/251 0/44 0/44 0/65 0/319	38.0 8.2 12.3 8.9 0.0 0.0 0.0 0.0 0.0
subtotal (I-squared = .%, P=.) 1.01 (0.14, 7.19) 2/393 2/396 1 p 100 1.05 (0.04, 25.87) 1/380 0/132 8 lodi (ipilimumab + gp100) (2010) 5.12 (0.24, 107.59) 2/131 0/132 8 subtotal (I-squared = 0.0%, P=0.482) 2.41 (0.26, 21.95) 3/511 0/264 1	Aaio (2017) teer (2017) Subtotal (I–squared = 28.1%, <i>P</i> =0.249) Chemotherapy ynch (ipilimumab, concurrent) (2012) teck (2016) Sovindan (2017) Keck (ipilimumab, phased) (2012) teck (ipilimumab, phased) (2012) teck (ipilimumab, Phased) (2012) tibas (2013) subtotal (I–squared = 0.0%, <i>P</i> =0.966)	2.79 (0.11, 69.64) 2.79 (0.11, 69.64) 4.01 (0.45, 36.03) (Excluded) ((Excluded) (((Excluded) ((((((((((((((12/399 119/1250 1/71 4/562 2/475 0/247 0/42 0/42 0/42 0/67 0/325	0/199 3/862 0/65 1/561 0/473 0/251 0/44 0/44 0/65 0/319	38.0 8.2 12.3 8.9 0.0 0.0 0.0 0.0 0.0
p 100 1.05 (0.04, 25.87) 1/380 0/132 8 lodi (ipilimumab + gp100) (2010) 5.12 (0.24, 107.59) 2/131 0/132 8 subtotal (I–squared = 0.0%, P=0.482) 2.41 (0.26, 21.95) 3/511 0/264 1	Maio (2017) leer (2017) Subtotal (I–squared = 28.1%, <i>P</i> =0.249) Chemotherapy ynch (ipilimumab, concurrent) (2012) leek (2016) Sovindan (2017) Robert (2011) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, concurrent) (2012) ynch (ipilimumab, Phased) (2012) Ribas (2013) Subtotal (I–squared = 0.0%, <i>P</i> =0.966) Radiotherapy	12.87 (0.76, 218.51) 21.45 (5.15, 89.35) 21.45 (5.15, 89.35) 2.79 (0.11, 69.64) 4.01 (0.45, 36.03) 5.00 (0.24, 104.43) (Excluded) 0 (Excluded) 0 (Ex	12/399 119/1250 1/71 4/562 2/475 0/247 0/42 0/42 0/42 0/67 0/325 7/1831	0/199 3/862 0/65 1/561 0/473 0/251 0/44 0/44 0/65 0/319 1/1822	38.6 8.26 12.8 8.9 0.00 0.00 0.00 0.00 0.00 0.00 0.0
Iodi (ipilimumab + gp100) (2010) 1.05 (0.04, 25.87) 1/380 0/132 8 Iodi (ipilimumab alone) (2010) 5.12 (0.24, 107.59) 2/131 0/132 8 Iubitotal (I–squared = 0.0%, P=0.482) 2.41 (0.26, 21.95) 3/511 0/264 1	taio (2017) ieer (2017) ubtotal (I-squared = 28.1%, <i>P</i> =0.249) :hemotherapy ynch (ipilimumab, concurrent) (2012) teck (2016) isovindan (2017) tobert (2011) teck (ipilimumab, phased) (2012) teck (ipilimumab, phased) (2012) teck (ipilimumab, Phased) (2012) tibas (2013) iubtotal (I-squared = 0.0%, <i>P</i> =0.966) tadiotherapy won (2014)	12.87 (0.76, 218.51) 21.45 (5.15, 89.35) 21.45 (5.15, 89.35) 2.79 (0.11, 69.64) 4.01 (0.45, 36.03) 5.00 (0.24, 104.43) (Excluded) (E	12/399 119/1250 1/71 4/562 2/475 0/42 0/42 0/42 0/42 0/42 0/42 0/325 7/1831	0/199 3/862 0/65 1/561 0/473 0/251 0/44 0/44 0/65 0/319 1/1822 2/396	38.6 8.20 12.8 8.9 0.00 0.00 0.00 0.00 0.00 0.00 0.0
Iodi (ipilimumab alone) (2010) 5.12 (0.24, 107.59) 2/131 0/132 8 Vubtotal (I–squared = 0.0%, P=0.482) 2.41 (0.26, 21.95) 3/511 0/264 1	taio (2017) ieer (2017) ubtotal (I-squared = 28.1%, <i>P</i> =0.249) :hemotherapy ynch (ipilimumab, concurrent) (2012) teck (2016) isovindan (2017) tobert (2011) teck (ipilimumab, phased) (2012) teck (ipilimumab, phased) (2012) teck (ipilimumab, Phased) (2012) tibas (2013) iubtotal (I-squared = 0.0%, <i>P</i> =0.966) tadiotherapy won (2014)	12.87 (0.76, 218.51) 21.45 (5.15, 89.35) 21.45 (5.15, 89.35) 2.79 (0.11, 69.64) 4.01 (0.45, 36.03) 5.00 (0.24, 104.43) (Excluded) (E	12/399 119/1250 1/71 4/562 2/475 0/42 0/42 0/42 0/42 0/42 0/42 0/325 7/1831	0/199 3/862 0/65 1/561 0/473 0/251 0/44 0/44 0/65 0/319 1/1822 2/396	38.6 8.20 12.8 8.9 0.00 0.00 0.00 0.00 0.00 0.00 0.0
Subtotal (I–squared = 0.0%, P=0.482) 2.41 (0.26, 21.95) 3/511 0/264 1	Maio (2017) Ideer (2017) Subtotal (I-squared = 28.1%, P=0.249) Chemotherapy ynch (ipilimumab, concurrent) (2012) Veck (2016) Sovindan (2017) Kobert (2011) Reck (ipilimumab, phased) (2012) teck (ipilimumab, phased) (2012) work (ipilimumab, Phased) (2012) Wibta (1-squared = 0.0%, P=0.966) Radiotherapy Kwon (2014) Subtotal (I-squared = .%, P=.) p 100	12.87 (0.76, 218.51) 21.45 (5.15, 89.35) 2.79 (0.11, 69.64) 4.01 (0.45, 36.03) 5.00 (0.24, 104.43) (Excluded) (Excluded) (Excluded) (Excluded) (Excluded) (Excluded) (Excluded) (Excluded) (0.14, 7.19) 1.01 (0.14, 7.19) 1.01 (0.	12/399 119/1250 1/71 4/562 2/475 0/247 0/42 0/42 0/42 0/67 7/1831 2/393	0/199 3/862 0/65 1/561 0/473 0/251 0/251 0/44 0/44 0/65 0/319 1/1822 2/396 2/396	38.6 8.26 12.8 8.9 0.00 0.00 0.00 0.00 30.0 14.2
	Maio (2017) Ideer (2017) Subtotal (I-squared = 28.1%, P=0.249) Chemotherapy ynch (ipilimumab, concurrent) (2012) Veck (2016) Sovindan (2017) Kobert (2011) Reck (ipilimumab, phased) (2012) teck (ipilimumab, phased) (2012) work (ipilimumab, Phased) (2012) Wibta (1-squared = 0.0%, P=0.966) Radiotherapy Kwon (2014) Subtotal (I-squared = .%, P=.) p 100	12.87 (0.76, 218.51) 21.45 (5.15, 89.35) 2.79 (0.11, 69.64) 4.01 (0.45, 36.03) 5.00 (0.24, 104.43) (Excluded) (Excluded) (Excluded) (Excluded) (Excluded) (Excluded) (Excluded) (Excluded) (0.14, 7.19) 1.01 (0.14, 7.19) 1.01 (0.	12/399 119/1250 1/71 4/562 2/475 0/247 0/42 0/42 0/42 0/67 7/1831 2/393	0/199 3/862 0/65 1/561 0/473 0/251 0/251 0/44 0/44 0/65 0/319 1/1822 2/396 2/396	38.6 8.26 12.8 8.9 0.00 0.00 0.00 0.00 30.0 14.2 14.2 8.30
Overall (I-squared = 50.1%, P=0.049) 5.30 (1.71, 16.46) 131/3985 6/3344 1	Maio (2017) ieer (2017) Stubtotal (I-squared = 28.1%, P=0.249) Chemotherapy ynch (ipilimumab, concurrent) (2012) Veck (2016) Sovindan (2017) Kobert (2011) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, phased) (2012) Nibas (2013) Subtotal (I-squared = 0.0%, P=0.966) Radiotherapy Won (2014) Bubtotal (I-squared = .%, P=.) p 100 Idoi (ipilimumab + gp100) (2010)	12.87 (0.76, 218.51) 21.45 (5.15, 89.35) 2.79 (0.11, 69.64) 4.01 (0.45, 36.03) 5.00 (0.24, 104.43) (Excluded)	12/399 119/1250 1/7/1 4/562 2/475 0/247 0/42 0/42 0/42 0/42 0/42 0/42 0/42 1/380	0/199 3/862 0/65 1/561 0/473 0/251 0/44 0/44 0/44 0/65 0/319 1/1822 2/396 2/396 2/396	38.6 8.26 12.8 8.9 0.00 0.00 0.00 0.00 30.0 14.2 14.2 8.30
Ť	Aaio (2017) Seer (2017) Subtotal (I-squared = 28.1%, P=0.249) Chemotherapy ynch (ipilimumab, concurrent) (2012) Teck (2016) Sovindan (2017) Robert (2011) Robert (2011) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, phased) (2012) Nbas (2013) Subtotal (I-squared = 0.0%, P=0.966) Radiotherapy (xwon (2014) Subtotal (I-squared = .%, P=.) pp 100 fodi (ipilimumab + gp100) (2010) fodi (ipilimumab alone) (2010)	12.87 (0.76, 218.51) 21.45 (5.15, 89.35) 21.45 (5.15, 89.35) 2.79 (0.11, 69.64) 4.01 (0.45, 36.03) 5.00 (0.24, 104.43) (Excluded) (12/399 119/1250 1/71 4/562 2/475 0/42 0/42 0/42 0/42 0/42 0/42 0/67 7/1831 2/393 2/393 1/380 2/131	0/199 3/862 0/65 1/561 0/473 0/251 0/44 0/45 0/319 1/1822 2/396 2/396 0/132 0/132	38.6 8.26 12.8 8.9 0.00 0.00 0.00 0.00 30.0 14.2
IOTE: weights are from random effects analysis	faio (2017) ieer (2017) iubtotal (I-squared = 28.1%, P=0.249) Shemotherapy ynch (ipilimumab, concurrent) (2012) teck (2016) Sovindan (2017) tobert (2011) teck (ipilimumab, phased) (2012) teck (ipilimumab, phased) (2012) tibas (2013) uubtotal (I-squared = 0.0%, P=0.966) tadiotherapy won (2014) uubtotal (I-squared = .%, P=.) p 100 lodi (ipilimumab alone) (2010) lodi (ipilimumab alone) (2010) uubtotal (I-squared = 0.0%, P=0.482)	12.87 (0.76, 218.51) 21.45 (5.15, 89.35) 2.79 (0.11, 69.64) 4.01 (0.45, 36.03) 5.00 (0.24, 104.43) (Excluded)	12/399 119/1250 1/71 4/562 2/475 0/247 0/22 0/27 0/325 7/1831 2/393 2/393 1/380 2/131 3/511	0/199 3/862 0/65 1/561 0/473 0/251 0/44 0/44 0/44 0/45 0/319 1/1822 2/396 2/396 0/132 0/132 0/132	38.0 8.20 12.8 8.9 0.00 0.00 0.00 0.00 30.0 14.2 14.2 14.2 8.30 8.80

Figure 3 Forest plot of the overall risk of adrenal insufficiency and hypophysitis related to anti-CTLA-4 drugs.

compared with control therapies, although our findings were largely the same with regard to rash and colitis.

Collection of the data directly from ClinicalTrials.gov enabled us to evaluate useful information on AEs with

Hy	perthyroidism				
Study			Events,		%
ID	OR ((95% CI)	Intervention	Control	Weight
Placebo					
Eggermont (2016)	\$ 3.03	(0.012, 74.46)	1/471	0/474	18.84
Beer (2017)	* 1.50	(0.06, 37.03)	1/399	0/199	18.81
Maio (2017)	(Exc	luded)	0/380	0/189	0.00
Subtotal (I-squard =0.0%, P=0.762)	2.13	(0.22, 20.55)	2/1250	0/862	37.65
Chemotherapy					
Reck (2016) -		(0.24, 104.57)	2/562	0/561	20.93
Govindan (2017)	2.99	(0.12, 73.67)	1/475	0/473	18.84
Robert (2011)	(Exc	luded)	0/247	0/251	0.00
Reck (ipilimumab, phased) (2012)	(Exc	luded)	0/42	0/44	0.00
Reck (ipilimumab, concurrent) (2012)	(Exc	luded)	0/42	0/44	0.00
Lynch (ipilimumab, phased) (2012)	(Exc	luded)	0/67	0/65	0.00
Lynch (ipilimumab, concurrent) (2012)	(Exc	luded) (0/71	0/65	0.00
Ribas (2013)	(Exc	luded) (0/325	0/319	0.00
Subtotal (I-squard =0.0%, <i>P</i> =0.819)	3.93	(0.43, 35.58)	3/1831	0/1822	39.77
Radiotherapy					
Known(2014)	9.16	(0.49, 170.74)	4/393	0/396	22.59
subtotal (I-squard =.%, P= .)	9.16	(0.49, 170.74)	4/393	0/396	22.59
gp100					
Hodi (ipilimumab + gp100) (2010)	(Exc	luded)			0.00
Hodi (ipilimumab alone) (2010)	(Exc	luded) (0/131	0/132	0.00
Subtotal (I-squard =0.0%, P=.)	. (,, .) (0/511		0.00
Heterogeneity between groups: P=0.897					
Overall (I-squard =0.0%, <i>P</i> =0.946)	3.78	(0.94, 15.17)	9/3985	0/3344	100.00
	i				
0.00586	1 171				
	Hypothyroidism				
Study		ſ	Events.	Events	%
ID			Intervention		
				Control	giit
Placebo Eggermont (2016)		(3.75, 20.89)	48/471	6/474	57.18
Aaio (2017)			46/47 1 2/380	0/189	4.56
Beer (2017) Subtotal (I-squard =0.0%, <i>P</i> =0.504)		6 (1.79, 485.45) (4.05, 19.76)		0/199 6/862	5.37 67.11

Maio (2017)			 2.50 (0.12, 52.40) 	2/380	0/189	4.56
Beer (2017)		*	29.46 (1.79, 485.45) 27/399	0/199	5.37
Subtotal (I-squard =0.0%, P=0.504)		\Leftrightarrow	8.94 (4.05, 19.76)	77/1250	6/862	67.11
Chemotherapy						
Ribas (2013)		•	8.75 (2.00. 38.18)	17/325	2/319	19.42
Reck (2016)		•	7.03 (0.36, 136.32)	3/562	0/561	4.80
Robert (2011)			(Excluded)	0/247	0/251	0.00
Reck (ipilimumab, phased) (2012)			(Excluded)	0/42	0/44	0.00
Reck (ipilimumab, concurrent) (2012)		i	(Excluded)	0/42	0/44	0.00
Lynch (ipilimumab, phased) (2012)		1	(Excluded)	0/67	0/65	0.00
Lynch (ipilimumab, concurrent) (2012)			(Excluded)	0/71	0/65	0.00
Govindan (2017)		i.	(Excluded)	0/475	0/473	0.00
Subtotal (I-squard =0.0%, P=0.897)			8.38 (2.24, 31.34)	20/1831	2/1822	24.22
Radiotherapy		i.				
Known(2014)		•	5.06 (0.24, 105.82)	2/393	0/396	4.56
Subtotal (I-squard =.%, P=.)			5.06 (0.24, 105.82)	2/393	0/396	4.56
gp100						
Hodi (ipilimumab + gp100) (2010)			1.05 (0.04, 25.87)	1/380	0/132	4.10
Hodi (ipilimumab alone) (2010)			(Excluded)	0/131	0/132	0.00
Subtotal (I-squard =.%, P=.)			1.05 (0.04, 25.87)	1/511	0/264	4.10
Heterogeneity between groups: P=0.635						
Overall (I-squard =0.0%, P=0.797)		\Leftrightarrow	7.86 (4.10, 15.04)	100/3985	8/3344	100.00
0.00206	1		l 485			

Figure 4 Forest plot of the overall risk of hyperthyroidism and hypothyroidism related to anti-CTLA-4 drugs.

relatively low clinical awareness, such as hematologic and musculoskeletal disorders.

Our findings are of considerable clinical importance for multidisciplinary cooperation. As the use of immune

checkpoint inhibitors in cancer treatment increases, AEs related to this drug class will require the participation of doctors from departments other than oncology²⁶ to ensure adequate management of multi-organ AEs. In our study, the

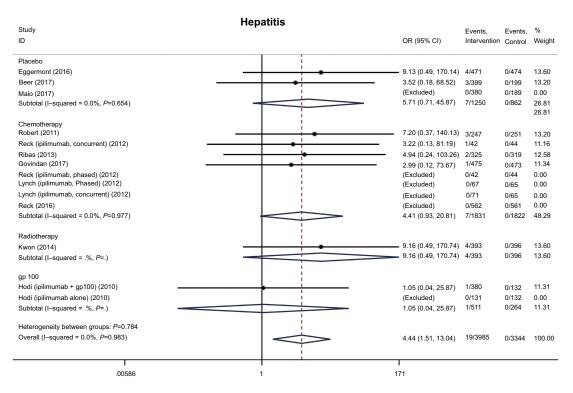


Figure 5 Forest plot of the overall risk of hepatitis related to anti-CTLA-4 drugs.

rates of all-grade pruritus, rash, diarrhea, and ALT elevation exceeded 10%, and serious diarrhea and colitis were also common (9.8% and 5.3%, respectively). Similarly, all-grade hematologic AEs were high (ranging from 18% to 5.2%), but serious events were less frequent (0.7–2%), consistent with previous reports.^{10,27,28} The incidence of musculoske-letal disorders associated with anti-PD-1–PD-L1 therapy has recently been investigated in a meta-analysis,¹¹ and inflammatory arthritis is a well-known AE associated with immune checkpoint inhibitors.^{29,30} Optimal management of these potentially serious AEs requires multidisciplinary cooperation to best serve cancer patients treated with checkpoint inhibitors.

Many of the increased risks of irAEs identified here were also noted in the recent meta-analysis of irAEs associated with anti-PD-1 drugs,¹¹ including all-grade rash (OR 4.03 here vs 2.34 in the study by Baxi et al¹¹), colitis (OR 14.62 vs 2.88), hypothyroidism (7.86 vs 6.92), and hypophysitis (5.30 vs 3.38), although the risks were higher with anti-CTLA-4 mAbs, especially colitis. However, we detected an increased risk of diarrhea and hepatitis with anti-CTLA-4 mAbs, which was not observed with anti-PD -1/PD-L1,¹¹ and conversely, an increased risk of pneumonitis (OR 3.82) was associated with anti-PD-1–PD-L1 drugs,¹¹ but not with anti-CTLA-4 drugs (this study), compared with the control therapies.

Questions remain about whether some of these discrepancies may be due to inaccurate and/or inconsistent identification of AEs associated with immune checkpoint inhibitors. To avoid this, we must have a better understanding of the characteristics, timing, and outcomes of these AEs. The full spectrum of irAEs associated with immune checkpoint drugs is not yet clear, because some may emerge early and result in a high mortality rate (eg, myocarditis³¹) and others may appear too late to be recognized within the restricted period of follow-up for most studies. It is crucial that clinical trials collect and report as much information as possible on AEs resulting from administration of immune checkpoint inhibitors, and their reporting should also follow the most up-to-date edition of the Common Terminology of Clinical Adverse Events.

In our meta-analysis, we detected some inconsistencies in reporting terms for the irAEs across trials. Although collection of data from ClinicalTrials.gov enabled us to access more information on AEs (reported according to the Common Terminology of Clinical Adverse Events guidelines) compared with the published literature, recognition of AEs is highly subjective and relies on personal experience, which may contribute to cross-trial inconsistencies. For instance, some well-described irAEs (colitis, hepatitis, and hypothyroidism) may be correctly recognized and reported, whereas less common AEs (eg, Guillain–Barre

Study ID	Pneumonitis	OR (95% CI)	Events, Intervention	Events Control	% Weight
Placebo	1				
Eggermont (2016)		7.09 (0.37, 137.63)	3/471	0/474	3.89
Maio (2017)			2/380	0/189	3.70
Beer (2017)		6.59 (0.37, 117.59)		0/199	4.12
Subtotal (I-squard =0.0%, P=0.866)		4.97 (0.90, 27.48)		0/862	11.72
Chemotherapy					
Robert (2011)		5.12 (0.24, 107.24)	2/247	0/251	3.70
Reck (ipilimumab, phased) (2012)	•	0.51 (0.04, 5.87)	1/42	2/44	5.76
Reck (ipilimumab, concurrent) (2012)		1.62 (0.26, 10.19)	3/42	2/44	10.09
Lynch (ipilimumab, phased) (2012)		0.97 (0.19, 4.98)	3/67	3/65	12.76
Lynch (ipilimumab, concurrent) (2012)	· · · · ·	4.20 (1.13, 15.65)	12/71	3/65	19.81
Reck (2016)	· · · · · · · · · · · · · · · · · · ·	0.50 (0.09, 2.73)	2/562	4/561	11.83
Govindan (2017)		1.00 (0.25, 4.00)	4/475	4/473	17.67
Ribas (2013)		(Excluded)	0/325	0/319	0.00
Subtotal (I-squard =0.0%, P=0.434)	\Leftrightarrow	1.39 (0.73, 2.65)	27/1831	18/1822	81.62
Radiotherapy					
Known(2014)		3.03 (0.12, 74.62)	1/393	0/396	3.34
subtotal (I-squard =.%, P= .)		3.03 (0.12, 74.62)	1/393	0/396	3.34
gp100					
Hodi (ipilimumab + gp100) (2010)		1.05 (0.04, 25.87)	1/380	0/132	3.33
Hodi (ipilimumab alone) (2010)		(Excluded)	0/131	0/132	0.00
Subtotal (I-squard =0.0%, P=.)		1.05 (0.04, 25.87)	1/511	0/264	3.33
Heterogeneity between groups: P=0.554					
Overall (I-squard =0.0%, P=0.688)	\Leftrightarrow	1.64 (0.91, 2.94)	40/3985	18/3344	100.00
l .00727	1	1 138			

Study ID	Pancreatitis	OR (95% CI)	Events, Intervention	Events Control	% Weight
Placebo					
Eggermont (2016)		3.03 (0.12, 74.46)	1/471	0/474	12.13
Beer (2017)		2.50 (0.12, 52.40)	2/380	0/189	13.46
Maio (2017)		(Excluded)	0/399	0/199	0.00
Subtotal (I-squard =0.0%, P=0.933)		2.74 (0.30, 24.85)	3/1250	0/862	25.59
Chemotherapy					
Robert (2011)		3.06 (0.12, 75.50)			
Reck (ipilimumab, phased) (2012)	*	0.34 (0.01, 8.61)			
Reck (ipilimumab, concurrent) (2012)	* 1	0.34 (0.01, 8.61)			
Ribas (2013)		6.93 (0.36, 134.80)			
Reck (2016)	• •	0.33 (0.01, 8.17) 2.99 (0.12, 73.67)			
Lynch (ipilimumab, phased) (2012)		(Excluded)	0/67	0/65	0.00
Lynch (ipilimumab, concurrent) (2012)		(Excluded)	0/71	0/65	0.00
Subtotal (I-squard =0.0%, P=0.584)		1.23 (0.34, 4.47)	5/1831	3/1822	74.41
Radiotherapy					
Known(2014)		(Excluded)			0.00
subtotal (I-squard =.%, P= .)		. (., .)	0/393	0/396	0.00
gp100					
Hodi (ipilimumab + gp100) (2010)					0.00
Hodi (ipilimumab alone) (2010)		(Excluded)	0/131	0/132	0.00
Subtotal (I-squard =0.0%, P=.)		. (., .)	0/511	0/264	0.00
Heterogeneity between groups: P=0.944					
Overall (I-squard =0.0%, P=0.762)		1.51 (0.49, 4.60)	8/3985	3/3344	100.00
l .00742					



syndrome and musculoskeletal disorders) may not. Increased attention should be paid to this topic to ensure that reporting of AEs in these clinical trials becomes more standardized and accurate. Overall, successful management of irAEs related to immune checkpoint inhibitors requires early diagnosis, high suspicion, excellent patient–provider communication, and rapid and aggressive use of corticos-teroids and other immunosuppressants.²⁶

Table 5 Incidence of treatment-related adverse events related to anti-CTLA-4 drugs. Values are percentages (95% confidence intervals)

Drugs	Ipilimumab (n=3280)		Tremelimumab (n=705)		Total (n=3985)			
Treatment-related AEs*	All [#]	Serious [†]	All	Serious	All	Serious		
Hematologic								
Anemia	20.1 (18.7–21.5)	2.3 (1.8–2.8)	8.4 (6.4–10.7)	0.7 (0.2–1.6)	18.0 (16.8–19.2)	2.0 (1.6–2.5)		
Neutropenia	13.6 (12.4–14.8)	1.3 (1.0–1.8)	0.7 (0.2–1.6)	0.6 (0.2–1.4)	11.3 (10.3–12.3)	1.2 (0.9–1.6)		
Thrombocytopenia	6.1 (5.3–6.9)	0.7 (0.5–1.1)	1.0 (0.4–2.0)	0.4 (0.1–1.2)	5.2 (4.5–5.9)	0.7 (0.4–1.0)		
Musculoskeletal problems								
Arthritis	0.1 (0.0-0.3)	0.1 (0.0-0.3)	0.0 (0.0–0.5)	0.0 (0.0–0.5)	0.1 (0.0-0.2)	0.1 (0.0-0.2)		
Arthralgia	11.4 (10.3–12.5)	0.2 (0.1–0.4)	0.0 (0.0-0.5)	0.0 (0.0–0.5)	9.4 (8.5–10.3)	0.2 (0.1–0.3)		
Back pain	10.4 (9.4–11.5)	0.6 (0.4–1.0)	3.0 (1.9-4.5)	0.0 (0.0-0.5)	9.1 (8.2–10.0)	1.5 (1.2–2.0)		
Musculoskeletal pain	5.5 (4.8–6.4)	0.2 (0.1–0.4)	0.1 (0.0–0.8)	0.1 (0.0–0.8)	4.6 (4.0–5.3)	0.2 (0.1–0.4)		
Bone pain	3.4 (2.8–4.0)	0.2 (0.1–0.5)	0.0 (0.0-0.5)	0.0 (0.0-0.5)	2.8 (2.3–3.3)	0.2 (0.1–0.4)		
Myalgia	4.7 (4.0–5.5)	0.0 (0.0–0.1)	0.1 (0.0–0.8)	0.1 (0.0–0.8)	3.9 (3.3–4.5)	0.0 (0.0–0.1)		

Notes: *AEs, adverse events. #Includes both serious and other adverse events if data were extracted from ClinicalTrials.gov; includes all Common Terminology of Clinical Adverse Events (CTCAE) grades if data were extracted from the publication. † Serious adverse events if data were extracted from ClinicalTrials.gov; CTCAE grades \geq 3 if data were extracted from the publication.

Some limitations of our study should also be noted. First, some AEs may not have been recognized and/or reported, leading to underestimation of their rate and overestimation of drug safety.³² Second, pooling of the irAEs may have been affected by inconsistencies in the definition of irAEs.8,23,25 Third, our study included only two randomized controlled trials of tremelimumab, with the majority focusing on ipilimumab; thus, the incidence of AEs might be related mainly to ipilimumab rather than anti-CTLA-4 drugs as a class. Fourth, some AEs were relatively rare and only reported in a few trials, potentially contributing to publication bias. Fifth, because the control therapies differed (placebo, chemotherapy, radiation therapy, vaccine), we performed subgroup analyses to try to eliminate confounding bias. Sixth, a previous study showed that the rate of AEs was associated with the ipilimumab dose.³³ Our dataset included one randomized controlled trial with 3 mg/kg ipilimumab, one with 15 mg/kg tremelimumab, and the remainder with 10 mg/kg mAb, which precluded analysis of dose dependency. Finally, the relatively short duration of follow-up may have underestimated the rates of some events. Going forward, standard criteria for irAEs and longer follow-up times might be helpful in understanding irAEs related to anti-CTLA-4 therapy.

Conclusion

In this meta-analysis, we found that anti-CTLA-4 mAbs carried an increased risk of serious organ-specific irAEs

compared with control therapies, most frequently involving the gastrointestinal system. However, the rates of hematologic abnormalities and severe musculoskeletal disorders were the same as with control therapies. Our results underscore the need for clinical awareness of irAEs related to the treatment of cancer patients with anti-CTLA-4 drugs.

Abbreviations

IrAEs, immune-related adverse events; Anti-CTLA-4, anticytotoxic T-lymphocyte-associated protein-4; ALT, alanine aminotransferase; AST, aspartate aminotransferase; OR, odds ratio; CI, confidence interval; CTCAE, Common Terminology of Clinical Adverse Events; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Acknowledgments

This program was supported by the National Natural Science Foundation of China (Grant No.81300627, No.81702536), Programs from Science and Technology Department of Sichuan Province (Grant No. 2018JY0089 and No. 2018HH0153), the Prostate Cancer Foundation Young Investigator Award 2013, Chengdu Technological Innovation Research and Development Project (Chengdu Science and Technology Bureau, 2018-YFYF-00131-SN), a grant from 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (ZYGD18011), and Young Investigator Award of Sichuan University 2017

(Grant No. 2017SCU04A17). The funders had no role in patient selection, data extraction, statistical analysis or interpretation, writing of this article, or the decision to publish. The authors would like to thank Anne M. O'Rourke, PhD, from Liwen Bianji, Edanz Group China, for editing the English text of a draft of this manuscript.

Author contributions

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

- Hossain MK, Nahar K, Donkor O, Apostolopoulos V. Immune-based therapies for metastatic prostate cancer: an update. *Immunotherapy*. 2018;10(4):283–298. doi:10.2217/imt-2017-0123
- Ugurel S, Röhmel J, Ascierto P, et al. Survival of patients with advanced metastatic melanoma: the impact of novel therapies-update 2017. *Eur J Cancer*. 2017;83:247–257. doi:10.1016/j.ejca.2017.06.028
- 3. Xia B, Herbst RS. Immune checkpoint therapy for non-small-cell lung cancer: an update. *Immunotherapy*. 2016;8(3):279–298. doi:10.2217/imt.15.123
- Calabro L, Ceresoli GL, D'Incecco A, Scherpereel A, Aerts J, Maio M. Immune checkpoint therapy of mesothelioma: pre-clinical bases and clinical evidences. *Cytokine Growth Factor Rev.* 2017;36:25–31. doi:10.1016/j.cytogfr.2017.07.003
- O'Day SJ, Hamid O, Urba WJ. Targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4): a novel strategy for the treatment of melanoma and other malignancies. *Cancer*. 2007;110(12):2614–2627. doi:10.1002/ cncr.23086
- Kaehler KC, Piel S, Livingstone E, Schilling B, Hauschild A, Schadendorf D. Update on immunologic therapy with anti-CTLA-4 antibodies in melanoma: identification of clinical and biological response patterns, immune-related adverse events, and their management. *Semin Oncol.* 2010;37(5):485–498. doi:10.1053/j. seminoncol.2010.09.003
- Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. *N Engl J Med.* 2016;375(19):1845–1855. doi:10.1056/NEJMoa1611299
- Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711–723. doi:10.1056/NEJMoa1003466
- Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252–264. doi:10.1038/ nrc3239
- Shiuan E, Beckermann KE, Ozgun A, et al. Thrombocytopenia in patients with melanoma receiving immune checkpoint inhibitor therapy. *J Immunother Cancer*. 2017;5:8. doi:10.1186/s40425-017-0210-0
- Baxi S, Yang A, Gennarelli RL, et al. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. *BMJ*. 2018;360:k793. doi:10.1136/bmj.k793

- 12. Komaki Y, Komaki F, Yamada A, Micic D, Ido A, Sakuraba A. Metaanalysis of the risk of immune-related adverse events with anticytotoxic T-lymphocyte-associated antigen 4 and antiprogrammed death 1 therapies. *Clin Pharmacol Ther.* 2017;103(2):318–331.
- 13. De Velasco G, Je Y, Bossé D, et al. Comprehensive meta-analysis of key immune-related adverse events from CTLA-4 and PD-1/PD-L1 inhibitors in cancer patients. *Cancer Immunol Res.* 2017;5(4):312. doi:10.1158/2326-6066.CIR-16-0237
- 14. 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. doi:10.1186/s12916-015-0455-8
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535. doi:10.1136/bmj.b2651
- 16. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj Br Med J.* 2011;343(7829):889–893. doi:10.1136/ bmj.d5928
- 17. Reck M, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. *Ann Oncol.* 2013;24 (1):75–83. doi:10.1093/annonc/mds213
- Lynch TJ, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. *J Clin Oncol.* 2012;30(17):2046–2054. doi:10.1200/JCO.2011.38.4032
- Maio M, Scherpereel A, Calabro L, et al. Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial. *Lancet Oncol.* 2017;18(9):1261–1273. doi:10.1016/S1470-2045(17)30446-1
- Govindan R, Szczesna A, Ahn MJ, et al. Phase III trial of ipilimumab combined with paclitaxel and carboplatin in advanced squamous non-small-cell lung cancer. *J Clin Oncol.* 2017;35(30):3449–3457. doi:10.1200/JCO.2016.71.7629
- 21. Beer TM, Kwon ED, Drake CG, et al. Randomized, double-blind, phase III trial of ipilimumab versus placebo in asymptomatic or minimally symptomatic patients with metastatic chemotherapy-naive castration-resistant prostate cancer. *J Clin Oncol.* 2017;35(1):40–47. doi:10.1200/JCO.2016.69.1584
- 22. Reck M, Luft A, Szczesna A, et al. Phase III randomized trial of ipilimumab plus etoposide and platinum versus placebo plus etoposide and platinum in extensive-stage small-cell lung cancer. J Clin Oncol. 2016;34(31):3740–3748. doi:10.1200/ JCO.2016.67.6601
- 23. Kwon ED, Drake CG, Scher HI, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2014;15(7):700–712. doi:10.1016/S1470-2045(14)70189-5
- 24. 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(5):616–622. doi:10.1200/JCO.2012.44.6112
- Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med.* 2011;364(26):2517–2526. doi:10.1056/NEJMoa1104621
- 26. Weber J, Yang J, Atkins M, Disis M. Toxicities of Immunotherapy for the Practitioner. J Clin Oncol. 2015;33(18):2092–2099. doi:10.1200/JCO.2014.60.0379
- Ban-Hoefen M, Burack R, Sievert L, Sahasrabudhe D. Ipilimumabinduced neutropenia in melanoma. J Investig Med High Impact Case Rep. 2016;4(3):2324709616661835. doi:10.1177/2324709616661835

- 28. Meyers DE, Hill WF, Suo A, Jimenez-Zepeda V, Cheng T, Nixon NA. Aplastic anemia secondary to nivolumab and ipilimumab in a patient with metastatic melanoma: a case report. *Exp Hematol Oncol.* 2018;7:6. doi:10.1186/s40164-018-0098-5
- Cappelli LC, Gutierrez AK, Baer AN, et al. Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab. *Annals of the Rheumatic Diseases*. 2016;76(1):43. doi:10.1136/annrheumdis-2016-209595
- 30. Leipe J, Christ LA, Arnoldi AP, et al. Characteristics and treatment of new-onset arthritis after checkpoint inhibitor therapy. *RMD Open.* 2018;4(2): e000714. doi: 10.1136/rmdopen-2018-000714
- Moslehi J, Salem J, Sosman J, Lebrun-Vignes B, Johnson D. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. *Lancet (London, England)*. 2018;391(10124):933. doi:10.1016/S0140-6736(18)30302-7
- 32. Saini P, Loke YK, Gamble C, Altman DG, Williamson PR, Kirkham JJ. Selective reporting bias of harm outcomes within studies: findings from a cohort of systematic reviews. *Bmj.* 2014;349(nov21 3):g6501. doi:10.1136/bmj.g6501
- 33. Feng Y, Roy A, Masson E, Chen TT, Humphrey R, Weber JS. Exposureresponse relationships of the efficacy and safety of ipilimumab in patients with advanced melanoma. *Clin Cancer Res Off J Am Assoc Cancer Res.* 2013;19(14):3977–3986. doi:10.1158/1078-0432.CCR-12-3243

Supplementary materials

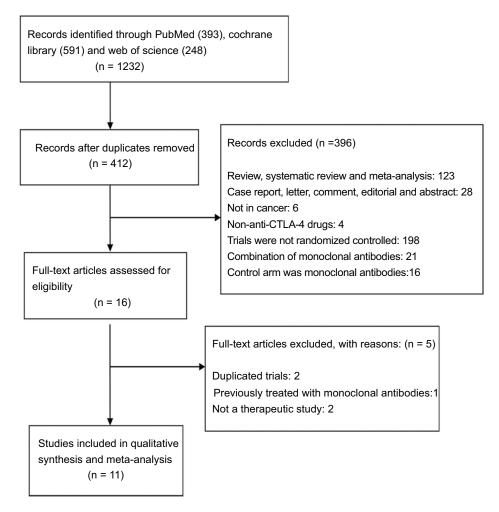


Figure SI Flow diagram for study selection.

	opituitarism				
Study		Events,	Events	%	
ID	OR (95% CI)	Intervention	Control	Weight	
Placebo					
Eggermont (2016)	* 19.49 (1.13, 335.88)	9/471	0/474	12.52	
Maio (2017)	 1.50 (0.06, 36.95) 	1/380	0/189	9.88	
Beer (2017)	4.54 (0.24, 84.74)	4/399	0/199	11.85	
Subtotal (I-squard =0.0%, P=0.495)	5.62 (1.00, 31.42)	14/1250	0/862	34.25	
Chemotherapy					
Lynch (ipilimumab, concurrent) (2012)	 2.79 (0.11, 69.64) 	1/71	0/65	9.80	
Reck (2016)	5.01 (0.24, 104.57)	2/562	0/561	10.99	
Govindan (2017)	5.00 (0.24, 104.43)	2/475	0/473	10.99	
Robert (2011)	(Excluded)	0/247	0/251	0.00	
Reck (ipilimumab, phased) (2012)	(Excluded)	0/42	0/44	0.00	
Reck (ipilimumab, concurrent) (2012)	(Excluded)	0/42	0/44	0.00	
Lynch (ipilimumab, phased) (2012)	(Excluded)	0/67	0/65	0.00	
Ribas (2013)	(Excluded)	0/325	0/319	0.00	
Subtotal (I-squard =0.0%, P=0.957)	4.18 (0.70, 24.95)	5/1831	0/1822	31.78	
Radiotherapy					
Known(2014)	7.11 (0.37, 138.05)	3/393	0/396	11.53	
subtotal (I-squard =.%, P= .)	7.11 (0.37, 138.05)	3/393	0/396	11.53	
gp100					
Hodi (ipilimumab + gp100) (2010)	2.46 (0.13, 47.88)	3/380	0/132	11.51	
Hodi (ipilimumab alone) (2010)	5.12 (0.24, 107.59)	2/131	0/132	10.94	
Subtotal (I-squard =0.0%, P=0.735)	3.51 (0.42, 29.45)	5/511	0/264	22.44	
Heterogeneity between groups: P=0.977					
Overall (I-squard =0.0%, P=0.986)	4.73 (1.73, 12.95)	27/3985	0/3344	100.00	
	i				
.00298 1	336				

Figure S2 Forest plot of the overall risk of hypopituitarism related to anti-CTLA-4 drugs.

ALT increas	ed			
Study		Events,	Events	%
ID	OR (95% CI)	Intervention	Control	Weight
Placebo				
Eggermont (2016)	5.38 (3.43, 8.42)	112/471	26/474	12.74
Beer (2017) -	19.64 (2.67, 144.30)	36/399	1/199	5.52
Maio (2017)	(Excluded)	0/380	0/189	0.00
Subtotal (I-squard =35.2%, P=0.214)	7.03 (2.51, 19.67)	148/1250	27/862	18.26
Chemotherapy				
Robert (2011)	12.43 (6.696, 22.18)	109/247	15/251	12.18
Reck (ipilimumab, phased) (2012)	13.05 (0.70, 243.84)	5/42	0/44	3.27
Reck (ipilimumab, concurrent) (2012)	15.85 (0.86, 290.81)	6/42	0/44	3.30
Lynch (ipilimumab, phased) (2012)	3.10 (0.60, 15.95)	6/67	2/65	6.85
Lynch (ipilimumab, concurrent) (2012)	2.39 (0.45, 12.75)	5/71	2/65	6.69
Reck (2016)	1.88 (1.15, 3.08)	47/562	26/561	12.56
Govindan (2017)	1.54 (0.92, 2.57)	39/475	26/473	12.47
Ribas (2013)	(Excluded)	0/325	0/319	0.00
Subtotal (I-squard =83.0%, P=0.000)	3.78 (1.57, 9.15)	217/1831	71/1822	57.30
Radiotherapy				
Known(2014)	3.81 (1.79, 8.10)	32/393	9/396	11.31
subtotal (I-squard =.%, P= .)	3.81 (1.79, 8.10)	32/393	9/396	11.31
gp100				
Hodi (ipilimumab + gp100) (2010)	0.23 (0.04, 1.38)	2/380	3/132	6.20
Hodi (ipilimumab alone) (2010)	1.01 (0.20, 5.09)	3/131	3/132	6.93
Subtotal (I-squard =31.1%, P=0.228)	0.51 (0.12, 2.17)	5/511	6/264	13.13
Overall (I-squard =79.6%, P=0.000)	3.28 (1.79, 6.02)	402/3985	113/3344	100.00
NOTE: weights are from random effects analysis	- 			
I I 0.00344 1	291			

ALT increased

ID						%
			OR (95% CI)	Intervention	Control	Weight
Placebo		1				
Eggermont (2016)			4.19 (2.61, 6.72)	86/471	24/474	14.31
Beer (2017)		•	8.88 (2.11, 37.40)	33/399	2/199	6.80
Maio (2017)			(Excluded)	0/380	0/189	0.00
Subtotal (I-squard =0.0%, P=0.330)		\diamond	4.51 (2.88, 7.06)	119/1250	26/862	21.10
Chemotherapy						
Robert (2011)			10.35 (5.79, 18.50)	98/247	15/251	13.39
Reck (ipilimumab, phased) (2012)	+	*	15.85 (0.86, 290.81)	6/42	0/44	2.41
Reck (ipilimumab, concurrent) (2012)	+	•	15.85 (0.86, 290.81)	6/42	0/44	2.41
Lynch (ipilimumab, phased) (2012)			1.67 (0.38, 7.28)	5/67	3/65	6.60
Lynch (ipilimumab, concurrent) (2012)			1.57 (0.36, 6.83)	5/71	3/65	6.61
Reck (2016)	-	•	1.99 (1.18, 3.34)	44/562	23/561	13.92
Govindan (2017)	-	•	1.80 (1.02, 3.17)	35/475	20/473	13.53
Ribas (2013)		i	(Excluded)	0/325	0/319	0.00
Subtotal (I-squard =77.6%, P=0.000)		\leq	3.28 (1.50, 7.18)	199/1831	61/1822	58.86
Radiotherapy						
Known(2014)	-	•	1.91 (1.10, 3.32)	38/393	21/396	13.64
subtotal (I-squard =.%, P= .)	<	>	1.91 (1.10, 3.32)	38/393	21/396	13.64
gp100						
Hodi (ipilimumab + gp100) (2010)		•	1.39 (0.15, 12.58)	4/380	1/132	3.80
Hodi (ipilimumab alone) (2010)	+	1	1.01 (0.06, 16.28)	1/131	1/132	2.60
Subtotal (I-squard =0.0%, P=0.858)	\sim		1.23 (0.22, 6.91)	5/511	2/264	6.40
Overall (I-squard =`68.1%, <i>P</i> =0.000)		\diamond	3.12 (1.92, 5.09)	361/3985	113/3344	100.00
NOTE: weights are from random effects analysis						
0.00344	1 1		291			

Figure S3 Forest plot of the overall risk of ALT and AST elevation related to anti-CTLA-4 drugs. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Guillant-barre	synarome			
Study		Events,	Events	%
ID	OR (95% CI)	Intervention	Control	Weig
Placebo				
Eggermont (2016)	• 3.03 (0.12, 74.46)	1/471	0/474	16.68
Maio (2017)	1.50 (0.06, 36.95)	1/380	0/189	16.66
Beer (2017)	1.50 (0.06, 37.03)	1/399	0/199	16.66
Subtotal (I-squard =0.0%, P=0.940)	1.90 (0.30, 12.06)	3/1250	0/862	49.99
Chemotherapy				
Reck (2016)	3 .00 (0.12, 73.80)	1/562	0/561	16.6
Govindan (2017)	• 2.99 (0.12, 73.67)	1/475	0/473	16.6
Robert (2011)	(Excluded)	0/247	0/251	0.00
Reck (ipilimumab, phased) (2012)	(Excluded)	0/42	0/44	0.00
Reck (ipilimumab, concurrent) (2012)	(Excluded)	0/42	0/44	0.00
Lynch (ipilimumab, phased) (2012)	(Excluded)	0/67	0/65	0.00
Lynch (ipilimumab, concurrent) (2012)	(Excluded)	0/71	0/65	0.00
Ribas (2013)	(Excluded)	0/325	0/319	0.00
Subtotal (I-squard =0.0%, P=0.999)	3.00 (0.31, 28.86)	2/1831	0/1822	33.36
Radiotherapy				
Known(2014)	(Excluded)			0.00
subtotal (I-squard =.%, P= .)	. (., .)	0/396	0/396	0.00
gp100				
Hodi (ipilimumab + gp100) (2010)	1.05 (0.04, 25.87)	1/380	0/132	16.6
Hodi (ipilimumab alone) (2010)	(Excluded)	0/131	0/132	0.00
Subtotal (I-squard =0.0%, P=.)	1.05 (0.04, 25.87)	1/511	0/264	16.6
Heterogeneity between groups: P=0.963				
Overall (I-squard =0.0%, P=0.995)	2.00 (0.54, 7.40)	6/3985	0/3344	100.
	1			
.0134 1	74.5			

Guillain-barre syndrome

Figure S4 Forest plot of the overall risk of Guillain-Barre syndrome related to anti-CTLA-4 drugs.

Drug Design, Development and Therapy

Publish your work in this journal

Drug Design, Development and Therapy is an international, peerreviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are a feature of the journal, which has also been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www. dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/drug-design-development-and-therapy-journal

