REVIEW

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

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**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

## Introduction

Recent years have seen increasing interest in immunotherapy-based immune checkpoint blockade for various advanced or metastatic solid tumors, such as prostate cancer,<sup>1</sup> melanoma,<sup>2</sup> lung cancer,<sup>3</sup> and mesothelioma.<sup>4</sup> 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.<sup>5,6</sup> 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.<sup>7,8</sup> Nevertheless, despite the beneficial effects of immune checkpoint inhibitors in promoting the anti-tumor response, their mechanism of action in enhancing T cell activity<sup>9</sup> also increases the risk of immune-related adverse events (irAEs), which often affect multiple organs.<sup>8</sup> 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.<sup>10</sup> 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);<sup>11</sup> 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,<sup>12–14</sup> 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,<sup>15</sup> 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  $\geq 3$  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 Tool<sup>16</sup> 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 I<sup>2</sup> 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,<sup>17</sup> Lynch et al,<sup>18</sup> and Hodi et al<sup>8</sup>), 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<sup>7,8,17–25</sup> 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,<sup>7,8,24,25</sup> two in metastatic non-small cell lung cancer,<sup>18,20</sup> two in small cell lung cancer,<sup>17,22</sup> two in metastatic castration-resistant prostate cancer,<sup>21,23</sup> and one in mesothelioma.<sup>19</sup> 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 al<sup>19</sup> and Ribas et al,<sup>24</sup> 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 al<sup>17</sup> and Lynch et al<sup>18</sup> 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 al<sup>8</sup> 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 al<sup>24</sup>); 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	Phase	Cancer type	Size (Intervention/ Control )	Intervention	Dose	Control	Follow-up duration (intervention)	Primary outcome	Description of irAEs
Maio 2017 <sup>19</sup> Govindan 2017 <sup>20</sup>	01843374 01285609	3	Mesothelioma NSCLC	569 (380/189) 948 (475/473)	Tremelimumab Ipilimumab + Chemotherapy	10 mg/kg 10 mg/kg	Placebo Chemotherapy + Placebo	NA 12.5 months	so SO	No Yes
Beer 2017 <sup>21</sup> Reck 2016 <sup>22</sup>	01057810 01450761	m m	mCRPC SCLC	600 (399/199) 954 (562/561)	lpilimumab Ipilimumab + Chemotherapy	I0 mg/kg I0 mg/kg	Placebo Chemotherapy + Placebo	NA 10.5 months	S SO	Yes Yes
Eggermont 2016 <sup>7</sup> kwon 2014 <sup>23</sup>	00636168 00861614	m m	Melanoma mCRPC	945 (471/474) 799 (393/396)	Ipilimumab Ipilimumab +	10 mg/kg 10 mg/kg	Placebo Radiotherapy +	63.6 months 9.9 months	RFS OS	Yes Yes
Ribas 2013 <sup>24</sup> Reck 2012 <sup>17</sup>	00257205 00527735	5 3	Melanoma SCLC	644 (325/319) 86 (42/44)	radiounerapy Tremelimumab Ipilimumab (Phased)#	I5 mg/kg I0 mg/kg	piacebo Chemotherapy Chemotherapy + Placebo	31 months NA	OS irPFS	No Yes
Lynch 2012 <sup>18</sup>	00527735	2	NSCLC	86 (42/44) 132 (67/65) 136 (71/65)	lpilimumab# (Concurrent) Ipilimumab# (Phased) Ipilimumab#	10 mg/kg 10 mg/kg 10 mg/kg	Chemotherapy + Placebo Chemotherapy + Placebo Chemotherapy	¥	ir PFS	Yes
Robert 2011 <sup>25</sup>	00324155	e	Melanoma	498 (247/251)	(Concurrent) Ipilimumab + Chemotherapy	10 mg/kg	+ Placebo Chemotherapy + Placebo	Υ	SO	Yes
Hodi 2010 <sup>8</sup>	00094653	ĸ	Melanoma	512 (380/132) 263 (131/132)	Ipilimumab + gp100 Ipilimumab	3 mg/kg 3 mg/kg	gp100 gp100	21 months 27.8 months	S	Yes
Notes: # concurrent, ip Abbreviations: NA, not related progression-free	ilimumab + pac t available; OS, survival.	litaxel/carbo overall survi	platin followed by pl: ival; NSCLC, non-sm:	acebo + paclitaxel/carboplati all cell lung cancer; SCLC, sn	n; phased, placebo + F nall cell lung cancer; m	aaclitaxel/carbop ICRPC, metastat	latin followed by ipilin ic castration resistant	numab + paclitaxel/carboplatin. prostate cancer; irAEs, immune.	related adverse e	ents; irPFS, immune-

 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 <sup>19</sup>	2017	Low	Low	Low	Low	High	High	Low
Govindan <sup>20</sup>	2017	Low	Low	Low	Low	High	High	Low
Beer <sup>21</sup>	2017	Low	Low	Low	Low	High	High	Low
Reck <sup>22</sup>	2016	Low	Low	Low	Low	High	High	Low
Eggermont <sup>7</sup>	2016	Low	Low	Low	Low	High	High	Low
kwon <sup>23</sup>	2014	Low	Low	Low	Low	High	High	Low
Ribas <sup>24</sup>	2013	Low	Low	High	High	High	High	Low
Reck <sup>17</sup>	2012	Low	Unclear	Low	Low	High	High	Low
Lynch <sup>18</sup>	2012	Low	Unclear	Low	Low	High	High	Low
Robert <sup>25</sup>	2011	Low	Unclear	Low	Low	High	High	Low
Hodi <sup>8</sup>	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)	1
IrAEs*	All <sup>#</sup>	Serious <sup>†</sup>	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  $\geq 3$  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 <sup>#</sup>			<b>S</b> erious <sup>†</sup>		
IrAEs*	OR	95%CI	Р	OR	95%CI	Р
Dermatologic						
Pruritus Rash	4.35 4.03	3.74–5.07 3.22–5.04	<0.0001 <0.0001	3.64 3.39	0.89–14.91 1.52–7.59	0.072 0.003
Gastrointestinal						
Diarrhea Colitis	2.88 14.62	2.35–3.78 8.61–24.83	<0.0001 <0.0001	6.57 14.01	4.09–10.58 7.34–26.77	<0.0001 <0.0001
Endocrine						
Hypophysitis Hypothyroidism Hyperthyroidism Adrenal insufficiency Hypopituitarism	5.30 7.86 3.78 3.88 4.73	1.71–16.46 4.10–15.04 0.94–15.17 1.46–10.36 1.73–12.95	0.004 <0.0001 0.061 0.007 0.003	4.22 3.72 3.78 3.77 4.73	1.72–10.34 1.18–11.75 0.94–15.17 1.41–10.06 1.73–12.95	0.002 0.025 0.061 0.008 0.003
Hepatic						
Hepatitis ALT increased AST increased	4.44 3.28 3.12	1.51–13.04 1.79–6.02 1.92–5.09	0.007 <0.0001 <0.0001	4.44 11.37 4.9	1.51–13.04 4.45–29.10 1.41–17.07	0.007 <0.0001 0.013
Other						
Pneumonitis Pancreatitis Guillain-Barre syndrome	1.64 1.51 2.00	0.91–2.94 0.49–4.60 0.54–7.40	0.098 0.472 0.299	1.27 1.51 2.00	0.66–2.44 0.49–4.60 0.54–7.40	0.477 0.472 0.299
Treatment-related AEs						
Hematologic						
Anemia Neutropenia Thrombocytopenia	1.11 1.05 0.84	0.83–1.49 0.66–1.68 0.47–1.52	0.484 0.826 0.569	0.95 0.72 0.57	0.68–1.34 0.37–1.42 0.34–0.96	0.782 0.349 0.035
Musculoskeletal problems						
Arthritis Arthralgia Back pain Musculoskeletal pain Bone pain	1.30 1.02 0.77 0.72 0.76	0.25-6.77 0.86-1.20 0.65-0.90 0.58-0.90 0.58-0.99	0.755 0.851 0.001 0.003 0.044	1.30 0.84 0.65 0.7 0.73	0.25-6.77 0.27-2.61 0.36-1.15 0.24-2.01 0.30-1.78	0.755 0.769 0.137 0.503 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

	Pruritus			
Study		Events,	Events,	%
ID	OR (95% CI)	Interventior	Control	Weight
Placebo	1			
Eggermont (2016)	4.37 (3.20, 5.9	3) 203/471	70/474	23.53
Maio (2017)	4.31 (2.43, 7.6	6) 103/380	15/189	6.98
Beer (2017)	3.78 (2.29, 6.2	3) 123/399	21/199	9.20
Subtotal (I-squared = 0.0%, <i>P</i> =0.885)	4.22 (3.31, 5.3	6) 429/1250	106/862	39.70
Chemotherapy				
Robert (2011)	4.45 (2.66, 7.4	5) 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, 6.3	9) 7/67	4/65	1.40
Lynch (ipilimumab, concurrent) (2012)	3.75 (1.16, 12.	)5) 14/71	4/65	1.68
Ribas (2013)	8.42 (4.83, 14.	6) 100/325	16/319	7.45
Reck (2016)	6.31 (3.59, 11.	8) 83/562	15/561	7.24
Govindan (2017)	3.30 (2.09, 5.2	I) 79/475	27/473	10.98
Subtotal (I-squared = 31.3%, <i>P</i> =0.178)	4.80 (3.77, 6.1	2) 376/1831	92/1822	39.22
Radiotherapy				
Kwon (2014)	5.72 (3.52, 9.3	I) 99/393	22/396	9.70
Subtotal (I-squared = .%, P=.)	5.72 (3.52, 9.3	1) 99/393	22/396	9.70
gp 100				
Hodi (ipilimumab + gp100) (2010)	2.21 (1.21, 4.0	6) 79/380	14/132	6.24
Hodi (ipilimumab alone) (2010)	3.57 (1.83, 6.9	7) 39/131	14/132	5.14
Subtotal (I-squared = 7.6%, P=0.298)	2.75 (1.75, 4.3	I) 118/511	28/264	11.37
Heterogeneity between groups: P=0.114	1			
Overall (I–squared = 25.6%, <i>P</i> =0.179)	4.35 (3.74, 5.0	7) 1022/3985	248/3344	100.00
I 0.0312	1 32.1			

Rash

Study				Events,	Events,	%
ID		0	R (95% CI)	Intervention	Control	Weight
Placebo						
Eggermont (2016)	•	3.2	1 (2.37, 4.35)	186/471	80/474	12.48
Maio (2017)		3.5	5 (1.92, 6.57)	79/380	13/189	7.27
Beer (2017)		4.8	0 (2.95, 7.81)	149/399	22/199	9.15
Subtotal (I-squared = 0.0%, <i>P</i> =0.393)		> 3.5	9 (2.83, 4.55)	414/1250	115/862	28.89
Chemotherapy						
Robert (2011)		4.8	1 (2.73, 8.50)	64/247	17/251	7.90
Reck (ipilimumab, phased) (2012)		5.4	7 (1.42, 21.09)	12/42	3/44	2.34
Reck (ipilimumab, concurrent) (2012)	— —	♦ > 9.2	9 (2.47, 34.94)	17/42	3/44	2.42
Lynch (ipilimumab, Phased) (2012)	*	1.4	5 (0.52, 4.08)	10/67	7/65	3.63
Lynch (ipilimumab, concurrent) (2012)		• 4.5	0 (1.79, 11.34)	25/71	7/65	4.30
Ribas (2013)		8.6	0 (5.01, 14.77)	106/325	17/319	8.31
Reck (2016)		<b>•</b> 5.3	9 (3.51, 8.28)	124/562	28/561	10.14
Govindan (2017)		2.3	2 (1.58, 3.39)	93/475	45/473	11.00
Subtotal (I-squared = 69.8%, <i>P</i> =0.002)	<	4.4	2 (2.85, 6.83)	451/1831	127/1822	50.04
Radiotherapy		1				
Kwon (2014)	•	3.5	7 (2.27, 5.62)	84/393	28/396	9.71
Subtotal (I-squared = .%, P=.)		3.5	7 (2.27, 5.62)	84/393	28/396	9.71
gp 100						
Hodi (ipilimumab + gp100) (2010)		3.6	4 (1.77, 7.49)	80/380	9/132	6.03
Hodi (ipilimumab alone) (2010)		3.8	9 (1.76, 8.58)	29/131	9/132	5.33
Subtotal (I-squared = 0.0%, <i>P</i> =0.907)		3.7	5 (2.20, 6.39)	109/511	18/264	11.36
Overall (I–squared = 50.1%, <i>P</i> =0.017)	<	4.0	3 (3.22, 5.04)	1058/3985	288/3344	100.00
NOTE: weights are from random effects analysis		I I				
0.0286	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 ID		OR (95% CI)	Events, Intervention	Events, Control	% Weight
Placebo Eggermont (2016) Maio (2017) Beer (2017)		20.23 (8.77, 46.66) 26.05 (1.58, 430.68) 7.72 (1.82, 32.69)	97/471 24/380 29/399	6/474 0/189 2/199	40.18 3.56 13.47
subtotal (I-squard =0.0%, <i>P</i> =0.498)	$\diamond$	16.38 (8.13, 33.00)	150/1250	8/862	57.21
Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012)	*	<b>—</b> 17.85 (1.02, 310.99) 3.22 (0.13, 81.19)	8/247 1/42	0/251 0/44	3.44 2.69
Lynch (ipilimumab, phased) (2012) - Ribas (2013)	*	5.00 (0.24, 106.17)	2/67 13/325	0/65 0/319	3.01 3.51
Reck (2016)		24.98 (3.37, 185.31)	24/562	1/561	6.99
Reck (ipilimumab, concurrent) (2012)		(Excluded)	0/42	2/473 0/44	0.00
Lynch (ipilimumab, concurrent) (2012) subtotal (I-squard =0.0%, <i>P</i> =0.807)		(Excluded) 10.83 (4.26, 27.49)	0/71 62/1831	0/65 3/1822	0.00 32.32
Radiotherapy Known(2014) subtotal (I-squard =.%, <i>P</i> = .)		45.77 (2.76, 758.28) 45.77 (2.76, 758.28)	21/393 21/393	0/396 0/396	3.56 3.56
gp100 Hodi (ipilimumab + gp100) (2010) Hodi (ipilimumab alone) (2010)		10.48 (0.62, 176.98) <b>-</b> 15.96 (0.90, 282.44)	14/380 7/131	0/132 0/132	3.51 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: <i>P</i> =0.765 Overall (I-squard =0.0%, <i>P</i> =0.937)		14.62 (8.61, 24.83)	254/3985	11/3344	100.00
I .00132		<b>I</b> 758			
	Diarrhea				
Study	Diarrhea	E OR (95% CI) In	Events, itervention	Events, Control	% Weight
Study ID Placebo	Diarrhea	E OR (95% CI) In	Events, itervention	Events, Control	% Weight
Study ID Placebo Eggermont (2016)	Diarrhea	E OR (95% CI) In 2.87 (2.19, 3.74)	Events, itervention 264/471	Events, Control 146/474	% Weight 9.14
Study ID Placebo Eggermont (2016) Maio (2017)	Diarrhea	E OR (95% Cl) In 2.87 (2.19, 3.74) 7.04 (4.64, 10.70)	Events, tervention 264/471 237/380	Events, Control 146/474 36/189	% Weight 9.14 7.83
Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) subtotal (I-squard =0.0%, P=0.498)	Diarrhea	E OR (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)	264/471 237/380 237/399 738/1250	Events, Control 146/474 36/189 48/199 230/862	% Weight 9.14 7.83 8.17 25.14
Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) subtotal (I-squard =0.0%, <i>P</i> =0.498) Chemotherapy	Diarrhea	E OR (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)	264/471 237/380 237/399 738/1250	Events, Control 146/474 36/189 48/199 230/862	% Weight 9.14 7.83 8.17 25.14
Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) subtotal (I-squard =0.0%, <i>P</i> =0.498) Chemotherapy Robert (2011)	Diarrhea	E OR (95% CI) 7.04 (4.64, 10.70) 4.60 (3.14, 6.74) 4.44 (2.62, 7.54) 2.04 (1.39, 2.99)	264/471 237/380 237/399 738/1250 99/247	Events, Control 146/474 36/189 48/199 230/862 62/251	% Weight 9.14 7.83 8.17 25.14 8.15
Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) subtotal (I-squard =0.0%, <i>P</i> =0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012)	Diarrhea	E OR (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)	Events, tervention 264/471 237/380 237/399 738/1250 99/247 16/42	Events, Control 146/474 36/189 48/199 230/862 62/251 8/44	% Weight 7.83 8.17 25.14 8.15 3.73
Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) subtotal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, concurrent) (2012) Locat (ipilimumab, concurrent) (2012)	Diarrhea	E OR (95% CI) 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)	vents, tervention 264/471 237/380 237/399 738/1250 99/247 16/42 13/42 23/27	Events, Control 146/474 36/189 48/199 230/862 62/251 8/44 7/44 19/25	% Weight 9.14 7.83 8.17 25.14 8.15 3.73 3.48 5.21
Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) subtotal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, phased) (2012) Lynch (ipilimumab, phased) (2012)	Diarrhea	E OR (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) 0.75 (1.44, 6.24) 0.75 (1.44, 6.24)	vents, tervention 264/471 237/380 237/399 738/1250 99/247 16/42 13/42 25/67	Events, Control 146/474 36/189 48/199 230/862 62/251 8/44 7/44 18/65	% Weight 9.14 7.83 8.17 25.14 8.15 3.73 3.48 5.21 5.24
Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) subtotal (I-squard =0.0%, P=0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Ribas (2013)	Diarrhea	<ul> <li>CR (95% CI)</li> <li>2.87 (2.19, 3.74)</li> <li>7.04 (4.64, 10.70)</li> <li>4.60 (3.14, 6.74)</li> <li>4.44 (2.62, 7.54)</li> <li>2.04 (1.39, 2.99)</li> <li>2.77 (1.03, 7.43)</li> <li>2.37 (0.84, 6.70)</li> <li>1.55 (0.75, 3.24)</li> <li>2.37 (1.11, 5.07)</li> <li>4.18 (2.91, 6.00)</li> </ul>	vents, tervention 264/471 237/380 237/380 237/399 738/1250 99/247 16/42 13/42 25/67 28/71 15/325	Events, Control 146/474 36/189 48/199 230/862 62/251 8/44 7/44 18/65 14/65 56/319	% Weight 9.14 7.83 8.17 25.14 8.15 3.73 3.48 5.21 5.04 8.34
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, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Ribas (2013)	Diarrhea	CR (95% CI)	vents, tervention 264/471 237/380 237/380 237/399 738/1250 99/247 16/42 13/42 25/67 28/71 153/325 201/562	Events, Control 146/474 36/189 48/199 230/862 62/251 8/44 7/44 18/65 56/319 129/561	% Weight 7.83 8.17 25.14 8.15 3.73 3.48 5.21 5.04 8.34 9.18
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) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Ribas (2013) Reck (2016) Govindan (2017)	Diarrhea	CR (95% CI) 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, 3.3)	vents, tervention 264/471 237/380 237/399 738/1250 99/247 16/42 13/42 25/67 28/71 153/325 201/562 182/475	Events, Control 146/474 36/189 48/199 230/862 62/251 8/44 7/44 18/65 56/319 129/561 99/473	% Weight 7.83 8.17 25.14 8.15 3.73 3.48 5.21 5.04 8.34 9.18 8.97
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)           Ribas (2013)           Reck (2016)           Govindan (2017)           subtotal (I-squard =0.0%, P= 0.042)	Diarrhea	CR (95% CI) 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)	vents, tervention 264/471 237/380 237/399 738/1250 99/247 16/42 13/42 25/67 28/71 15/325 201/562 182/475 717/1831	Events, Control 146/474 36/189 48/199 230/862 62/251 8/44 7/44 18/65 56/319 129/561 99/473 393/1822	% Weight 7.83 8.17 25.14 8.15 3.73 3.48 5.21 5.04 8.34 9.18 8.97 2 52.11
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, phased) (2012) Lynch (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	Diarrhea	CR (95% CI) 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)	vents, tervention 264/471 237/380 237/399 738/1250 99/247 16/42 25/67 28/71 153/325 201/562 182/475 717/1831	Events, Control 146/474 38/189 48/199 230/862 82/251 8/44 18/65 56/319 129/661 199/473 393/1822	% Weight 9.14 7.83 8.17 25.14 8.15 3.73 3.48 5.21 5.04 8.34 9.18 8.97 52.11
Study           ID           Placebo           Eggermont (2016)           Maic (2017)           Beer (2017)           subtotal (I-squard =0.0%, P=0.498)           Chemotherapy           Robert (2011)           Reck (ipilimumab, phased) (2012)           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           Known(2014)           subtotal (I-squard =-%, P= .)	Diarrhea	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)	264/471 237/380 237/399 738/1250 99/247 16/42 13/42 25/67 28/71 153/325 201/562 182/475 717/1831 245/393 245/393	Events, Control 146/474 36/189 48/199 230/862 62/251 8/44 7/44 18/65 56/319 129/561 99/473 393/1822 100/396	% Weight 9.14 7.83 8.17 25.14 8.15 3.73 3.48 5.21 5.04 8.34 9.18 8.97 5.2.11 8.83 8.83
Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) Beer (2017) subtotal (I-squard =0.0%, <i>P</i> =0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Lynch (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Reck (2016) Govindan (2017) subtotal (I-squard =0.0%, <i>P</i> = 0.042) Radiotherapy Known(2014) subtotal (I-squard =.%, <i>P</i> = .) gp100	Diarrhea	CR (95% CI) 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)	vents, tervention 264/471 237/380 237/399 738/1250 99/247 16/42 25/67 28/71 153/325 201/562 182/475 717/1831 245/393 245/393	Events, Control 146/474 36/189 48/199 230/862 62/251 8/44 18/65 56/319 129/561 129/561 99/473 393/1822 100/396	% Weight 7.83 8.17 25.14 8.15 3.73 3.48 5.21 5.21 5.21 5.21 5.21 5.21 5.21 8.83 8.83 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)         Lynch (ipilimumab, concurrent) (2012)         Lynch (ipilimumab, concurrent) (2012)         Ribas (2013)         Reck (2016)         Govindan (2017)         subtotal (I-squard =0.0%, P= 0.042)         Radiotherapy         Known(2014)         subtotal (I-squard =.%, P= .)         gp100         Hodi (ipilimumab + gp100) (2010)	Diarrhea	CR (95% CI) 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	vents, tervention 264/471 237/380 237/399 738/1250 99/247 16/42 25/67 28/71 153/325 201/562 182/475 717/1831 245/393 245/393 245/393	Events, Control 146/474 36/189 48/199 230/862 62/251 8/44 18/65 56/319 129/561 99/473 393/1822 100/396 100/396	% Weight 7.83 8.17 25.14 8.15 3.73 3.48 5.21 5.21 5.21 5.21 5.21 5.21 5.21 8.83 8.83 8.83 8.83 7.32
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)         Lynch (ipilimumab, concurrent) (2012)         Lynch (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)         Hodi (ipilimumab alone) (2010)	Diarrhea	CR (95% CI) 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 2.28 (1.31, 3.99) 4	vents, tervention 264/471 237/380 237/399 738/1250 99/247 16/42 25/67 28/71 153/325 201/562 182/475 717/1831 245/393 245/393 245/393	Events, Control 146/474 36/189 48/199 230/862 62/251 8/44 18/65 56/319 129/661 99/473 393/1822 100/396 100/396 100/396	% Weight 7.83 8.17 25.14 8.15 3.73 3.48 5.21 5.21 8.83 8.97 5.2.11 8.83 8.83 8.83 7.32 6.59
Study JD Placebo Eggermont (2016) Maio (2017) Beer (2017) Beer (2017) subtotal (l-squard =0.0%, $P$ =0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Lynch (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Reck (2016) Govindan (2017) subtotal (l-squard =0.0%, $P$ = 0.042) Radiotherapy Known(2014) subtotal (l-squard =.%, $P$ = .) gp100 Hodi (ipilimumab ± gp100) (2010) Hodi (ipilimumab ± gp100) (2010) Hodi (ipilimumab ± gp100) (2010)	Diarrhea	CR (95% CI) 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 2.28 (1.31, 3.99) 4 2.62 (1.83, 3.77) 2	Events, tervention 264/471 237/380 237/399 738/1250 99/247 16/42 25/67 28/71 153/325 201/562 182/475 717/1831 245/393 245/393 58/380 7/131 05/511	Events, Control 146/474 36/189 48/199 230/862 62/251 8/44 18/65 56/319 99/473 393/1822 100/396 100/396 100/396 100/396	% Weight 7.83 8.17 25.14 8.15 5.21 5.21 5.24 8.83 8.83 8.83 7.32 6.59 13.92
Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) Butotal (I-squard =0.0%, $P$ =0.498) Chemotherapy Robert (2011) Reck (ipilimumab, phased) (2012) Lynch (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Lynch (ipilimumab, concurrent) (2012) Reck (2016) Govindan (2017) subtotal (I-squard =0.0%, $P$ = 0.042) Radiotherapy Known(2014) subtotal (I-squard =7, $P$ = .) gp100 Hodi (ipilimumab + gp100) (2010) Hodi (ipilimumab alone) (2010) subtotal (I-squard =77.6%, $P$ =0.520)	Diarrhea	CR (95% CI)         E           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)           2.90 (1.80, 4.67)         1           2.28 (1.31, 3.99)         4           2.62 (1.83, 3.77)         2           2.98 (2.35, 3.78)         7	vents, tervention 264/471 237/380 237/399 738/1250 99/247 16/42 25/67 26/67 26/67 26/67 28/71 153/325 201/562 182/475 717/1831 245/393 245/393 245/393 58/380 7/131 05/511	Events, Control 146/474 36/189 48/199 230/862 62/251 8/44 18/65 56/319 129/561 9393/1822 100/396 100/396 100/396 26/132 26/132 26/132	% Weight 9.14 7.83 8.17 25.14 8.15 3.73 3.48 5.21 5.04 8.37 8.97 5.2.11 8.83 8.83 7.32 6.59 13.92 100.00
Study JD 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) 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) Subtotal (I-squard =77.6%, $P$ =0.520) Overall (I-squard =77.6%, $P$ =0.520) Note: weights are from random effects analysis	Diarrhea	CR (95% CI) 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) 2.90 (1.80, 4.67) 1 2.28 (1.31, 3.99) 4 2.62 (1.83, 3.77) 2 2.98 (2.35, 3.78)	vents, tervention 264/471 237/380 237/399 738/1250 99/247 16/42 25/67 28/71 153/325 201/562 28/71 153/325 201/562 28/71 153/325 201/562 182/475 717/1831 245/393 245/393 58/380 7/131 05/511	Events, Control 146/474 36/189 48/199 230/862 62/251 8/44 18/65 56/319 129/661 99/473 393/1822 100/396 100/396 26/132 26/132 26/132 26/132	% Weight 7.83 8.17 25.14 8.15 3.73 3.48 5.21 5.21 5.21 5.21 5.21 5.21 5.21 5.21

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,<sup>12–14</sup> 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,<sup>13</sup> we found an increased risk of all-grade AST elevation and high-grade hypothyroidism with CTLA-4 inhibitors

#### Adrenal insufficiency

Study	OR (95% CI)	Events,	Events, Control	% Weight
		Intervention	0011101	
Placebo	12 25 (0 74 225 90)		0/474	11 61
Eggermont (2016)	2.50 (0.12, 52,40)	6/4/1 2/380	0/474	10.40
Beer (2017)	6.59 (0.37, 117.59)	6/399	0/199	11.59
Subtotal (I-squared = 0.0%, P=0.737)	6.22 (1.14, 33.77)	14/1250	0/862	33.61
Chemotherapy				
Ribas (2013)	<ul> <li>8.94 (0.48, 166.81)</li> <li>2.00 (0.42, 72.80)</li> </ul>	4/325	0/319	11.24
Reck (2016)	5.00 (0.12, 73.80) 5.00 (0.24, 104.43)	2/475	0/561	9.38
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, concurrent) (2012)	(Excluded)	0/71	0/65	0.00
Subtotal (I-squared = 0.0%, P=0.884)	5.29 (0.91, 30.76)	7/1831	0/1822	31.05
Radiotherapy				
Kwon (2014)	2.02 (0.18, 22.37)	2/393	1/396	16.65
Subtotal (I-squared = .%, P=.)	2.02 (0.18, 22.37)	2/393	1/396	16.65
gp 100			e 115 -	
Hodi (ipilimumab + gp100) (2010)	1.05 (0.04, 25.87)	1/380	0/132	9.36
Subtotal (I-squared = 0.0%, P=0.645)	1.79 (0.18, 17.26)	2/511	0/264	18.70
	,			
Heterogeneity between groups: P=0.765	3.88 (1.46, 10.36)	25/3985	1/3344	100.00
0.0424	236			
Hypophysitis				
Hypophysitis Study	OR (95% CI)	Events, Intervention	Events, Control	% Weight
Hypophysitis Study ID	OR (95% CI)	Events, Intervention	Events, Control	% Weight
Hypophysitis Study ID Placebo	OR (95% CI)	Events, Intervention	Events, Control	% Weight
Hypophysitis Study ID Placebo Eggermont (2016) Main (2017)	OR (95% CI) - 44.49 (14.00, 141.34) 3.51 (0.18, 68.38)	Events, Intervention 104/471 3/380	Events, Control 3/474 0/189	% Weight 19.70 9.18
Hypophysitis Study ID Placebo Eggermont (2016) Maio (2017) Ber (2017)	OR (95% CI) - 44.49 (14.00, 141.34) 3.51 (0.18, 68.38) - 12.87 (0.76, 218.51)	Events, Intervention 104/471 3/380 12/399	Events, Control 3/474 0/189 0/199	% Weight 19.70 9.18 9.73
Hypophysitis Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) Subtotal (I-squared = 28.1%, P=0.249)	OR (95% CI) - 44.49 (14.00, 141.34) 3.51 (0.18, 68.38) - 12.87 (0.76, 218.51) 21.45 (5.15, 89.35)	Events, Intervention 104/471 3/380 12/399 119/1250	Events, Control 3/474 0/189 0/199 3/862	% Weight 19.70 9.18 9.73 38.61
Hypophysitis Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) Subtotal (I-squared = 28.1%, P=0.249) Chemotherapy	OR (95% CI) - 44.49 (14.00, 141.34) 3.51 (0.18, 68.38) - 12.87 (0.76, 218.51) 21.45 (5.15, 89.35)	Events, Intervention 104/471 3/380 12/399 119/1250	Events, Control 3/474 0/189 0/199 3/862	% Weight 19.70 9.18 9.73 38.61
Hypophysitis Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) Subtotal (I-squared = 28.1%, P=0.249) Chemotherapy Lynch (iplimumab, concurrent) (2012)	OR (95% CI) - 44.49 (14.00, 141.34) 3.51 (0.18, 68.38) - 12.87 (0.76, 218.51) 21.45 (5.15, 89.35) 2.79 (0.11, 69.64) 4.04 (9.45, 20.20)	Events, Intervention 104/471 3/380 12/399 119/1250	Events, Control 3/474 0/189 0/199 3/862 0/65	% Weight 9.18 9.73 38.61 8.26
Hypophysitis Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) Subtotal (I-squared = 28.1%, P=0.249) Chemotherapy Lynch (iplimumab, concurrent) (2012) Reck (2016) Govindra (2017)	OR (95% CI) - 44.49 (14.00, 141.34) 3.51 (0.18, 68.38) - 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)	Events, Intervention 104/471 3/380 12/399 119/1250 1/71 4/562 2/475	Events, Control 3/474 0/189 0/199 3/862 0/65 1/561 0/473	% Weight 19.70 9.18 9.73 38.61 8.26 12.84 8.91
Hypophysitis Study ID Placebo Eggermont (2016) Maio (2017) Beer (2017) Subtotal (I-squared = 28.1%, P=0.249) Chemotherapy Lynch (ipilinumab, concurrent) (2012) Reck (2016) Govindan (2017) Robert (2011)	OR (95% CI) - 44.49 (14.00, 141.34) 3.51 (0.18, 68.38) - 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)	Events, Intervention 104/471 3/380 12/399 119/1250 1/71 4/562 2/475 0//247	Events, Control 3/474 0/189 0/199 3/862 0/65 1/561 0/473 0/251	% Weight 19.70 9.18 9.73 38.61 8.26 12.84 8.91 0.00
Hypophysitis Study JD Placebo Eggermont (2016) Maio (2017) Beer (2017) Subtotal (I-squared = 28.1%, P=0.249) Chemotherapy Lynch (ipilinumab, concurrent) (2012) Reck (2016) Govindan (2017) Robert (2011) Reck (ipilinumab, phased) (2012)	OR (95% CI) - 44.49 (14.00, 141.34) 3.51 (0.18, 68.38) - 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)	Events, Intervention 104/471 3/380 12/399 119/1250 1/71 4/562 2/475 0/247 0/247	Events, Control 3/474 0/189 0/199 3/862 0/65 1/561 0/473 0/251 0/44	% Weight 19.70 9.18 9.73 38.61 8.26 12.84 8.91 0.00 0.00
Hypophysitis Study JD Placebo Eggermont (2016) Maio (2017) Beer (2017) Subtotal (I-squared = 28.1%, P=0.249) Chemotherapy Lynch (iplimumab, concurrent) (2012) Reck (2016) Govindan (2017) Robert (2011) Reck (iplimumab, concurrent) (2012) Reck (iplimumab, concurrent) (2012)	OR (95% CI) - 44.49 (14.00, 141.34) 3.51 (0.18, 68.38) - 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)	Events, Intervention 104/471 3/380 12/399 119/1250 1/71 4/562 2/475 0/247 0/247 0/247	Events, Control 3/474 0/189 0/199 3/862 0/65 1/561 0/473 0/251 0/44 0/44	% Weight 19.70 9.18 9.73 38.61 8.26 12.84 8.91 0.00 0.00 0.00
Hypophysitis Study JD Placebo Eggermont (2016) Maio (2017) Beer (2017) Subtotal (I-squared = 28.1%, P=0.249) Chemotherapy Lynch (ipilinumab, concurrent) (2012) Reck (2016) Govindan (2017) Robert (2011) Reck (ipilinumab, phased) (2012) Reck (ipilinumab, phased) (20	OR (95% CI) - 44.49 (14.00, 141.34) 3.51 (0.18, 68.38) - 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)	Events, Intervention 104/471 3/380 12/399 119/1250 1/71 4/562 2/475 0/247 0/247 0/247 0/27 0/42 0/67	Events, Control 3/474 0/189 0/199 3/862 0/65 1/561 0/473 0/251 0/44 0/44 0/44 0/319	% Weight 19.70 9.18 9.73 38.61 8.26 12.84 8.91 0.00 0.00 0.00 0.00 0.00
Hypophysitis           Study ID           Placebo           Eggermont (2016)           Maia (2017)           Beer (2017)           Subtotal (I–squared = 28.1%, P=0.249)           Chemotherapy           Lynch (ipilimumab, concurrent) (2012)           Reck (2016)           Govindan (2017)           Robert (2011)           Reck (ipilimumab, phased) (2012)           Lynch (ipilimumab, concurrent) (2012)           Lynch (ipilimumab, phased) (2012)           Ribas (2013)           Subtotal (I–squared = 0.0%, P=0.966)	OR (95% CI) - 44.49 (14.00, 141.34) 3.51 (0.18, 68.38) - 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) 3.90 (0.82, 18.53)	Events, Intervention 104/471 3/380 12/399 119/1250 1/71 4/562 2/475 0/247 0/42 0/42 0/42 0/67 0/325 7/1831	Events, Control 3/474 0/189 0/199 3/862 0/65 1/561 0/473 0/251 0/44 0/44 0/45 0/319 1/1822	% Weight 19.70 9.18 9.73 38.61 8.26 12.84 8.91 0.00 0.00 0.00 0.00 0.00 0.00 30.01
Hypophysitis Study JD Placebo Eggermont (2016) Maio (2017) Beer (2017) Subtotal (I-squared = 28.1%, P=0.249) Chemotherapy Lynch (ipilimumab, concurrent) (2012) Reak (2016) Govindan (2017) Robert (2011) Reak (ipilimumab, phased) (2012) Reak (ipilimumab, concurrent) (2012) Lynch (ipilimumab, phased) (2012) Reak (ipilimumab, phased	OR (95% CI) - 44.49 (14.00, 141.34) 3.51 (0.18, 68.38) - 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)	Events, Intervention 104/471 3/380 12/399 119/1250 1/71 4/562 2/475 0/247 0/42 0/42 0/42 0/42 0/42 0/325 7/1831	Events, Control 0/199 3/862 0/65 1/561 0/473 0/251 0/44 0/44 0/65 0/319 1/1822	% Weight 9.70 9.18 9.73 38.61 2.84 8.91 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0
Hypophysitis Study JD Placebo Eggermont (2016) Maio (2017) Beer (2017) Subtotal (I-squared = 28.1%, P=0.249) Chemotherapy Lynch (ipilimumab, concurrent) (2012) Reck (2016) Govindan (2017) Robert (2011) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, phased) (20	OR (95% CI) 44.49 (14.00, 141.34) 3.51 (0.18, 68.38) 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) 3.90 (0.82, 18.53) 1.01 (0.14, 7.19)	Events, Intervention 104/471 3/380 12/399 119/1250 1/71 4/562 2/475 0/247 0/42 0/42 0/42 0/42 0/42 0/42 0/325 7/1831	Events, Control 0/199 3/862 0/65 1/561 0/473 0/251 0/44 0/65 0/319 1/1822 2/396	% Weight 19.70 9.18 9.73 38.61 12.84 8.91 0.00 0.00 0.00 0.00 0.00 0.00 30.01 14.20
Hypophysitis Study JD Placebo Eggermont (2016) Maio (2017) Beer (2017) Subtotal (I–squared = 28.1%, P=0.249) Chemotherapy Lynch (ipilimumab, concurrent) (2012) Reck (2016) Govindan (2017) Robert (2011) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, phased) (2012) Ribas (2013) Subtotal (I–squared = 0.0%, P=0.966) Radiotherapy Kwon (2014) Subtotal (I–squared = .%, P=.)	OR (95% CI) - 44.49 (14.00, 141.34) 3.51 (0.18, 68.38) - 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) 1.01 (0.14, 7.19) 1.01 (0.14, 7.19)	Events, Intervention 104/471 3/380 12/399 119/1250 1/71 4/562 2/475 0/247 0/247 0/247 0/247 0/247 0/25 7/1831 2/393 2/393	Events, Control 0/199 3/862 0/65 1/561 0/473 0/251 0/44 0/44 0/44 0/251 0/319 1/1822 2/396	% Weight 19.70 9.18 9.73 38.61 2.84 8.91 0.00 0.00 0.00 0.00 0.00 30.01 14.20
Hypophysitis	OR (95% CI) 44.49 (14.00, 141.34) 3.51 (0.18, 68.38) 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) 3.90 (0.82, 18.53) 1.01 (0.14, 7.19) 1.01 (0.14, 7.19)	Events, Intervention 104/471 3/380 12/399 119/1250 1/71 4/562 2/475 0/247 0/42 0/42 0/42 0/42 0/67 0/325 7/1831 2/393 2/393	Events, Control 0/199 0/199 3/862 0/65 0/473 0/251 0/44 0/44 0/44 0/44 0/45 0/319 1/1822 2/396	% Weight 9.73 38.61 2.84 8.91 0.00 0.00 0.00 30.01 14.20
Hypophysitis Study JD Placebo Eggermont (2016) Maio (2017) Beer (2017) Subtotal (I–squared = 28.1%, P=0.249) Chemotherapy Lynch (ipilimumab, concurrent) (2012) Reck (2016) Govindan (2017) Robert (2011) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, phased) (2012) Readiotherapy Kwon (2014) Subtotal (I–squared = .%, P=.) gp 100 Hodi (ipilimumab + gp100) (2010)	OR (95% CI) 44.49 (14.00, 141.34) 3.51 (0.18, 68.38) 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) 3.90 (0.82, 18.53) 1.01 (0.14, 7.19) 1.05 (0.04, 25.87) 5.12 (0.24, 107, CD)	Events, Intervention 104/471 3/380 12/399 119/1250 1/71 4/562 2/475 0/247 0/42 0/42 0/67 0/325 7/1831 2/393 2/393	Events, Control 0/199 3/862 0/65 0/473 0/251 0/44 0/44 0/65 0/319 1/1822 2/396 0/132 0/132	% Weight 19.70 9.18 9.73 38.61 12.84 8.26 12.84 8.91 0.00 0.00 0.00 0.00 0.00 30.01 14.20 8.88
Hypophysitis Study JD Placebo Eggermont (2016) Maio (2017) Beer (2017) Subtotal (I–squared = 28.1%, P=0.249) Chemotherapy Lynch (ipilimumab, concurrent) (2012) Reck (2016) Govindan (2017) Robert (2011) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, phased) (2012) Reck (ipilimumab, phased) (2012) Readiate (I-squared = 0.0%, P=0.966) Radiotherapy Kwon (2014) Subtotal (I–squared = .%, P=.) gp 100 Hodi (ipilimumab alone) (2010) Subtotal (I–squared = .0%, P=0.482)	OR (95% Cl) 44.49 (14.00, 141.34) 3.51 (0.18, 68.38) 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) 3.90 (0.82, 18.53) 1.01 (0.14, 7.19) 1.05 (0.04, 25.87) 5.12 (0.24, 107.59) 2.41 (0.26, 21.95)	Events, Intervention 104/471 3/380 12/399 119/1250 1/71 4/562 2/475 0/247 0/42 0/42 0/42 0/67 0/325 7/1831 2/393 2/393 1/380 2/131 3/511	Events, Control 0/199 3/862 0/65 0/473 0/251 0/44 0/44 0/44 0/44 0/45 0/319 1/1822 2/396 2/396 0/132 0/132 0/132	% Weight 19.70 9.18 9.73 38.61 12.84 8.26 12.84 8.91 0.00 0.00 0.00 0.00 0.00 30.01 14.20 14.20 8.88 17.18
Hypophysitis         Study ID         Placebo         Eggermont (2016)         Maia (2017)         Beer (2017)         Subtotal (I-squared = 28.1%, P=0.249)         Chemotherapy         Lynch (ipilimumab, concurrent) (2012)         Reck (2016)         Govindan (2017)         Robert (2011)         Reck (ipilimumab, concurrent) (2012)         Lynch (ipilimumab, concurrent) (2012)         Lynch (ipilimumab, phased) (2012)         Ribas (2013)         Subtotal (I-squared = 0.0%, P=0.966)         Radiotherapy         Kwon (2014)         Subtotal (I-squared = .%, P=.)         gp 100         Hodi (ipilimumab + gp100) (2010)         Hodi (pilimumab alone) (2010)         Subtotal (I-squared = 0.0%, P=0.482)         Output (I - squared = 5.1%, P=0.492)	OR (95% CI) 44.49 (14.00, 141.34) 3.51 (0.18, 68.38) 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) 3.90 (0.82, 18.53) 1.01 (0.14, 7.19) 1.05 (0.04, 25.87) 5.12 (0.24, 107.59) 2.41 (0.26, 21.95) 5.90 (4.74, 10.40)	Events, Intervention 104/471 3/380 12/399 119/1250 1/71 4/562 2/475 0/247 0/42 0/42 0/42 0/42 0/42 0/67 0/325 7/1831 2/393 2/393 2/393 1/380 2/131 3/511	Events, Control 3/474 0/189 0/199 3/862 0/65 1/561 0/473 0/251 0/44 0/473 0/251 0/44 0/42 0/65 0/319 1/1822 2/396 2/396 0/132 0/132 0/132	% Weight 19.70 9.18 9.73 38.61 12.84 8.26 12.84 8.91 0.00 0.00 0.00 0.00 0.00 0.00 0.00 14.20 14.20 8.30 8.88 17.18
Hypophysitis         Study ID         Placebo         Eggermont (2016)         Maia (2017)         Beer (2017)         Subtotal (I–squared = 28.1%, P=0.249)         Chemotherapy         Lynch (pilimumab, concurrent) (2012)         Reck (2016)         Govindan (2017)         Robert (2011)         Reck (2016)         Govindan (2017)         Robert (2011)         Reck (pilimumab, concurrent) (2012)         Lynch (pilimumab, phased) (2012)         Lynch (pilimumab, Pased) (2012)         Ribas (2013)         Subtotal (I–squared = 0.0%, P=0.966)         Radiotherapy         Kwon (2014)         Subtotal (I–squared = .%, P=.)         gp 100         Hodi (pilimumab alone) (2010)         Hodi (pilimumab alone) (2010)         Hodi (I-squared = 0.0%, P=0.482)         Overall (I–squared = 50.1%, P=0.049)	OR (95% Cl) 44.49 (14.00, 141.34) 3.51 (0.18, 68.38) 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) 3.90 (0.82, 18.53) 1.01 (0.14, 7.19) 1.05 (0.04, 25.87) 5.12 (0.24, 107.59) 2.41 (0.26, 21.95) 5.30 (1.71, 16.46)	Events, Intervention 104/471 3/380 12/399 119/1250 1/71 4/562 2/475 0/247 0/42 0/42 0/42 0/67 0/325 7/1831 2/393 2/393 1/380 2/131 3/511 131/3985	Events, Control 0/199 3/862 0/65 1/561 0/473 0/251 0/44 0/44 0/65 0/319 1/1822 2/396 2/396 0/132 0/132 0/132 0/132 0/264 6/3344	% Weight 19.70 9.18 9.73 38.61 8.26 12.84 8.91 0.00 0.00 0.00 0.00 0.00 0.00 0.00 14.20 14.20 8.80 8.88 17.18 100.00
Study ID         Placebo         Eggermont (2016)         Maio (2017)         Beer (2017)         Subtotal (I-squared = 28.1%, P=0.249)         Chemotherapy         Lynch (pilimumab, concurrent) (2012)         Reck (2016)         Govindan (2017)         Robert (2011)         Reck (2016)         Govindan (2017)         Robert (2011)         Reck (2016)         Govindan (2017)         Robert (2011)         Reck (2018)         Subtotal (I-squared = 0.0%, P=0.966)         Radiotherapy         Kwon (2014)         Subtotal (I-squared = 0.0%, P=0.966)         Radiotherapy         Kwon (2014)         Subtotal (I-squared = 0.0%, P=0.482)         Overall (I-squared = 50.1%, P=0.049)         NOTE: weights are from random effects analysis	OR (95% CI) - 44.49 (14.00, 141.34) 3.51 (0.18, 68.38) - 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) (Excluded) 1.01 (0.14, 7.19) 1.05 (0.04, 25.87) 5.12 (0.24, 107.59) 2.41 (0.26, 21.95) 5.30 (1.71, 16.46)	Events, Intervention 104/471 3/380 12/399 119/1250 1/71 4/562 2/475 0/247 0/250 1/1831 1/380 1/380 1/380 1/380 1/399 1/370 1/320 1/27 0/247 0/225 1/399 1/320 1/27 0/247 0/247 0/255 1/399 1/320 1/325 1/380 1/380 1/380 1/380 1/380 1/380 1/380 1/380 1/380 1/370 1/380 1/325 1/31 1/380 1/370 1/380 1/375 1/380 1/375 1/380 1/375 1/380 1/375 1/311 1/380 1/375 1/311 1/380 1/375 1/311 1/380 1/375 1/311 1/310 1/375 1/311 1/380	Events, Control 0/199 3/862 0/65 1/561 0/473 0/251 0/44 0/44 0/44 0/251 0/44 2/396 2/396 2/396 0/132 0/132 0/132 0/132 0/132 0/264 6/3344	% Weight 19.70 9.18 9.73 38.61 12.84 8.91 0.00 0.00 0.00 0.00 0.00 0.00 0.00 14.20 14.20 8.80 8.88 8.71 17.18 100.00

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

Study         Events.         Events.         Events.         %           ID         OR (95%,C)         Intervention         Control         Weight           Eggermont (2016)         3.03 (0.012, 74.46)         1471         0.474         18.84           Beer (2017)         15.90 (0.06, 37.03)         15.99         0.989         0.189         0.038           Studbut (I-squard =0.0%, P=0.762)         21.90 (0.22, 20.59)         21.260         0.661         20.93           Chemotherapy         Reak (2016)         0.047, 10.225         0.0561         20.93           Reak (2017)         2.99 (0.12, 73.67)         14.75         0.473         18.84           Reak (2016)         0.24, 104.57)         2.562         0.561         20.93           Covindin (2017)         2.99 (0.12, 73.67)         14.75         0.473         18.84           Reak (pilimumab, concurrent) (2012)         (Excluded)         0.42         0.44         0.00           Lynch (pilimumab, concurrent) (2012)         (Excluded)         0.42         0.44         0.00           Lynch (pilimumab, concurrent) (2012)         (Excluded)         0.42         0.44         0.00           Lynch (pilimumab, concurrent) (2012)         (Excluded)         0.433         0.398	Hypert	iyroidism				
ID     OR (65%, C)     Intervention     Control     Weight       Placebo     Eggermont (2016)     3.03 (0.012, 74.46)     1471     0474     18.84       Beer (2017)     Esckuled)     0.0380     0189     0.008     0789     0.008       Subbtal (Fsquare1=0.0%, P=0.762)     0.041, 104.77     2562     0561     2.033     2.031     0.213 (0.22, 20.59)     27250     0862     37.65       Chemotherapy     Esckuled-ii     0.024, 104.77)     2562     0561     2.033     2.031     2.044     0.00       Covindan (2017)     Esckuled-ii     0.024, 104.77)     2562     0561     2.033       Covindan (2017)     Esckuled-ii     0.024, 104.77)     2562     0561     2.033       Covindan (2017)     Esckuled-ii     0.047     0.041     0.00       Reck (pilimumab, phased) (2012)     Esckuled-ii     0.047     0.044     0.00       Lynch (pilimumab, concurrent) (2012)     Esckuled-ii     0.025     0.039     0.039     0.039     0.039     0.039     0.039     0.039     0.039     0.039     0.039     0.00     102.2     0.00       Radiotariar = 0.0%, P=0.819     3.33 (0.43, 35.58)     3.118.11     0.022     25.9     9.16 (0.49, 170.74)     4.033     0.036     22.59	Study			Events,	Events	%
Placebo Eggermont (2016) Beer (2017) Maio (2017) Subbtal (I-squard =0.0%, P=0.762) Chemotherapy Reck (2016) Govindan (2017) Reck (2017) Rec	ID		OR (95% CI)	Intervention	Control	Weight
Placebo Eggermont (2016) Ber (2017) Maio (2017) Subbial (Lisquard = 0.0%, P=0.762) Chemoherapy Reck (2016) Chemoherapy Reck (2016) Control (2017) Reck (2016) Control (2017) Reck (2017) Reck (2016) Control (2017) Reck (2017)		· ·				
Eggemont (2016) Beer (2017) Subtal (L-squard = 0.0%, P=0.762) Chemotherapy Reak (2016) Chemotherapy Reak (2016) Covindian (2017) Equation (2017) Covindian (2017) Equation (2017) Chemotherapy Reak (2016) Chemotherapy Reak (2016) Chemotherapy Reak (2017) Equation (2017) Covindian (2017) Covindian (2017) Chemotherapy Reak (2018) Covindian (2017) Covindian (2016) Covindian (2017) Covindian (2016) Covindian (2017) Covindian (1-squard = 0.0%, P=0.847) Covindian (1-squard = 0.0%, P=0.847 Covindian (1-squard = 0.0%, P=0.847 Covindian (1-squard = 0.0%, P=0.9487 Covindian (1-squard = 0.0%, P=0	Placebo					
Ber (2017) Maio (2017) Subbal (4-squard -0.0%, P=0.762) Chemotherapy Rack (2016) Govindan (2017) Rack (2016) Rack (2017) Rack (2016) Rack (2017) Rack (2017) Rack (2016) Rack (2017) Rack (2016) Rack (2017) Rack (	Eggermont (2016)	*	3.03 (0.012, 74.46)	1/471	0/474	18.84
Maic (2017)       (Excluded)       0/380       0/189       0.00         Subball (I-squard =0.0%, P=0.762)       21/250       0/862       37.65         Chemotherapy Reck (2016)       7.13 (0.22, 20, 55)       21/250       0/862       37.65         Gouindan (2017)       2.99 (0.12, 73.67)       1/475       0.473       18.84         Reck (2016)       (Excluded)       0/247       0/251       0.00         Reck (10)Imumab, oncourrent) (2012)       (Excluded)       0/42       0/44       0.00         Lynch (10)Imumab, concurrent) (2012)       (Excluded)       0/71       0/65       0.00         Subtotal (L-squard = 0.0%, P=0.819)       3.93 (0.43, 3.568)       3/18.10       0/18.22       2.59         gp100       (Excluded)       0/131       0/132       0/00       0/131       0/132       0/00         Subtotal (L-squard = 0.0%, P=0.346)       1       1/1       1/1       0.00       0/131       0/132 <t< td=""><td>Beer (2017)</td><td>+ + +</td><td>1.50 (0.06, 37.03)</td><td>1/399</td><td>0/199</td><td>18.81</td></t<>	Beer (2017)	+ + +	1.50 (0.06, 37.03)	1/399	0/199	18.81
Subtotal (I-squard =0.0%, P=0.762) 2.13 (0.22, 20.55) 2/1250 0/862 37.65 Chemotherapy Reck (2016) Govindan (2017) Reck (plinimumab, phased) (2012) Reck (plinimumab, concurrent) (2012) Lynch (plinimumab, concurrent) (2012) Lynch (plinimumab, concurrent) (2012) Lynch (plinimumab, concurrent) (2012) Reck (plinimumab, concurrent) (2012) Lynch (plinimumab, concurrent) (2012) Reck (plinimumab alone) (2010) Hodi (plinimumab alone) (2010) Heterogeneity between groups: P=0.897 Overall (L-squard =0.0%, P=). Hypothyroidism Study ID Placebo Eggemont (2016) Linitervention Placebo Eggemont (2016) Linitervention Reck (Plinimumab alone) (2016) Linitervention Reck (Plinimumab alone) (2016) Linitervention Reck (Plinimumab alone) (2010) Heterogeneity between groups: P=0.897 Oregoting (Placebo Eggemont (2016) Reck (Placebo Eggemont (2016) Linitervention Reck (Placebo Linitervention Reck (Placebo Linitervention Reck (Placebo Linitervention Reck (Placebo Linitervention Reck (Pl	Maio (2017)		(Excluded)	0/380	0/189	0.00
Chemotherapy Reak (2016) Govindar (2017) Robert (2011) Reak (pilinumab, phased) (2012) Reak (pilinumab, phased) (2012) Lynch (pilinumab, phased) (2010) Hodi (pilinumab + gp100) (2010) Hodi (pilinumab + gp1	Subtotal (I-squard =0.0%, P=0.762)		2.13 (0.22, 20.55)	2/1250	0/862	37.65
Chemotherapy Reek (2016)       5.01 (0.24, 104.57)       2562       0/561       20.93         Covindan (2017)       2.99 (0.12, 73.67)       1/475       18.84         Robert (2011)       (Excluded)       0/247       0/251       0.00         Reck (plinnumab, phased) (2012)       (Excluded)       0/42       0/44       0.00         Lynch (plinnumb, phased) (2012)       (Excluded)       0/67       0/65       0.00         Lynch (plinnumb, concurrent) (2012)       (Excluded)       0/67       0/65       0.00         Lynch (plinnumb, concurrent) (2012)       (Excluded)       0/67       0/65       0.00         Subtotal (I-squard =0.0%, P=0.819)       3.93 (0.43, 35.58)       3/1831       0/1822       39.77         Radiotherapy       Stotal (I-squard =0.0%, P=.)       9.16 (0.49, 170.74)       4/393       0/396       22.59         gp100       (Excluded)       0/131       0/132       0.00         Hodi (plinnumab atone) (2010)       (Excluded)       0/131       0/132       0.00         Hodi (plinnumab atone) (2010)       (Excluded)       0/131       0/132       0.00         Hodi (plinnumab atone) (2010)       (Excluded)       0/131       0/132       0.00         Lotal (I-squard =0.0%, P=0.987						
Solutionality       5.01 (0.24, 104.57)       2562       0.0561       20.93         Gevindan (2017)       2.99 (0.12, 73.67)       1/475       0/473       16,84         Redk (2011)       (Excluded)       0/247       0/251       0.00         Redk (pliniumab, phased) (2012)       (Excluded)       0/42       0/44       0.00         Lynch (pliniumab, concurrent) (2012)       (Excluded)       0/42       0/44       0.00         Redk (2013)       (Excluded)       0/71       0/65       0.00         Subtal (I-squard =0.0%, P=0.819)       3.93 (0.43, 35.58)       3/1831       0/1822       2.59         gp100       (Excluded)       0/131       0/132       0.00         Hodi (iplinumab + gp100) (2010)       (Excluded)       0/131       0/132       0.00         Heterogeneity between groups: P=0.897       0.00586       1       171       0.00         Up       0.00586       1       171       0/3344       100.00         Ibace 02(16)       0.00       0.0344       100.00       0.0344       100.00         Leadod       0.00586       1       171       0.00       111       0.00         Leadod       0.00586       1       171       0.00	Chemotherany					
Govindan (2017)       2.99 (0.12, 73.67)       1/475       0.0473       18.84         Robert (2011)       (Excluded)       0/42       0/44       0.00         Reck (ipilinumab, phased) (2012)       (Excluded)       0/42       0/44       0.00         Lynch (ipilinumab, concurrent) (2012)       (Excluded)       0/42       0/44       0.00         Lynch (ipilinumab, concurrent) (2012)       (Excluded)       0/42       0/44       0.00         Lynch (ipilinumab, concurrent) (2012)       (Excluded)       0/42       0/44       0.00         Radiotherapy       (Scluded)       0/42       0/44       0.00         Subtotal (I-squard =0.0%, P=0.819)       3.93 (0.43, 35.58)       3/18.31       0/1822       9.77         Radiotherapy       Subtotal (I-squard =0.0%, P=0.319)       9.16 (0.49, 170.74)       4/393       0/396       22.59         gp100       Hodi (ipilinumab store) (2010)       (Excluded)       0/131       0/132       0.00         Subtotal (I-squard =0.0%, P=.)       9.16 (0.49, 170.74)       4/393       0/396       22.59         gp100       (Excluded)       0/131       0/132       0.00         Notoral (I-squard =0.0%, P=.)       1       1       0/132       0.00         Study </td <td>Reck (2016)</td> <td>•</td> <td>5.01 (0.24, 104.57)</td> <td>2/562</td> <td>0/561</td> <td>20.93</td>	Reck (2016)	•	5.01 (0.24, 104.57)	2/562	0/561	20.93
Constructory       1473       0.4473       0.044       0.00       (Excluded)       0.0423       0.044       0.00       (Excluded)       0.0423       0.044       0.00       (Excluded)       0.0423       0.044       0.00       (Excluded)       0.0423       0.044       0.00       (Excluded)       0.033       0.331       0.1822       977         Radioherapy       Known(2014)       Subtolal (I-squard = 0.0%, P=0.397       9.16 (0.49, 170.74)       4/393       0.396       2.2.59<	Govindan (2017)	•	2.99 (0.12, 73.67)	1/475	0/473	18.84
Roder (pillinumab, phased) (2012)       (Excluded)       0.42       0.44       0.00         Reck (pillinumab, concurrent) (2012)       (Excluded)       0.42       0.44       0.00         Lynch (pillinumab, concurrent) (2012)       (Excluded)       0.42       0.44       0.00         Reck (pillinumab, concurrent) (2012)       (Excluded)       0.67       0.65       0.00         Lynch (pillinumab, concurrent) (2012)       (Excluded)       0.71       0.65       0.00         Reds (pillinumab, concurrent) (2012)       (Excluded)       0.71       0.65       0.00         Ribbas (2013)       3.93 (0.43, 35.58)       3/181       0.1822       9.77         Radiotherapy       (Fisculated)       0.71       4/393       0.736       22.59         gp100       (Excluded)       0.1731       0.7396       22.59         gp100       (Excluded)       0.131       0.02       0.00         Subtotal (I-squard =0.0%, P=.)       .(.,.)       0.511       0.00         Hodi (pillinumab alone) (2010)       (Excluded)       0.131       0.132       0.00         Veral (I-squard =0.0%, P=.)       .(.,.)       0.511       0.00       0.00         Lodo (pilloginamb alone) (2010)       .(.,.)       0.731       <	D-b		(Evoluded)	0/247	0/251	0.00
Netw. (pilimunata), priase() (2012)       (Excluded)       0.42       0.44       0.00         Lynch (pilimunab, concurrent) (2012)       (Excluded)       0.67       0.65       0.00         Lynch (pilimunab, concurrent) (2012)       (Excluded)       0.71       0.65       0.00         Subtotal (I-squard =0.0%, P=0.819)       3.93 (0.43, 35.58)       3/1831       0.1822       39.77         Radiotherapy       Subtotal (I-squard =-%, P=.)       9.16 (0.49, 170.74)       4/393       0/396       22.59         gp100       (Excluded)       0/131       0/132       0.00         Hodi (ipilimumab alone) (2010)       (Excluded)       0/131       0/132       0.00         Verall (I-squard =0.0%, P=.)       9.16 (0.49, 170.74)       4/393       0/396       22.59         gp100       (Excluded)       0/131       0/132       0.00         Hodi (ipilimumab alone) (2010)       (Excluded)       0/131       0/132       0.00         Verall (I-squard =0.0%, P=.)       3.78 (0.94, 15.17)       9/3985       0/344       100.00         Heterogeneity between groups: P=0.897       0.00586       1       171       1       1         0.00586       1       0.0       1       0.0       1       1       1	Robert (2011) Beek (initimumeh, phened) (2012)		(Excluded)	0/42	0/231	0.00
Heek (plimiumab, concurrent) (2012)       (Excluded)       0/42       0/44       0/06         Lynch (plimiumab, phased) (2012)       (Excluded)       0/71       0/65       0.00         Lynch (plimiumab, concurrent) (2012)       (Excluded)       0/71       0/65       0.00         Ribs (2013)       3.93 (0.43, 35.58)       3/1831       0/1822       39.7         Radiotherapy       9.16 (0.49, 170.74)       4/393       0/396       22.59         gp100       (Excluded)       0/131       0/132       0.00         Hodi (plimumab adone) (2010)       (Excluded)       0/131       0/132       0.00         Subtotal (I-squard =0.0%, P=.)	Reck (ipilinumab, phased) (2012)		(Excluded)	0/42	0/44	0.00
Lynch (pilimumab, pansed) (2012) Lynch (pilimumab, concurrent) (2012) Radiotherapy Known(2014) subtotal (I-squard =.%, P=.) gp100 Hodi (pilimumab 4 gp100) (2010) Hodi (pilimumab 4 gp100) (2010) (Excluded) 0.00586 1 171 Hypothyroidism Study ID OR (95% CI) Events, Events % Hypothyroidism Study ID Placebo Eggermont (2016) Hodi (2016	Reck (ipilimumab, concurrent) (2012)		(Excluded)	0/42	0/44	0.00
Lynch (pilimumab, concurrent) (2012) Ribas (2013) Subtotal (I-squard =0.0%, P=0.819) Radiotherapy Known(2014) subtotal (I-squard =.%, P=.) gp100 Hodi (ipilimumab agne) (2010) Hodi (ipilimumab agne) (2010) Hodi (ipilimumab agne) (2010) Heterogeneity between groups: P=0.897 Overall (I-squard =0.0%, P=.). Hypothyroidism Study ID Placebo Eggermont (2016) Har (2016) Subtotal (1-squard =0.0%, P=0.946) Study ID Placebo Eggermont (2016) Hodi (2016) Heterogeneity between groups: P=0.897 Overall (I-squard =0.0%, P=0.946) Hypothyroidism Study ID Placebo Eggermont (2016) Hodi (2016) Hum (2016) Hodi (2016) Hodi (2016) Hodi (2016) Hodi (2017) Heterogeneity between groups: P=0.897 Overall (I-squard =0.0%, P=0.946) Hypothyroidism Study ID Placebo Eggermont (2016) Hodi (2017 Hodi (2017) Hodi (2017)	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=0.819)       3.93 (0.43, 35.58)       3/1831       0/1822       39.77         Radiotherapy       9.16 (0.49, 170.74)       4/393       0/396       22.59         gp100       9.16 (0.49, 170.74)       4/393       0/396       22.59         gp100       (Excluded)       0/131       0/132       0.00         Hodi (ipilimumab + gp100) (2010)       (Excluded)       0/131       0/132       0.00         Subtotal (I-squard =0.0%, P=.)       .()       0/511       0.00         Heterogeneity between groups: P=0.897       .()       0/511       0.00         Oursald (I-squard =0.0%, P=.)       1       171       1          Huppothyroidism       3.78 (0.94, 15.17)       9/3985       0/3344       100.00         Grade       1       171            Backs (3.75, 20.89)              Study               Backs               Leade </td <td>Lynch (Ipilimumab, concurrent) (2012)</td> <td></td> <td>(Excluded)</td> <td>0/71</td> <td>0/65</td> <td>0.00</td>	Lynch (Ipilimumab, concurrent) (2012)		(Excluded)	0/71	0/65	0.00
Subtotal (I-squard =0.0%, P=0.819) Radiotherapy Known(2014) subtotal (I-squard =.%, P= .) gp100 Hodi (iplimumab + gp100) (2010) Hodi (iplimumab + gp100) (2010) Hodi (iplimumab alone) (2010) Subtotal (I-squard =0.0%, P=.) Heterogeneity between groups: P=0.897 Overall (I-squard =0.0%, P=0.946)	Ribas (2013)	1	(Excluded)	0/325	0/319	0.00
Radiotherapy Known(2014) subtotal (I-squard =.%, P=.)       9.16 (0.49, 170.74)       4/393       0/396       22.59         gp100       9.16 (0.49, 170.74)       4/393       0/396       22.59         Hodi (ipilimumab + gp100) (2010)       (Excluded)       0.00       0.00         I-doi (ipilimumab alone) (2010)       0.0131       0/132       0.00         Subtotal (I-squard =0.0%, P=.)       0.05586       0.3344       100.00         I-doi (ipilimumab alone) (2010)       1       171       Verall (I-squard =0.0%, P=.946)       0.378 (0.94, 15.17)       9/3985       0/3344       100.00         I-doi (ipilimumab - gp.0%, P=.946)       <	Subtotal (I-squard =0.0%, P=0.819)		3.93 (0.43, 35.58)	3/1831	0/1822	39.77
Radiotherapy       9.16 (0.49, 170.74)       4/393       0/396       22.59         gp100       9.16 (0.49, 170.74)       4/393       0/396       22.59         gp100       (Excluded)       0.00       0.00         Hodi (ipilimumab + gp100) (2010)       (Excluded)       0/131       0/132       0.00         Hodi (ipilimumab alone) (2010)       (Excluded)       0/131       0/132       0.00         Heterogeneity between groups: P=0.897       0.0586       1       171       0.00         0.00586       1       171       Verity       Verity <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>						
Known(2014)       9.16 (0.49, 170.74)       4/393       0/396       22.59         gp100       9.16 (0.49, 170.74)       4/393       0/396       22.59         gp100       (jeilimumab + gp100) (2010)       0.00       0.00       0.00         Hodi (ipilimumab alone) (2010)       (Excluded)       0/131       0/132       0.00         Subtotal (I-squard =0.0%, P=.)       .()       0/511       0.00         Heterogeneity between groups: P=0.897       .()       0/511       0.00         Overall (I-squard =0.0%, P=.).       171       .()       0/344       100.00         Hypothyroidism       171       Versts, Events %       Kents, Events %       Kents, Events %         ID       OR (95% Cl)       Events, Events %       Neight       Neight         Placebo       8.85 (3.75, 20.89)       48/471       6/474       57.18         Eggermont (2016)              Muis (0012)	Radiotherapy					
subtotal (I-squard =.%, P=.) 9.16 (0.49, 170.74) 4/393 0/396 22.59 9100 Hodi (ipilimumab + gp100) (2010) Hodi (ipilimumab alone) (2010) Subtotal (I-squard =0.0%, P=.) Heterogeneity between groups: P=0.897 Overall (I-squard =0.0%, P=.946) 1 171 U U U U U U U U U U U U U	Known(2014)	*	9.16 (0.49, 170.74)	4/393	0/396	22.59
gp100 Hodi (ipilimumab + gp100) (2010) Hodi (ipilimumab alone) (2010) Subtotal (I-squard =0.0%, P=.) Heterogeneity between groups: P=0.897 Overall (I-squard =0.0%, P=0.946) 0.00586 1 171 Hypothyroidism Study ID OR (95% CI) Events, Events % Intervention Control Weight Placebo Eggermont (2016) Hair (2016) Hair (2016) Placebo	subtotal (I-squard =.%, P= .)		<ul> <li>9.16 (0.49, 170.74)</li> </ul>	4/393	0/396	22.59
gp100       (Excluded)       0.00         Hodi (ipilinumab + gp100) (2010)       (Excluded)       0/131       0/132       0.00         Subtotal (I-squard =0.0%, P=.)       0.0511       0.00       0.00         Heterogeneity between groups: P=0.897       0.00       .()       0/511       0.00         0.00586       1       171       1000       1000         Hypothyroidism         Study         D       OR (95% CI)       Events, Events %       Intervention Control Weight         Placebo       8.85 (3.75, 20.89)       48/471       6/474       57.18         Eggermont (2016)       0.910 12 0.51 02 0000       0.9000 01000       155						
Hodi (ipilinumab + gp100) (2010) Hodi (ipilinumab alone) (2010) Subtotal (I-squard =0.0%, P=.) Heterogeneity between groups: P=0.897 Overall (I-squard =0.0%, P=0.946) 3.78 (0.94, 15.17) 9/3985 0/3344 100.00 1 171 BUD DOC 9586 1 171 BUD DOC 95% CI) Events, Events % Intervention Control Weight Placebo Eggermont (2016) Huis (0012) DOC 95% CI) 48/471 6/474 57.18	gp100					
Hot (pillman balone) (2010)       Image: Constraint of the con	Hodi (ipilimumab + gp100) (2010)	1	(Excluded)			0.00
Subtotal (I-squard =0.0%, P=.)       . ()       0/511       0.00         Heterogeneity between groups: P=0.897       . ()       0/511       0.00         Overall (I-squard =0.0%, P=.)46)       3.78 (0.94, 15.17)       9/3985       0/3344       100.00         Image: Display in the state of t	Hodi (ipilimumab alone) (2010)		(Excluded)	0/131	0/132	0.00
Heterogeneity between groups: P=0.897     3.78 (0.94, 15.17)     9/3985     0/3344     100.00       0.00586     1     171       Hypothyroidism       Study       D     OR (95% Cl)     Intervention     Control     Weight       Placebo     485 (3.75, 20.89)     48/471     6/474     57.18       Eggermont (2016)     48/471     6/474     57.18	Subtotal (I-squard =0.0% P= )		()	0/511		0.00
Heterogeneity between groups: P=0.897         Overall (I-squard =0.0%, P=0.946)         1         0.00586         1         <			. (., .)	0/011		0.00
Interrogenerity between groups. 1=0.037         Overall (I-squard =0.0%, P=0.946)         3.78 (0.94, 15.17)         9/3985         0.00586         1         171         Hypothyroidism         Events, Events %         ID         0.00586         1         0.00586         1         0.00586         1         0.00586         1         0.00586         1         0.00586         1         0.00586         1         0.00586         1         0.00586	Heterogeneity between groups: P=0.807					
Strail (I-squard =0.0%, P=0.946)         Strail (0.94, 15.17)         9/3965         003344         100.00           0.00586         1         171         171           Hypothyroidism           Study           ID         OR (95% Cl)         Intervention         Control         Weight           Placebo         Eggermont (2016)         8.85 (3.75, 20.89)         48/471         6/474         57.18           Main (2017)         0.00         0.000         0.000         0.000         0.000			2 70 (0 04 45 47)	0/2005	0/2244	100.00
Hypothyroidism           Study ID         OR (95% CI)         Events, Events % Intervention Control Weight           Placebo         ####################################	Overall (I-squard =0.0%, P=0.946)		3.78 (0.94, 15.17)	9/3985	0/3344	100.00
Image: Non-Study ID						
0.00586         1         171           Hypothyroidism           Study ID         Events, Events, % Intervention Control Weight           Placebo         48/471         6/474         57.18           Eggermont (2016)         2.56 (0.12 - 57.10)         2000         01000			1			
Hypothyroidism Study ID OR (95% Cl) Events, Events, % Intervention Control Weight Placebo Eggermont (2016) 8.85 (3.75, 20.89) 48/471 6/474 57.18 0.85 (0.12, 51.01) 0,000 0,100 0,455	0.00586	1	171			
Hypothyroidism ID Placebo Eggermont (2016) Bass (3.75, 20.89) Bass (3.75, 20.89)						
Hypothyroidism           Study ID         Events, OR (95% Cl)         Events, Intervention         Events, Control         Weight           Placebo Eggermont (2016)         48/471         6/474         57.18           Nais (0017)         35.50 (12)         9000         01000         6/474         57.18						
Study ID         Events, OR (95% Cl)         Events, Intervention         Events, Control         Weight           Placebo	Нур	othyroidism				
ID         OR (95% Cl)         Intervention         Control         Weight           Placebo         -         8.85 (3.75, 20.89)         48/471         6/474         57.18           Main (2016)         -         -         8.85 (3.75, 20.89)         48/471         6/474         57.18	Study	-		Events,	Events	%
Placebo Eggermont (2016) 8.85 (3.75, 20.89) 48/471 6/474 57.18 Naio (2017) 2.55 (0.12) 57 (0) 2000 0 (100 4.55	ID		OR (95% CI)	Intervention	Control	Weight
Placebo						
Eggermont (2016) 8.85 (3.75, 20.89) 48/471 6/474 57.18	Placebo					
	Eggermont (2016)	<b>_</b>	8.85 (3.75, 20.89)	48/471	6/474	57.18
VIAU 2010 2010 2010 2010 2010 2010 2010 201	Maio (2017)	• · · · · · · · · · · · · · · · · · · ·	2.50 (0.12, 52.40)	2/380	0/189	4.56
Pager (2017) 2000 0/100 5 37	Beer (2017)		- 29.46 (1.79.485.45	27/300	0/199	5 37
Subtrail (Issuard = 0.0% P=0.504)	Subtotal (I-squard =0.0% P=0.504)		20.40 (1.70, 400.40	77/1250	6/862	67 11
0.34 (4.05, 19.76) 7771250 0/062 07.11			0.34 (4.03, 18.70)	11/1200	0/002	57.11
Subtotal (I-squard =0.0%, P=0.504)	Subtotal (I-squard =0.0%, P=0.504)	$\Leftrightarrow$	8.94 (4.05, 19.76)	77/1250	6/862	67.11

Maio (2017)		2.00 (0.12, 02.40)	2/000	0/100	1.00
Beer (2017)	*	29.46 (1.79, 485.45)	27/399	0/199	5.37
Subtotal (I-squard =0.0%, P=0.504)		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)		(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
Govindan (2017)		(Excluded)	0/475	0/473	0.00
Subtotal (I-squard =0.0%, <i>P</i> =0.897)		8.38 (2.24, 31.34)	20/1831	2/1822	24.22
Radiotherapy					
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
ap100					
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)		7.86 (4.10, 15.04)	100/3985	8/3344	100.00
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0.00200		400			

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 oncology<sup>26</sup> 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.<sup>10,27,28</sup> The incidence of musculoske-letal disorders associated with anti-PD-1–PD-L1 therapy has recently been investigated in a meta-analysis,<sup>11</sup> and inflammatory arthritis is a well-known AE associated with immune checkpoint inhibitors.<sup>29,30</sup> 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,<sup>11</sup> including all-grade rash (OR 4.03 here vs 2.34 in the study by Baxi et al<sup>11</sup>), 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,<sup>11</sup> and conversely, an increased risk of pneumonitis (OR 3.82) was associated with anti-PD-1–PD-L1 drugs,<sup>11</sup> 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, myocarditis<sup>31</sup>) 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	i				
Eggermont (2016)		7.09 (0.37, 137.63)	3/471	0/474	3.89
Maio (2017)		2.50 (0.12, 52.40)	2/380	0/189	3.70
Beer (2017)		6.59 (0.37, 117.59)	6/399	0/199	4.12
Subtotal (I-squard =0.0%, P=0.866)		4.97 (0.90, 27.48)	11/1250	0/862	11.72
Chemotherapy					
Robert (2011)	*	<ul> <li>5.12 (0.24, 107.24)</li> </ul>	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)	<b>→</b>	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)		1.39 (0.73, 2.65)	27/1831	18/1822	81.62
Radiotherapy					
Known(2014)	<b>+ •</b>	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%, <i>P</i> =0.688)		1.64 (0.91, 2.94)	40/3985	18/3344	100.00
.00727	1	138			

ID       OR (95% CI)       Intervention       Control       Weight         Placebo       3.03 (0.12, 74.46)       1/471       0/474       12.13         Beer (2017)       3.03 (0.12, 74.46)       1/471       0/474       12.13         Subtolal (I-squard = 0.0%, P=0.933)       0.082       2.50 (0.12, 52.40)       2/380       0/189       0.34         Chemotherapy       3.06 (0.12, 75.50)       0.75.50       0.74       0.75.50       0.85       2.55.9         Chemotherapy       3.06 (0.12, 75.50)       0.44 (0.01, 861)       0.44 (0.01, 965)       0.000<	Study	Pancreatitis		Events,	Events	%
Placebo       3.03 (0.12, 74.46)       1/471       0/474       12.13         Beer (2017)       2.50 (0.12, 52.40)       2/300       0/189       13.46         Malo (2017)       2.50 (0.12, 52.40)       2/300       0/189       13.46         Subtotal (I-squard = 0.0%, P=0.933)       2.74 (0.30, 24.85)       3/1250       0/862       25.59         Chemotherapy       3.06 (0.12, 75.50)       0.34 (0.01, 8.61)       0.34 (0.01, 8.61)       0.34 (0.01, 8.61)         Reck (pilimumab, concurrent) (2012)       0.34 (0.01, 8.61)       0.34 (0.01, 8.61)       0.34 (0.01, 8.61)         Reck (pilimumab, concurrent) (2012)       0.33 (0.01, 8.17)       2.96 (0.12, 73.67)       V         Lynch (pilimumab, phased) (2012)       (Excluded)       0.71       0/65       0.00         Lynch (pilimumab, concurrent) (212)       (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       (Excluded)       0.731       0/132       0.00         Subtotal (I-squard = 0.0%, P=.)       (Excluded)       0.01       0.00         gravita       (Excluded)       0.131       0/132       0.00         Subtotal (I-squard = 0.0%, P=.) <t< th=""><th>ID</th><th></th><th>OR (95% CI)</th><th>Intervention</th><th>Control</th><th>Weight</th></t<>	ID		OR (95% CI)	Intervention	Control	Weight
Eggermont (2016) Beer (2017) Subtotal (I-squard =0.0%, P=0.933) Chemotherapy Robert (2011) Reck (pillinumab, oncurrent) (2012) Lynch (pillinumab, phased) (2012) Lynch (pillinumab, oncurrent) (2012) Lynch (pillinumab alone) (2010) Hodi (l-squard =0.0%, P=.) Lynch (pillinumab alone) (2010) Hodi (ipillinumab alone) (2010) Lynch (pillinumab alone) (2010) L	Placebo					
Beer (2017)       2.50 (0.12, 52.40)       2/380       0/189       13.46         Maio (2017)       2.74 (0.30, 24.85)       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       7.66 (0.12, 75.50)       0.34 (0.01, 8.61)       0.34 (0.01, 8.61)       0.34 (0.01, 8.61)       0.34 (0.01, 8.61)       0.34 (0.01, 8.61)       0.33 (0.01, 8.17)         Reck (zo16)       0.33 (0.01, 8.17)       2.99 (0.12, 73.67)       Excluded)       0/67       0/65       0.00         Lynch (iplimumab, 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       (Excluded)       0/67       0/65       0.00       0.00         Subtotal (I-squard =0.0%, P=0.584)       (Excluded)       0/131       0/132       0.03         Subtotal (I-squard =0.0%, P=0.584)       (Excluded)       0/131       0/132       0.00         Subtotal (I-squard =0.0%, P=.)       (Excluded)       0/131       0/132       0.00         Subtotal (I-squard =0.0%, P=.)       (I-, -)       0/511       0/264       0.00         Lynch (iplim	Eggermont (2016)		3.03 (0.12, 74.46)	1/471	0/474	12.13
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       3.06 (0.12, 75.50)       0.34 (0.01, 8.61)       0.34 (0.01, 8.61)       0.34 (0.01, 8.61)         Reck (ipilimumab, concurrent) (2012)       0.33 (0.01, 8.17)       2.99 (0.12, 73.67)       V       V         Lynch (ipilimumab, phased) (2012)       (Excluded)       0/71       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       (Excluded)       0/131       0/132       0.00         gp100       (Excluded)       0/131       0/132       0.00         Hodi (ipilimumab alone) (2010)       (Excluded)       0/131       0/132       0.00         Subto	Beer (2017)		2.50 (0.12, 52.40)	2/380	0/189	13.46
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)       0.34 (0.01, 8.61)       0.34 (0.01, 8.61)         Reck (pilinumab, phased) (2012)       0.34 (0.01, 8.61)       0.33 (0.01, 8.17)       0.33 (0.01, 8.17)         Reck (2016)       0.33 (0.01, 8.17)       0.33 (0.01, 8.17)       0.065       0.00         Cynch (pilinumab, phased) (2012)       (Excluded)       0/67       0/65       0.00         Lynch (pilinumab, phased) (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       (Excluded)       0.71       0/65       0.00       0.00         gp100       (fiplimumab alone) (2010)       0.03       0.0131       0/132       0.00         Subtotal (I-squard = 0.0%, P=.)       (fiplimumab alone) (2010)       0.00       (Excluded)       0/131       0/132       0.00         Subtotal (I-squard = 0.0%, P=.)       1.51 (0.49, 4.60)       8/3985       3/3344       100.00	Maio (2017)		(Excluded)	0/399	0/199	0.00
Chemotherapy Robert (2011)       3.06 (0.12, 75.50)         Reck (pilimumab, phased) (2012)       0.34 (0.01, 8.61)         Reck (pilimumab, concurrent) (2012)       0.34 (0.01, 8.61)         Reck (2016)       0.33 (0.01, 8.17)         Govindan (2017)       2.99 (0.12, 73.67)         Lynch (pilimumab, phased) (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)       0.01       0.00         subtotal (I-squard =.%, P= .)       (Excluded)       0/131       0/132       0.00         gp100       (bdi (ipilimumab alone) (2010)       0.00       (c)       0/393       0/396       0.00         Heterogeneity between groups: P=0.944       0/671       0/651       0.00       (c)       0/511       0/264       0.00         Verall (I-squard =0.0%, P=0.762)       1.51 (0.49, 4.60)       8/3985       3/3344       100.00	Subtotal (I-squard =0.0%, P=0.933)		2.74 (0.30, 24.85)	3/1250	0/862	25.59
Robert (2011)       3.06 (0.12, 75.50)         Reck (ipilimumab, phased) (2012)       0.34 (0.01, 8.61)         Reck (2013)       0.33 (0.01, 8.61)         Reck (2016)       0.33 (0.01, 8.17)         Govindan (2017)       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)       0.71       0/65       0.00         Subtotal (I-squard =.%, P=.)       (Excluded)       0/71       0/65       0.00         gp100       (c,)       0/393       0/396       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       0.00       (., .)       0.511       0/264       0.00         Overall (I-squard =0.0%, P=0.762)       1.51 (0.49, 4.60)       8/3985       3/3344       100.00	Chemotherapy					
Reck (ipilimumab, phased) (2012)       0.34 (0.01, 8.61)         Reck (ipilimumab, concurrent) (2012)       0.33 (0.01, 8.61)         Ribas (2013)       6.93 (0.36, 134.80)         Reck (2016)       0.33 (0.01, 8.7)         Govindan (2017)       2.99 (0.12, 73.67)         Lynch (ipilimumab, concurrent) (2012)       (Excluded)       0/67       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       (Excluded)       0/71       0/65       0.00         subtotal (I-squard =0.0%, P=0.584)       0.00       .(.,.)       0/393       0/396       0.00         gp100       (Excluded)       0/131       0/132       0.00         Hodi (ipilimumab alone) (2010)       0.00       .(.,.)       0/511       0/264       0.00         Heterogeneity between groups: P=0.944       0.00       .()       0.511       0/264       0.00         Uverall (I-squard =0.0%, P=0.762)       1.51 (0.49, 4.60)       8/3985       3/3344       100.00         125       125       125       125       125       125	Robert (2011)		3.06 (0.12, 75.50)			
Reck (ipilimumab, concurrent) (2012)       0.34 (0.01, 8.61)         Ribas (2013)       6.33 (0.36, 134.80)         Reck (2016)       0.33 (0.01, 8.17)         Govindan (2017)       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       (Excluded)       0.71       0/65       0.00         subtotal (I-squard =.%, P=.)       0.39 (0.013, 6.17)       0.00       0.00         gp100       (Excluded)       0.71       0/65       0.00         Hodi (ipilimumab signe) (2010)       0.00       .(., .)       0/393       0/396       0.00         Subtotal (I-squard =0.0%, P=.)       .(., .)       0/511       0/132       0.00         Heterogeneity between groups: P=0.944       .(, .)       0.511       0/264       0.00         Overall (I-squard =0.0%, P=0.762)       1.51 (0.49, 4.60)       8/3985       3/344       100.00	Reck (ipilimumab, phased) (2012)		0.34 (0.01, 8.61)			
Ribas (2013)       6.93 (0.36, 134.80)         Reck (2016)       0.33 (0.01, 8.17)         Govindan (2017)       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       (Excluded)       0.71       0/65       0.00         Subtotal (I-squard =.%, P=.)       (Excluded)       0.03       0/396       0.00         gp100       (Excluded)       0/131       0/132       0.00         Hodi (ipilimumab alone) (2010)       0.00       (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       0.00       . (., .)       0.511       0/264       0.00         00742       135       0.3344       100.00       . ()       135       . ()	Reck (ipilimumab, concurrent) (2012)		0.34 (0.01, 8.61)			
Reck (2016)       0.33 (0.01, 8.17)         Govindan (2017)       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       . (,)       0/393       0/396       0.00         gp100       Hodi (ipilimumab + gp100) (2010)       0.00       . (,)       0/311       0/132       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	Ribas (2013)		6.93 (0.36, 134.80)	1		
Govindan (2017)       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       (Excluded)       0.71       0/65       0.00         subtotal (I-squard =.%, P=.)       (Excluded)       0.733       0/396       0.00         gp100       (fullimumab + gp100) (2010)       0.01       0.00       0.00         Hodi (ipilimumab alone) (2010)       0.011       0.0264       0.00         Subtotal (I-squard =0.0%, P=.)       1.51 (0.49, 4.60)       8/3985       3/3344       100.00         Heterogeneity between groups: P=0.944       0       1.51 (0.49, 4.60)       8/3985       3/3344       100.00         100742       135       1.51 (0.49, 4.60)       8/3985       3/344       100.00	Reck (2016)	* !	0.33 (0.01, 8.17)			
Lynch (ipilimumab, phased) (2012) Lynch (ipilimumab, concurrent) (2012) Subtotal (I-squard =0.0%, P=0.584) Radiotherapy Known(2014) subtotal (I-squard =.%, P= .) gp100 Hodi (ipilimumab + gp100) (2010) Hodi (ipilimumab alone) (2010) Heterogeneity between groups: P=0.944 Overall (I-squard =0.0%, P=0.762) D0742 Overall (I-squard =0.0%, P=0.762) D0742 D074 D0742 D074 D0742 D074	Govindan (2017)		2.99 (0.12, 73.67)			
Lynch (ipilimumab, concurrent) (2012) Subtotal (I-squard =0.0%, P=0.584) Radiotherapy Known(2014) subtotal (I-squard =.%, P= .) gp100 Hodi (ipilimumab alone) (2010) Heterogeneity between groups: P=0.944 Overall (I-squard =0.0%, P=.762) 125 (Excluded) (Excluded) 071 0/65 0.00 1.23 (0.34, 4.47) 0.00 (Excluded) 0.00 (Excluded) 0/131 0/132 0.00 (Excluded) 0/131 0/132 0.00 (Excluded) 0/131 0/132 0.00 1.51 (0.49, 4.60) 8/3985 3/3344 100.00	Lynch (ipilimumab, phased) (2012)		(Excluded)	0/67	0/65	0.00
Subtotal (I-squard =0.0%, P=0.584) Radiotherapy Known(2014) subtotal (I-squard =.%, P= .) gp100 Hodi (iplimumab + gp100) (2010) Hodi (iplimumab alone) (2010) Heterogeneity between groups: P=0.944 Overall (I-squard =0.0%, P=.762) 125	Lynch (ipilimumab, concurrent) (2012)		(Excluded)	0/71	0/65	0.00
Radiotherapy       (Excluded)       0.00         Subtotal (I-squard =.%, P=.)       .(.,.)       0/393       0/396       0.00         gp100       .(.,.)       0/393       0/396       0.00         Hodi (ipilimumab + gp100) (2010)       0.00       0.00       0.00         Subtotal (I-squard =0.0%, P=.)       .(.,.)       0/511       0/132       0.00         Heterogeneity between groups: P=0.944       0verall (I-squard =0.0%, P=0.762)       1.51 (0.49, 4.60)       8/3985       3/344       100.00	Subtotal (I-squard =0.0%, P=0.584)		1.23 (0.34, 4.47)	5/1831	3/1822	74.41
Known(2014)       (Excluded)       0.00         subtotal (I-squard =.%, P=.)       .(.,.)       0/393       0/396       0.00         gp100       .(.,.)       0/393       0/396       0.00         Hodi (ipilimumab + gp100) (2010)	Radiotherapy					
subtotal (I-squard =.%, P=.)       . (, .)       0/393       0/396       0.00         gp100       Hodi (ipilimumab + gp100) (2010)       0.00       0.00         Hodi (ipilimumab alone) (2010)       0.01       0.00       0.00         Subtotal (I-squard =0.0%, P=.)       0.7131       0/132       0.00         Heterogeneity between groups: P=0.944       0verall (I-squard =0.0%, P=0.762)       1.51 (0.49, 4.60)       8/3985       3/344       100.00	Known(2014)		(Excluded)			0.00
gp100	subtotal (I-squard =.%, P= .)		. (., .)	0/393	0/396	0.00
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     151 (0.49, 4.60)     8/3985     3/3344     100.00       0verall (I-squard =0.0%, P=0.762)     151 (0.49, 4.60)     8/3985     3/344     100.00	gp100					
Hodi (ipilimumab alone) (2010) Subtotal (I-squard =0.0%, P=.) 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 1 1.51 (0.49, 4.60) 8/3985 3/3344 100.00 1 1.55	Hodi (ipilimumab + gp100) (2010)					0.00
Subtotal (I-squard =0.0%, P=.) Heterogeneity between groups: P=0.944 Overall (I-squard =0.0%, P=0.762) . (., .) 0/511 0/264 0.00 . (., .) 0/511 0/264 0.00  1.51 (0.49, 4.60) 8/3985 3/3344 100.00  135	Hodi (ipilimumab alone) (2010)		(Excluded)	0/131	0/132	0.00
Heterogeneity between groups: P=0.944 Overall (I-squard =0.0%, P=0.762) 00742 1.51 (0.49, 4.60) 8/3985 3/3344 100.00 1 1.51 (0.49, 4.60) 8/3985 3/3344 100.00 1 1.51 (0.49, 4.60) 8/3985 3/3344 100.00	Subtotal (I-squard =0.0%, P=.)		. (., .)	0/511	0/264	0.00
Overall (I-squard =0.0%, P=0.762)	Heterogeneity between groups: P=0.944					
	Overall (I-squard =0.0%, <i>P</i> =0.762)		1.51 (0.49, 4.60)	8/3985	3/3344	100.00
	00742		125			



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 corticosteroids and other immunosuppressants.<sup>26</sup> 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 <sup>#</sup>	Serious <sup>†</sup>	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	.4 ( 0.3– 2.5)	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.  $^{\dagger}$ 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.<sup>32</sup> 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.<sup>33</sup> 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.

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## **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.

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# Supplementary materials



Figure SI Flow diagram for study selection.

Нуро	pituitarism			
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%, <i>P</i> =0.986)	4.73 (1.73, 12.95)	27/3985	0/3344	100.00
I 00208				
.00230				

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

ALT in	creased			
Study ID	OR (95% CI)	Events, Intervention	Events 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%, <i>P</i> =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%, <i>P</i> =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%, <i>P</i> =0.000)	3.28 (1.79, 6.02)	402/3985	113/3344	100.00
NOTE: weights are from random effects analysis				
0.00344	I I 1 291			

#### ALT increased

Study		Events,	Events	%
ID	OR (95% CI)	Intervention	Control	Weight
Placebo				
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)	<b>4.51 (2.88, 7.06)</b>	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)	(Excluded)	0/325	0/319	0.00
Subtotal (I-squard =77.6%, P=0.000)	<b>3.28 (1.50, 7.18)</b>	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)	1.01 (0.06, 16.28)	1/131	1/132	2.60
Subtotal (I-squard =0.0%, P=0.858)	1.23 (0.22, 6.91)	5/511	2/264	6.40
Overall (I-squard = `68.1%, <i>P</i> =0.000)	3.12 (1.92, 5.09)	361/3985	113/3344	100.00
NOTE: weights are from random effects analysis				
I I 0.00344 1	l 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.

Study		Events,	Events	%
ID	OR (95% CI)	Intervention	Control	Weigh
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	16.68
Govindan (2017)	2.99 (0.12, 73.67)	1/475	0/473	16.68
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	16.64
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	16.64
Heterogeneity between groups: P=0.963				
Overall (I-squard =0.0%, P=0.995)	2.00 (0.54, 7.40)	6/3985	0/3344	100.00
I	1			

Guillain-barre syndrome

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

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