Original Paper

Safety profile of nivolumab, a programmed death 1 checkpoint inhibitor, in solid tumors: a meta-analysis of randomized clinical trials

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Abstract

Background: Nivolumab, an immune checkpoint inhibitor which inhibit the programmed death 1/programmed death ligand 1 interaction, has revolutionized the treatment of multiple cancers including melanoma, non-small cell lung cancer, renal cell cancers and head and neck carcinoma.

Objective: The present meta-analysis of randomized clinical trials aimed to summarize current knowledge regarding the safety profile of nivolumab.

Methods: Randomized controlled trials focusing on efficacy and safety of nivolumab therapy were searched in PubMed databases up to July 2018. Safety end points included the rate of all-grade, grade≥3 any adverse events and all-grade individual adverse events including fatigue, nausea, vomiting, decreased appetite, diarrhea, asthenia, anemia, alopecia, neutropenia, rash, pruritus, pneumonitis, hypothyroidism and hyperthyroidism. Data were analyzed using random effects meta-analysis for risk ratios (RR) and risk differences (RD). Heterogeneity across studies was analyzed using I^2 statistics.

Results: Eight randomized trials including 3,900 patients (nivolmab arms:2,114; control arms; 1,786 patients) were selected in our meta-analysis. There was evidence of significant heterogeneity between studies. Compared with control arm, the pooled RR in nivolumab arm for all-grade and grade≥ 3 any adverse events was 0.84 (95% CI 0.77-0.91; P<0.0001) and 0.35 (95% CI 0.25-0.49; P<0.00001) respectively. Nivolumab arm had a decreased risk of many adverse events including fatigue, nausea, vomiting, decreased appetite, diarrhea, asthenia, anemia, alopecia and neutropenia. However, nivolumab

arm had an increased risk of pruritus [RR 1.33; 95% CI 1.10-1.59; *P*=0.003], hypothyroidism (RR 5.65; 95%CI 1.98-16.16; *P*=0.001) and hyperthyroidism (RR 4.26; 95%CI 1.72-10.56; *P*=0.003).

Conclusions: Nivolumab was well tolerated, associated with significant lower risk of many adverse events, but significant higher risk of thyroid dysfunctions. Clinicians need to be aware of these safety profiles of nivolumab.

Keywords

adverse events, meta-analysis, nivolumab, randomized clinical trials, safety profile, thyroid dysfunction

Introduction

Immune checkpoint inhibitors (ICIs) which inhibit the programmed death 1(PD-1) /programmed death ligand 1(PD-L1) interaction has revolutionized the treatment of many cancers including melanoma, non-small cell lung cancer, urothelial and renal cell cancers[1-2]. ICIs have shown especially significant improvement in progression-free and overall survival compared with standard care in different advanced solid tumors[3-10].

ICIs are overall better tolerated than chemotherapy, but can lead to the appearance of the newly called immune-related adverse events (irAEs). ICIs can disrupt immune tolerance resulting in enhancing immune activation in normal tissue site with significant toxicities. The basis for the majority of these adverse events is an unregulated activation of T-cells directed at normal tissues. The irAEs affects a wide range of organ including endocrine organ, thyroid, adrenal gland and pituitary, skin with rash or vitiligo, gastrointestinal tract, kidney, liver, pancreas and nervous systems[11-14]. Therefore, clinicians should be aware of the broad range of clinical manifestations and symptoms of irAEs and keep in mind that toxicities may occur at any point along a patient's treatment course. Although the most common irAEs are rarely severe, some of them may be associated with great morbidity and even become life-threatening. The rate of occurrence, type and severity of irAEs may vary with the type of ICIs. Nivolumab, a human IgG4 monoclonal antibody inhibitor of PD-1, was the first ICI approved in Japan and the USA in 2015.

In the present study, we conducted a meta-analysis of randomized controlled trials focusing on efficacy and safety of nivolumab therapy to summarize current knowledge regarding the safety profile of nivolumab.

Methods

Search Strategy

The present meta-analysis was conducted according to the recommendations of the Preferred Reporting Items for Systemic Reviews and Meta-analysis (PRISMA) statement and the Cochrane Handbook. Ethics Committee approval was waived because this study did not involve any human participants or animals. The PubMed database was comprehensively searched for the articles published up to July 2018. The following keywords or corresponding MeSH terms were used: “nivolumab”

"programmed cell death-1" "clinical trial". The eligible studies were independently assessed and selected by four investigators (HS, HY, YM and YB) from all the potentially relevant studies.

Data Extraction and Quality Assessment

Four investigators (HS, HY, YM and YB) independently performed data extraction. Any discrepancies between reviewers were resolved by consensus. The following information was recorded for each study; first author's name, year of publication, underling malignancy, treatment regimen, number of patients. According to the National Cancer Institute Common Terminology Criteria Adverse Events (NCI CTCAE) version 4.0, the numbers of all-grade and grade≥3 any adverse events were extracted. Also, the numbers of all-grade individual adverse events were extracted. For the individual adverse events, we included clinically relevant symptoms (fatigue, nausea, vomiting, decreased appetite, diarrhea, asthenia and alopecia), hematologic adverse events (neutropenia and anemia) and irAEs (rash, pruritus, hypothyroidism, hyperthyroidism and pneumonitis). The quality of enrolled studies was evaluated in accordance with Jadad score, which is based on the reporting of randomization method, blinding method, withdrawals, and dropouts[15]. We selected the studies with a score 3 or higher as Jadad score for our meta-analysis.

Inclusion and Exclusion Criteria

Eligible studies for our meta-analysis met the following criteria: (a) the study was designed as a random control trial; (b) The sample size and the number of all-grade, grade≥3 any adverse events and all-grade individual adverse events were recorded in publications. All non-comparative, in vitro and animal studies were excluded. In addition, we excluded poor quality studies with a Jadad score with less than 3 and those with incomplete data or duplicate reports.

Safety End Points

The safety end points were defined as the rate of all-grade, grade≥3 any adverse events and all-grade individual adverse events (fatigue, nausea, vomiting, decreased appetite, diarrhea, asthenia, anemia, alopecia, neutropenia, rash, pruritus, pneumonitis, hypothyroidism and hyperthyroidism).

Statistical Analysis

Review Manager 5.3 was used to conduct our meta-analysis. Data were analyzed using random effects meta-analysis for risk ratios (RR) and risk differences (RD) and their 95% confidence interval (95% CI). *P*-values less than 0.05 were considered statistically significant. Heterogeneity across studies was assessed by I^2 statistics. I^2 >25% was considered to indicate significant heterogeneity; I^2 <25% and I^2 >75% indicated low and considerable heterogeneity, respectively.

Results

Characteristics of Clinical Studies

Initially our strategy yielded 1,072 publications through PubMed search. After title, abstracts and full-text articles were reviewed, 8 studies involving 3,900 patients (nivolmab arms: 2,114 patients; control arms: 1,786 patients) were enrolled in our meta-analysis (Figure 1). The characteristics of clinical studies included in our meta-analysis are presented in Table 1.

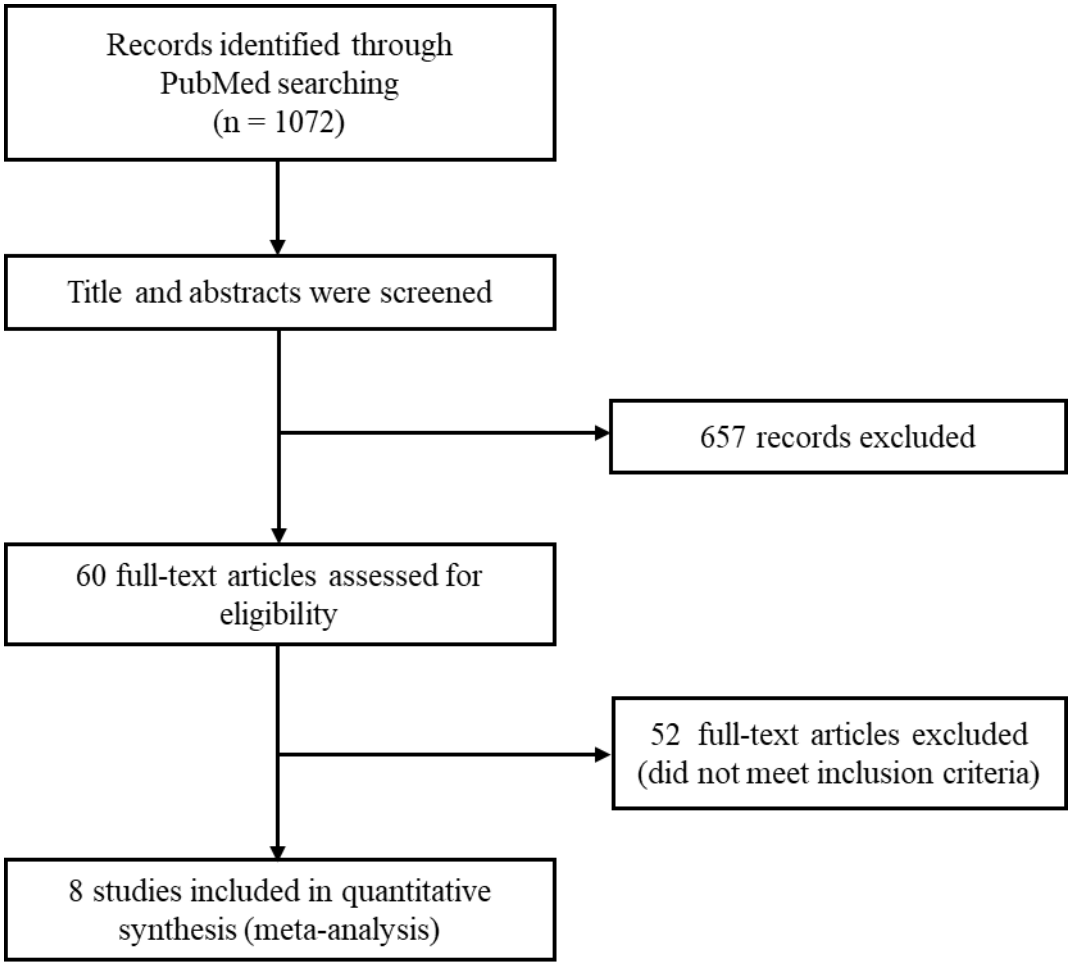


Figure 1. Flow chart for study selection.

Table 1 Characteristics and Jadad score of the clinical studies included in the present meta-analysis.

First author (year)	Number of subject		Disease	Progress	Nivolumab regimen	Control regimen	Jadad score
	Nivolumab	Control					
Borghaei (2015)	292	290	NSCLC /stage Ⅲb orⅣ	Previously treated	Nivolumab 3 mg/kg every 2weeks	Docetaxel 75 mg/m^2 every 3weeks	3
Brahmer (2015)	135	137	NSCLC/stage Ⅲb orⅣ	Previously treated		Docetaxel 75 mg/m^2 every 3weeks	3
Carbone (2017)	211	212	NSCLC/stage Ⅳ	Untreated		Platinum-based chemotherapy	3
Ferris (2016)	240	121	Head and neck carcinoma	Previously treated		Standard therapy (Methotrexate, Docetaxel, or Cetuximab)	3
Larkin (2015)	316	315	Melanoma/stage ⅢorⅣ	Untreated		Ipilimumab 3 mg/kg every 3weeks	4
Motzer (2015)	410	411	Renal cell carcinoma	Previously treated		Everolimus 10 mg orally onec a day	3
Robert (2015)	210	208	Melanoma/stage ⅢorⅣ	Untreated		Dacarbazine 1000 mg/m^2 every 3weeks	4
Weber (2015)	272	133	Melanoma/stage ⅢorⅣ	Previously treated		Dacarbazine 1000 mg/m^2 every 3w eeks or Paclitaxel 175 mg/m^2 combined with Carboplatin	3

Any adverse events (all-grade and grade≥3)

The pooled RR of any adverse events (all-grade) (RR 0.84; 95% CI 0.77-0.91; I^2=82%, Figure 2 (A)) and any adverse events (grade≥3) (RR 0.35; 95% CI 0.25-0.49; I^2=85%, Figure 2(B)) showed that nivolumab arm had a significantly decreased risk compared with control arm.

Individual adverse events (all-grade)

The pooled RR of nausea [RR 0.44; 95% CI 0.31-0.62; I^2=84%, Figure 2 (D)], vomiting [RR 0.38; 95% CI 0.24-0.61; I^2=68%, Figure 2 (E)], decrease appetite [RR 0.59; 95% CI 0.47-0.74; I^2=39%, Figure 2 (F)], diarrhea [RR 0.62; 95% CI 0.47-0.81; I^2=67%, Figure 2 (G)], asthenia [RR 0.52; 95% CI 0.35-0.78; I^2=53%, Figure 2 (H)], anemia [RR 0.21; 95% CI 0.11-0.42; I^2=82%, Figure 2 (I)], alopecia [RR 0.06; 95% CI 0.01-0.44; I^2=85%, Figure 2 (J)], neutropenia [RR 0.02; 95% CI 0.01-0.04; I^2=0%, Figure 2 (K)] showed that nivolumab arm had a significantly decreased risk compared with control arm. On the other hand, the pooled RR of pruritus [RR 1.33; 95% CI 1.10-1.59; I^2=90%, Figure 2 (M)] hypothyroidism [RR 5.65; 95% CI 1.98-16.16; I^2=43%, Figure 2 (O)] and hyperthyroidism [RR 4.26; 95% CI 1.72-10.56; I^2=0%, Figure 2 (P)] showed that nivolumab arm had a significantly increased risk compared with control arm. The pooled risk difference (RD) and the number needed to harm (NNH) for individual adverse events in patients receiving nivolumab compared with control are summarized in Table 2.

Discussion

We compared the safety profile of nivolumab and standard care in patient with cancer patients by performing a meta-analysis of randomized clinical trials. In the present meta-analysis, we found that nivolumab arm had a decreased risk of many adverse events including fatigue, nausea, vomiting, decreased appetite, diarrhea, asthenia, anemia, alopecia and neutropenia compared with control arm. However, nivolumab arm had an increased risk of irAEs including pruritus (1.33; 95% CI 1.10-1.59), hypothyroidism (5.65; 95% CI 1.98-16.16) and hyperthyroidism (4.26; 95% CI 1.72-10.56) compared with control arm.

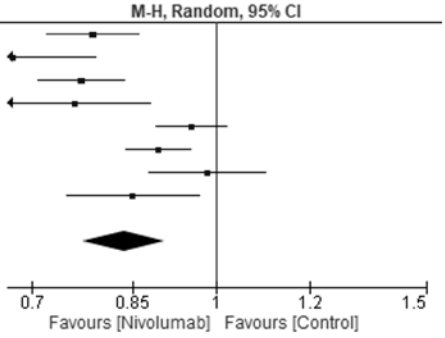
In addition, our analysis of summary safety endpoints revealed the pooled RR for grade≥3 any adverse events (0.35; 95% CI 0.25-0.49) was significantly lower than that for all-grade any adverse events (0.84; 95% CI 0.77-0.91). This difference of RR according to grade in any adverse events suggests that nivolumab therapy was better tolerated than standard therapy. Furthermore, the NNH of individual adverse events in patients receiving nivolumab compared to controls was 5-100, implying that the difference is clinically significant.

Compared with the toxicities caused by conventional therapy, irAEs due to unbalancing the immune system by treatment with ICIs are unique in term of the organs involved, onset patterns, and severity. Numerous randomized controlled trials have outlined a crude profile of irAEs, including skin,

(A) Any adverse events (All grade)

Study or Subgroup	Nivolumab Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Borghaei(2015)	199	287	236	268	13.5%	0.79 [0.72, 0.86]
Brahmer(2015)	76	131	111	129	9.7%	0.67 [0.57, 0.79]
Carbone(2017)	190	267	243	263	13.7%	0.77 [0.71, 0.84]
Ferris(2016)	139	236	86	111	10.4%	0.76 [0.66, 0.88]
Larkin(2015)	257	313	268	311	14.4%	0.95 [0.89, 1.02]
Motzer(2015)	319	406	349	397	14.7%	0.89 [0.84, 0.95]
Robert(2015)	153	206	155	205	12.2%	0.98 [0.88, 1.10]
Weber(2015)	181	268	81	102	11.3%	0.85 [0.75, 0.97]
Total (95% CI)		**2114**		**1786**	**100.0%**	**0.84 [0.77, 0.91]**
Total events	1514		1529			

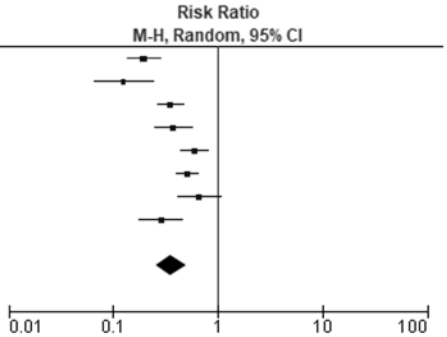
Heterogeneity: Tau² = 0.01; Chi² = 38.07, df = 7 (P < 0.00001); I² = 82%
Test for overall effect: Z = 4.41 (P < 0.0001)



(B) Any adverse events (Grade≥3)

Study or Subgroup	Nivolumab Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Borghaei(2015)	30	287	144	268	13.0%	0.19 [0.14, 0.28]
Brahmer(2015)	9	131	71	129	9.7%	0.12 [0.07, 0.24]
Carbone(2017)	47	267	133	263	13.8%	0.35 [0.26, 0.46]
Ferris(2016)	31	236	39	111	12.4%	0.37 [0.25, 0.57]
Larkin(2015)	51	313	85	311	13.5%	0.60 [0.44, 0.81]
Motzer(2015)	76	406	145	397	14.2%	0.51 [0.40, 0.65]
Robert(2015)	24	206	36	205	11.7%	0.66 [0.41, 1.07]
Weber(2015)	24	268	32	102	11.7%	0.29 [0.18, 0.46]
Total (95% CI)		**2114**		**1786**	**100.0%**	**0.35 [0.25, 0.49]**
Total events	292		685			

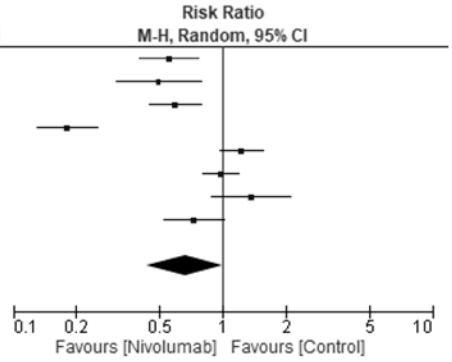
Heterogeneity: Tau² = 0.19; Chi² = 46.39, df = 7 (P < 0.00001); I² = 85%
Test for overall effect: Z = 6.11 (P < 0.00001)



(C) Fatigue

Study or Subgroup	Nivolumab Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Borghaei(2015)	46	287	78	268	12.6%	0.55 [0.40, 0.76]
Brahmer(2015)	21	131	42	129	11.7%	0.49 [0.31, 0.78]
Carbone(2017)	56	267	93	263	12.8%	0.59 [0.45, 0.79]
Ferris(2016)	33	236	86	111	12.5%	0.18 [0.13, 0.25]
Larkin(2015)	107	313	87	311	13.0%	1.22 [0.97, 1.55]
Motzer(2015)	134	406	134	397	13.2%	0.98 [0.80, 1.19]
Robert(2015)	41	206	30	205	11.9%	1.36 [0.89, 2.09]
Weber(2015)	67	268	35	102	12.5%	0.73 [0.52, 1.02]
Total (95% CI)		**2114**		**1786**	**100.0%**	**0.66 [0.43, 1.01]**
Total events	505		585			

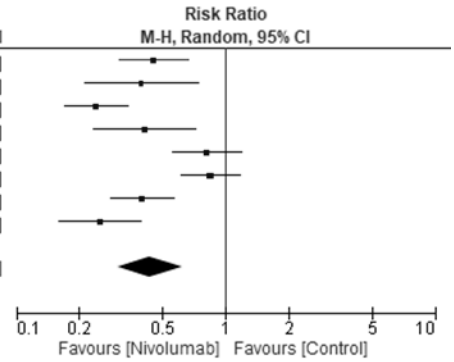
Heterogeneity: Tau² = 0.35; Chi² = 110.98, df = 7 (P < 0.00001); I² = 94%
Test for overall effect: Z = 1.93 (P = 0.05)



(D) Nausea

Study or Subgroup	Nivolumab Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Borghaei(2015)	34	287	70	268	13.1%	0.45 [0.31, 0.66]
Brahmer(2015)	12	131	30	129	10.4%	0.39 [0.21, 0.73]
Carbone(2017)	31	267	127	263	13.3%	0.24 [0.17, 0.34]
Ferris(2016)	20	236	23	111	11.1%	0.41 [0.23, 0.71]
Larkin(2015)	41	313	50	311	13.0%	0.81 [0.56, 1.19]
Motzer(2015)	57	406	66	397	13.5%	0.84 [0.61, 1.17]
Robert(2015)	34	206	85	205	13.3%	0.40 [0.28, 0.56]
Weber(2015)	25	268	38	102	12.3%	0.25 [0.16, 0.39]
Total (95% CI)		**2114**		**1786**	**100.0%**	**0.44 [0.31, 0.62]**
Total events	254		489			

Heterogeneity: Tau² = 0.22; Chi² = 42.92, df = 7 (P < 0.00001); I² = 84%
Test for overall effect: Z = 4.57 (P < 0.00001)



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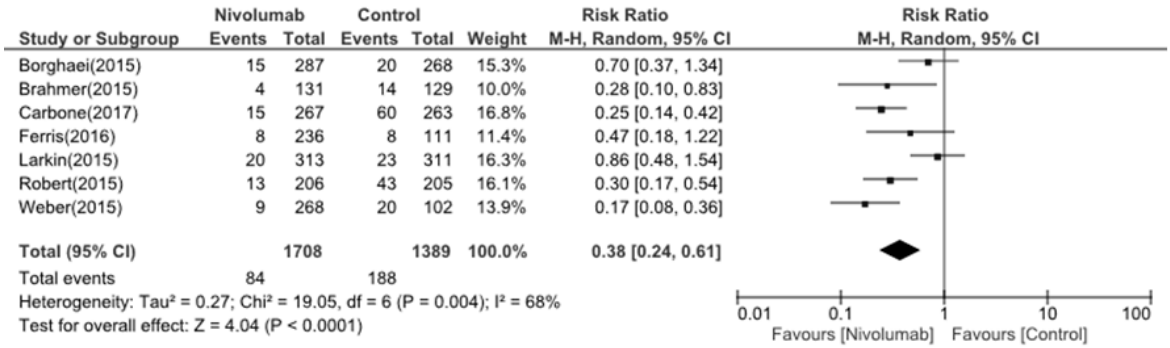
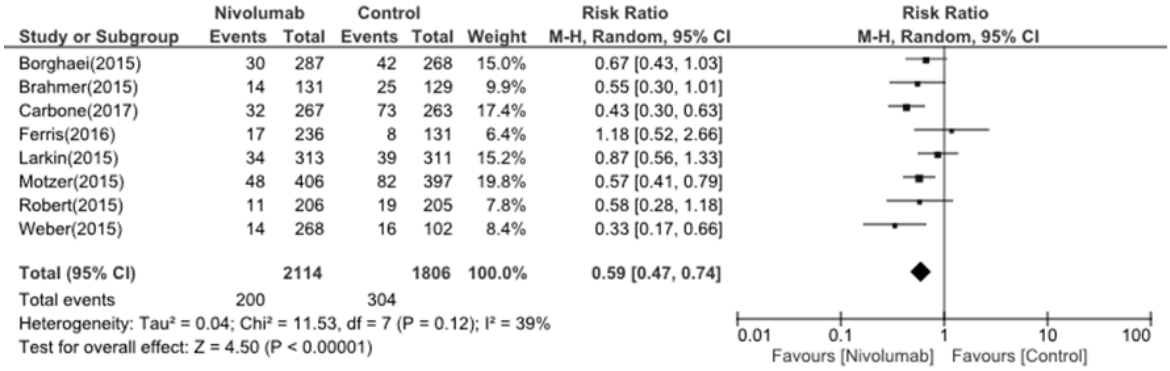
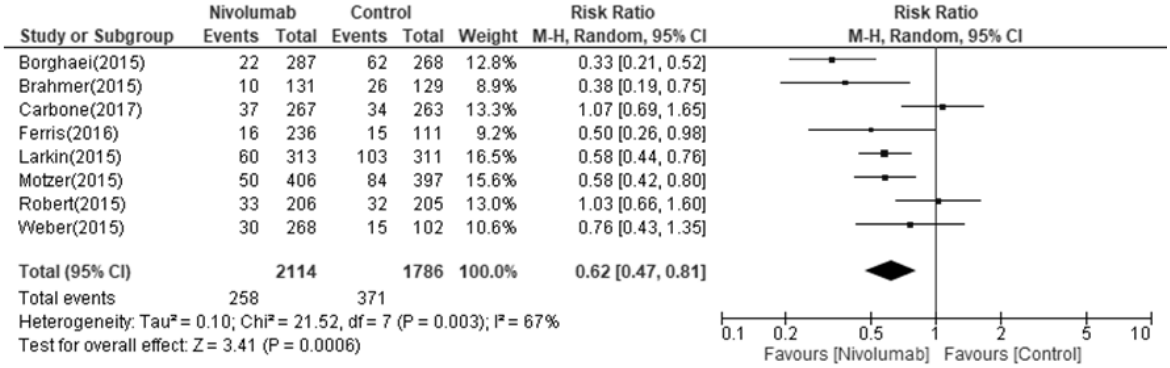
(E) Vomiting



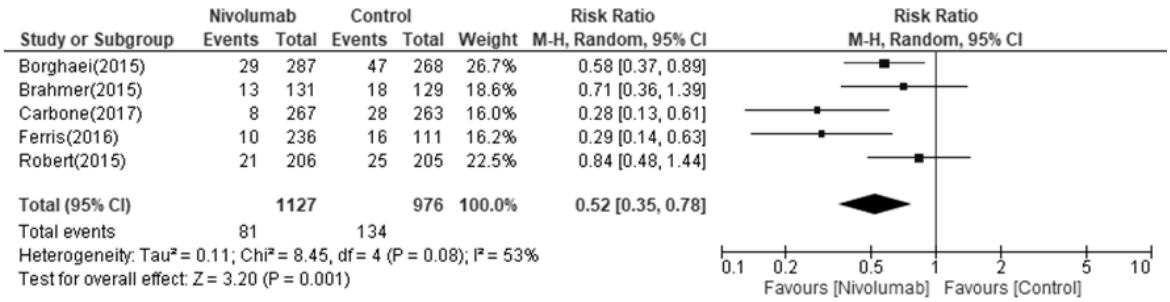
(F) Decreased appetite



(G) Diarrhea



(H) Asthenia



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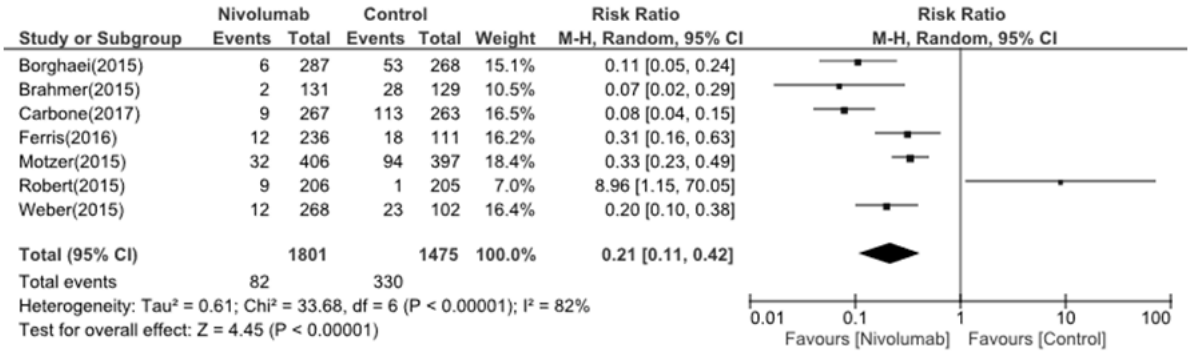
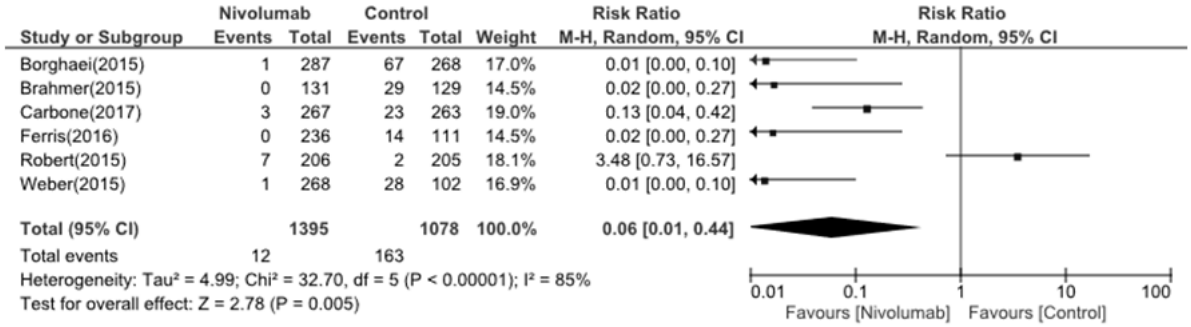
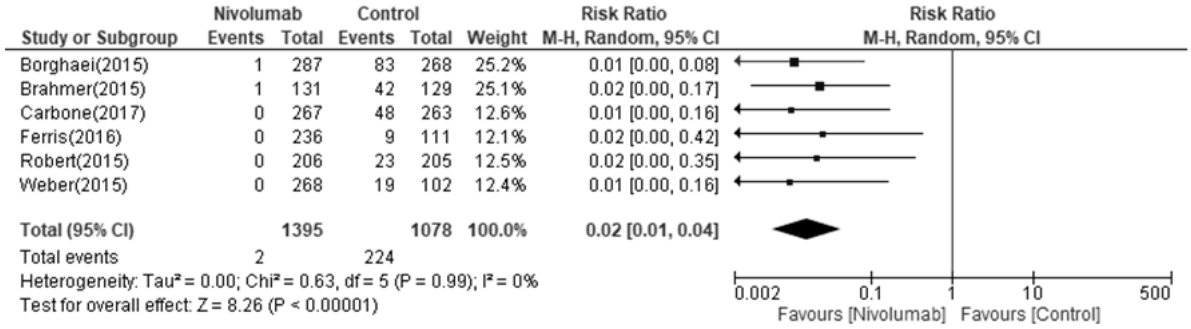
(I) Anemia



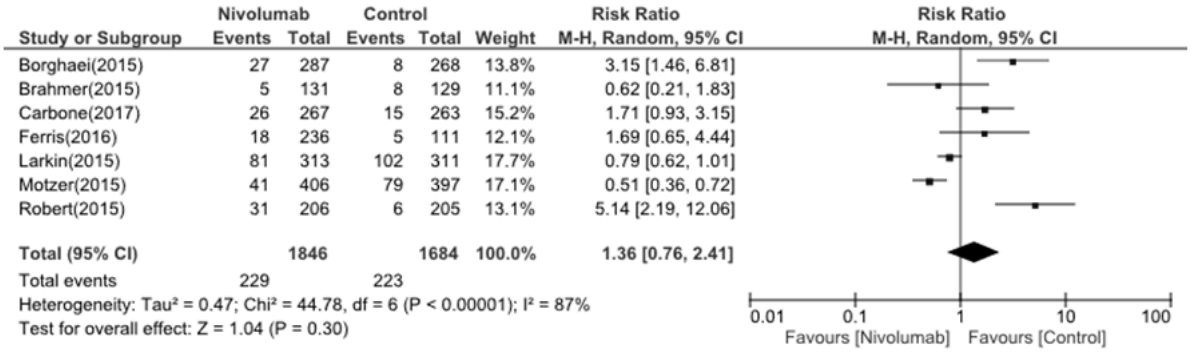
(J) Alopecia



(K) Neutropenia



(L) Rash



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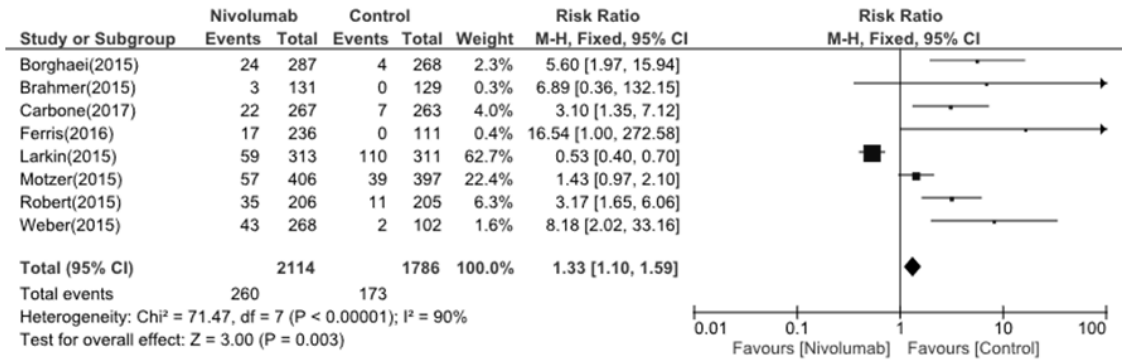
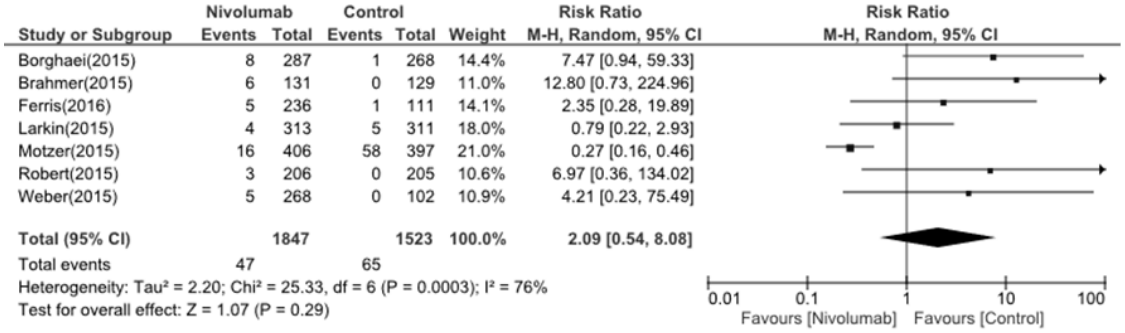
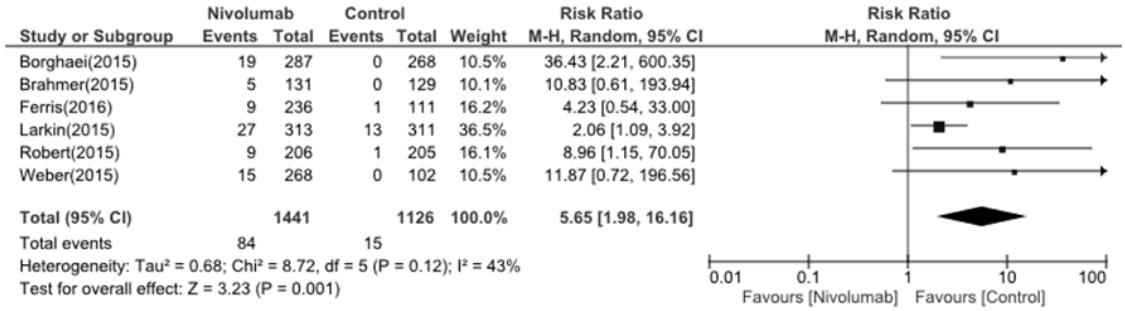
(M) Pruritus



(N) Pneumonitis



(O) Hypothyroidism



(P) Hyperthyroidism

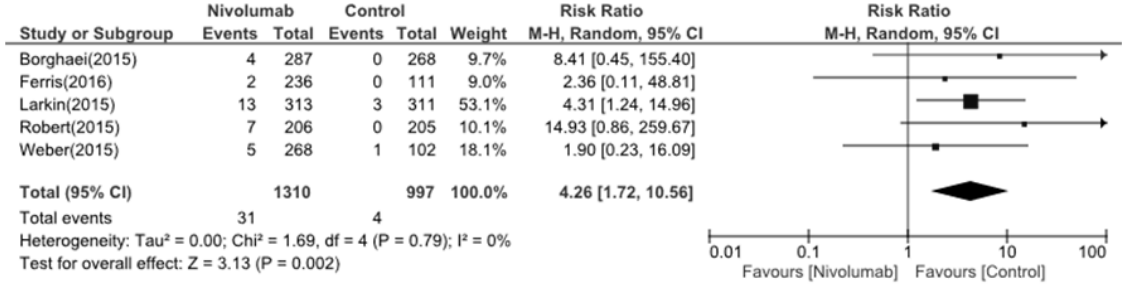


Figure 2. Forrest plot showing the risk ratio for adverse events in patients treated with nivolumab versus control. The pooled risk ratio was calculated with random effects according to the Mantel-Haenszel(M-H) method. (A) Any adverse events (All-Grade), (B) Any adverse events (Grade≥3), (C) Fatigue, (D) Nausea, (E) Vomiting, (F) Decreased appetite, (G) Diarrhea, (H) Asthenia, (I) Anemia, (J) Alopecia, (K) Neutropenia, (L) Rash, (M) Pruritus, (N) Pneumonitis, (O) Hypothyroidism, (P) Hyperthyroidism

Table 2 The pooled risk difference (RD) and the number needed to harm (NNH) for individual adverse events in patients receiving nivolumab compared with control.

Adverse events	RD (95% CI) [a)]	NNH
Fatigue	−0.13 (−0.27, 0.01)	8
Nausea	−0.17 (−0.26, −0.06)	6
Vomiting	−0.09 (−0.14, −0.03)	11
Decreased appetite	−0.06 (−0.10, −0.03)	17
Diarrhea	−0.07 (−0.012, −0.03)	14
Asthenia	−0.07 (−0.09, −0.04)	14
Anemia	−0.17 (−0.30, −0.03)	6
Alopecia	−0.15 (−0.27, −0.03)	7
Neutropenia	−0.20 (−0.27, −0.12)	5
Rash	0.01 (−0.05, 0.07)	100
Pruritus	0.03 (0.01, 0.05)	33
Pneumonitis	0.00 (−0.03, 0.03)	-
Hypothyroidism	0.05 (0.03, 0.06)	20
Hyperthyroidism	0.02 (0.01, 0.03)	50

a) The pooled risk difference was calculated with random effects according to the Mantel-Haenszel (M-H) method. CI: confidence interval.

gastrointestinal, pulmonary, hepatic, and endocrine toxicities[16-27].Although most irAEs can be well controlled by supportive treatment and glucocorticoids, fatal irAEs are an increasing concern regarding the safety of ICIs and patients' tolerability. Clinicians need to be aware of these safety profiles of ICIs and manage them appropriately according to the algorithm for diagnosis and treatment.

Our study has some limitations. First, the results described here are affected by the limitations of individual clinical trials that were selected for our meta-analysis. As six of eight included trials used an open-label design, these trials might have affected the reliability of the results because of observation bias. Second, similarly to most other meta-analyses[16-27], we extracted data from published articles without individual patient data. Therefore, variables at the patient level were not included in the analysis. Thus, we could not establish risk factors associated with the development of toxicities. Third, the patients in studies selected for our meta-analysis were a select group of patients with good performance status who were recruited into clinical trials. The actual incidence of toxicities in patients with organ dysfunction is likely to be higher in real-world clinical practice. Fourth, in our meta-analysis there was evidence of significant heterogeneity between studies in several comparisons, which could be caused by different stage of disease (untreated or refractory), different underlying malignancy and diversity of treatment modalities in controls arms in eight randomized clinical trials. The treatment regimens in control arms considered as standard care options in each of the tumors included docetaxel, dacarbazine, everolimus, ipilimumab, cetuximab, methotrexate, carboplatin combined with paclitaxel. This heterogeneity might have affected the reliability of the results.

Conclusion

We conducted a meta-analysis to summarize current knowledge regarding the safety profile in nivolumab therapy. Nivolumab therapy was well tolerated, associated with a significant lower risk of many treatment-related symptoms (fatigue, nausea, vomiting, decreased appetite, diarrhea, asthenia, anemia, alopecia and neutropenia), but a significant higher risk of irAEs including pruritus, hypothyroidism and hyperthyroidism. Clinicians need to be aware of these safety profiles of nivolumab and manage them appropriately according to the algorithm for diagnosis and treatment.

Author's Note

HS designed the study and drafted the manuscript. HS, HY, YM and YB searched the literature, reviewed the literature and screened the record. HS, HY, YM and YB extracted the data, performed the statistical analysis and assessed the quality of studies. All authors contributed to data review and interpretation and manuscript revision. All authors have read and approved the final manuscript.

Declaration of Conflicting Interests

The authors declare there are no conflicts of interest.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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