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ORIGINAL RESEARCH

Evidence from a meta-analysis: is nivolumab neurotoxic in cancer patients?

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Xiangyi Kong[1,2]
Yanguo Kong[1]

[1]Department of Neurosurgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Dongcheng District, Beijing, People's Republic of China; [2]Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Harvard University, Boston, MA, USA

Abstract: The aim of this study was to summarize the findings of previous studies focusing on whether the risks of certain neurotoxicities are correlated to the programmed death 1 (PD-1) inhibitor nivolumab versus other chemotherapy or immunotherapy drugs. Six eligible studies, including 3,023 patients, were considered in the meta-analysis. The risk ratios (RRs) of fatigue, headache, dysgeusia, vertigo, paresthesia, anxiety or malaise and peripheral neuropathy were 0.908 (95% confidence interval [95% CI]: 0.724, 1.138; *P*=0.402), 0.841 (95% CI: 0.606, 1.168; *P*=0.302), 0.423 (95% CI: 0.132, 1.357; *P*=0.148), 0.762 (95% CI: 0.475, 1.223; *P*=0.261), 0.411 (95% CI: 0.232, 0.730; *P*=0.002), 1.049 (95% CI: 0.094, 11.752; *P*=0.969) and 0.192 (95% CI: 0.039, 0.935; *P*=0.041), respectively. Our analysis supported that the PD-1 inhibitor nivolumab did not cause increased or decreased risks of fatigue, headache, dysgeusia, vertigo and anxiety or malaise and was associated with decreased risks of paresthesia and peripheral neuropathy as compared with controls. These outcomes indicated that although clinicians should be attentive of the side effects of nivolumab, in terms of nervous system side effects, nivolumab is generally safe.

Keywords: PD-1 inhibitor, nivolumab, neurotoxicity, cancer

Introduction

Immunotherapy has been considered to be one of the most important breakthroughs in cancer treatments in the last decade. Immune checkpoint inhibitors against cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death 1 (PD-1) topped the list of the most noticeable and encouraging cancer therapies.[1,2] As PD-1 is able to limit cytokine secretion, function and proliferation of T-cells, especially in cancer-bearing hosts or chronic viral infections, PD-1 inhibitors have been developed and have achieved many achievements.[3] On the surface of tumor-infiltrating T-cells and circulating T-cells from melanoma patients, high levels of PD-1s have been tested, indicating that PD-1 inhibition might prevent cancer-correlated exhaustion of T-cells.[4] The first batch of PD-1-inhibiting agents includes pembrolizumab (also named lambrolizumab) and nivolumab. Nivolumab, scientifically named BMS-936558/MDX-1106, is a fully human immunoglobulin G4 (IgG4) monoclonal PD-1-blocking antibody that abrogates its interaction with PD-L1 and PD-L2.[5] In several of Phase III studies regarding non-small-cell lung cancer (NSCLC), renal cancer and melanoma, nivolumab administration has been shown to generate survival benefits. Because of this, the US Food and Drug Administration (FDA) approved its marketing in 2015.[6]

Unlike traditional antineoplastic chemotherapies, nivolumab can potentially lead to some side effects, such as gastrointestinal, hepatotoxic, orthopedic and mucocutaneous toxicities.[7] However, the incidence of nervous system adverse effects among

Correspondence: Yanguo Kong
Department of Neurosurgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, No 1 Shuaifuyuan, Dongcheng District, Beijing 100730, People's Republic of China
Email kong0126@126.com

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clinical studies (such as fatigue, headache, dysgeusia, vertigo, paresthesia, anxiety or malaise and peripheral neuropathy) has shown a great variation.[8–13] Until now, there are no comprehensive reviews and analyses to synthesize these data; thus, the overall neurotoxicity risks caused by nivolumab need to be further clarified. We performed this meta-analysis of randomized clinical studies to assess the overall risks of neurotoxicities in cancer patients receiving nivolumab as the anticancer therapy.

Methods

Overview of systematic literature review

We performed a systematic literature review to identify all studies that detailed PD-1 inhibitor nivolumab with its toxic and side effects.

Search strategy and study selection

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, 2 authors independently searched the databases Embase, PubMed, Chinese National Knowledge Infrastructure (CNKI) and Web of Knowledge (time: approximately September 2016) to enroll studies that met the inclusion criteria. The search term was "nivolumab". Search results were limited to randomized clinical studies without language limitations. If there were duplicate studies, only the most updated and complete ones were adopted. If there were disagreements between the 2 investigators, a discussion would be carried out or a third investigator would intervene. Inclusion criteria and exclusion criteria are listed in Table 1. We also reviewed related references to identify other potentially eligible studies.

Table 1 Inclusion and exclusion criteria for study selection in this meta-analysis

Number	Inclusion criteria
1	Randomized Phase II and III studies in patients with solid tumors.
2	The outcome of the study includes neurotoxicities such as fatigue, headache, dysgeusia, vertigo, paresthesia, anxiety or malaise and peripheral neuropathy.
3	Participants received treatment with nivolumab.
4	The RR with a 95% CI of the risk of selected neurotoxicities associated with nivolumab could be obtained from articles directly or calculated based on the figures or tables given in articles or through contacting the authors.
5	For the duplicate articles, only the most complete or the most newly published one was included.
	Exclusion criteria
1	Phase I trials were excluded.
2	The treatments in experimental groups should not include other drugs.

Abbreviations: CI, confidence interval; RR, risk ratio.

Data extraction and clinical end points

We retrieved the data independently. We gathered the following data: author name, publication year, phase of the trial, total number of patients enrolled for analysis, number of events for neurotoxicities (fatigue, headache, dysgeusia, vertigo, paresthesia, anxiety or malaise and peripheral neuropathy) and treatment arms. Jadad score scale was used to evaluate the methodological qualities of these studies (Table 2).

Any discrepancies between us were resolved by consensus. The common terminology criteria of adverse events (CTCAE, version 4.0) were used to record the toxicities and their grades in the included clinical trials.[14] In these criteria, Grade 1 means mild, asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated; Grade 2 means moderate, minimal, local or noninvasive intervention indicated, limiting age-appropriate instrumental activities of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc); Grade 3 means severe or medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, limiting self-care activities of daily living (bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden); Grade 4 means life-threatening consequences, urgent intervention indicated; and Grade 5 means death related to adverse effects.

Data synthesis

Differences were expressed as risk ratios (RRs) with 95% confidence intervals (95% CIs). The Labbe plot, I^2 test and Cochran's Q-test (Table 3) were conducted to estimate the heterogeneity among the studies.[15,16] If no evidence of statistical heterogeneity was detected, we chose to use a fixed-effects model. Otherwise, the random-effects model of Laird and DerSimonian was adopted. To assess the stability of the pooled values, we also performed sensitivity analyses (Table 3).[15] Using contour-enhanced funnel plots (Table 3), potential publication biases were estimated. Since only 6 studies were included, meta-regression analyses were not performed.

The P-value <0.05 was deemed as statistical significance. The statistical analysis was done through Review Manager 5.3 (The Cochrane Collaboration, Oxford, UK) and STATA 12.0 (StataCorp LP, College Station, TX, USA) software.

Table 2 Baseline characteristics of included studies comparing nivolumab to other drugs

Study	Year	Country	Study type	Treatment arms	Indication	Fatigue[a]	Headache[a]	Dysgeusia[a]	Vertigo[a]	Paresthesia[a]	Anxiety malaise[a]	Peripheral neuropathy[a]
Robert et al[12]	2015	France	Phase III	Arm A: nivolumab 3 mg/kg of body weight every 2 weeks (206 pts) Arm B: dacarbazine (205 pts)	Stage III or IV unresectable melanoma without a BRAF mutation	41 (20%) versus 30 (14.6%)	9 (4.4%) versus 14 (6.8%)	6 (2.9%) versus 2 (1%)	2 (1%) versus 5 (2.4%)	2 (1%) versus 7 (3.4%)	1 (0.5%) versus 4 (2%)	–
Weber et al[13]	2015	USA	Phase III	Arm A: nivolumab 3 mg/kg of body weight every 2 weeks (268 pts) Arm B: investigator choice chemotherapy (102 pts)	Patients with advanced melanoma who progressed after anti-CTLA-4 treatment	67 (25%) versus 35 (34%)	–	–	–	–	–	–
Larkin et al[10]	2015	USA	Phase III	945 patients were randomized in a 1:1:1 fashion into: 1) nivolumab 3 mg/kg combined with placebo (316 pts) 2) ipilimumab (3 mg/kg) combined with nivolumab (1 mg/kg) (314 pts) 3) ipilimumab (3 mg/kg) combined with placebo (315 pts)	Advanced melanoma	107 (34.2%) versus 87 (28%)	23 (7.3%) versus 24 (7.7%)	–	–	–	–	–
Borghaei et al[8]	2015	USA	Phase III	Arm A: nivolumab 3 mg/kg of body weight every 2 weeks (292 pts) Arm B: docetaxel (290 pts)	Advanced non-squamous cell NSCLC	91 (32%) versus 102 (38%)	29 (10%) versus 32 (12%)	7 (2%) versus 27 (10%)	25 (9%) versus 24 (9%)	12 (4%) versus 23 (9%)	16 (6%) versus 5 (2%)	9 (3%) versus 25 (9%)
Brahmer et al[9]	2015	USA	Phase III	Arm A: nivolumab 3 mg/kg of body weight every 2 weeks (131 pts) Arm B: docetaxel (129 pts)	Advanced squamous cell NSCLC	21 (16%) versus 42 (33%)	–	–	2 (2%) versus 7 (5%)	2 (2%) versus 7 (5%)	–	1 (1%) versus 15 (12%)
Motzer et al[11]	2015	USA	Phase III	821 patients were randomly assigned (in a 1:1 ratio) to receive 3 mg of nivolumab per kilogram of body weight intravenously every 2 weeks or a 10 mg everolimus tablet orally once daily	Advanced clear-cell renal cell carcinoma for which they had received previous treatment with 1 or 2 regimens of antiangiogenic therapy	134 (33%) versus 134 (34%)	–	11 (3%) versus 51 (13%)	–	–	–	–

Notes: [a]Data presented as number of patients with versus number of patients without.
Abbreviations: pts, patients; BRAF, B-Raf; CTLA-4, cytotoxic T lymphocyte antigen-4; NSCLC, non-small-cell lung cancer.

Table 3 The statistical methods used in this meta-analysis and their explanation

Statistical means	Goals and usages	Explanation
Labbe plot	To evaluate heterogeneity between the included studies	In Labbe figure, if the points basically present as a linear distribution, it can be taken as an evidence of homogeneity.
Cochran's Q test	To evaluate heterogeneity between the included studies	Cochran's Q test is an extension to the McNemar test for related samples that provides a method for testing for differences between 3 or more matched sets of frequencies or proportions. Heterogeneity was also considered significant if $P<0.05$ using the Cochran's Q test.
I^2 index test	To evaluate heterogeneity between the included studies	The I^2 index measures the extent of true heterogeneity dividing the difference between the result of the Q test and its degrees of freedom (k – 1) by the Q value itself and multiplied by 100. I^2 values of 25%, 50% and 75% were used as evidence of low, moderate and high heterogeneity, respectively.
Sensitivity analysis	To examine the stability of the pooled results	A sensitivity analysis was performed using the one-at-a-time method, which involved omitting one study at a time and repeating the meta-analysis. If the omission of one study significantly changed the result, it implied that the result was sensitive to the studies included.
Contour-enhanced funnel plot	Publication bias test	Visual inspection of the contour-enhanced funnel plots was used to assess potential publication bias. Asymmetry in the plots, which may be due to studies missing on the left-hand side of the plot that represents low statistical significance, suggested publication bias. If studies were missing in the high statistical significance areas (on the right-hand side of the plot), the funnel asymmetry was not considered to be due to publication bias.

Results

Search results and characteristics of the studies

The article search process was conducted as shown in Figure 1. A total of 6 articles involving 3,023 patients finally met the inclusion criteria.[8–13] All the 6 studies were written in English and were randomized Phase III trials. Five of the 6 studies[8–11,13] were carried out in the US and 1 in France.[12] Their baseline characteristics, including treatment arms, interventions and clinical indications, are shown in Table 2.

Quality of the included studies

Table 4 shows the different elements of the Jadad scale for all the included studies in terms of blinding, randomization, an account of all patients and the overall score.

Meta-analysis regarding nivolumab and neurotoxicity

Fatigue was reported in all the 6 studies;[8–13] headache,[8,10,12] dysgeusia,[8,11,12] vertigo[8,9,12] and paresthesia[8,9,12] were reported in 3 of the 6 studies; anxiety or malaise[8,12] and peripheral neuropathy[8,9] were, respectively, reported in 2 studies. RRs of all-grade neurotoxic events were calculated on the basis of the included studies. For example, in the case of fatigue, from the Labbe figure (Figure 2A), the points did not present as a linear distribution, which can be taken as evidence of heterogeneity among the included studies (Q=18.47, *df*=5, I^2=72.9%, *P*=0.002). Consequently, a random-effects model was utilized to summarize the data. As revealed in Figure 3A, the forest plot demonstrated that nivolumab administration did not increase or decrease the fatigue risk (RR 0.908, 95% CI 0.724, 1.138; *P*=0.402).

We also tested the correlation between the risks of headache, dysgeusia, vertigo, paresthesia, anxiety or malaise and peripheral neuropathy and nivolumab administration (versus dacarbazine, docetaxel, ipilimumab or everolimus according to the effect models) (headache: Q=0.63, *df*=2, I^2=0.0%, *P*=0.730, fixed-effects model, Figure 2B; dysgeusia: Q=9.42, *df*=2, I^2=78.8%, *P*=0.009, random-effects model, Figure 2C; vertigo: Q=2.99, *df*=2, I^2=33.2%, *P*=0.224, fixed-effects model, Figure 2D; paresthesia: Q=0.68, *df*=2, I^2=0.0%, *P*=0.710, fixed-effects model, Figure 2E; anxiety or malaise: Q=4.17, *df*=1, I^2=76.0%, *P*=0.041, random-effects model, Figure 2F; peripheral neuropathy: Q=2.42, *df*=1, I^2=58.7%, *P*=0.120, random-effects model). The results also suggest no significant differences in terms of headache (RR 0.841, 95% CI 0.606, 1.168; *P*=0.302; Figure 3B), dysgeusia (RR 0.423, 95% CI 0.132, 1.357; *P*=0.148; Figure 3C), vertigo (RR 0.762, 95% CI 0.475, 1.223; *P*=0.261; Figure 3D) and anxiety or malaise (RR 1.049, 95% CI 0.094, 11.752; *P*=0.969; Figure 3F). In addition, regarding paresthesia and peripheral neuropathy, nivolumab was even statistically associated with decreased risks (paresthesia: RR 0.411,

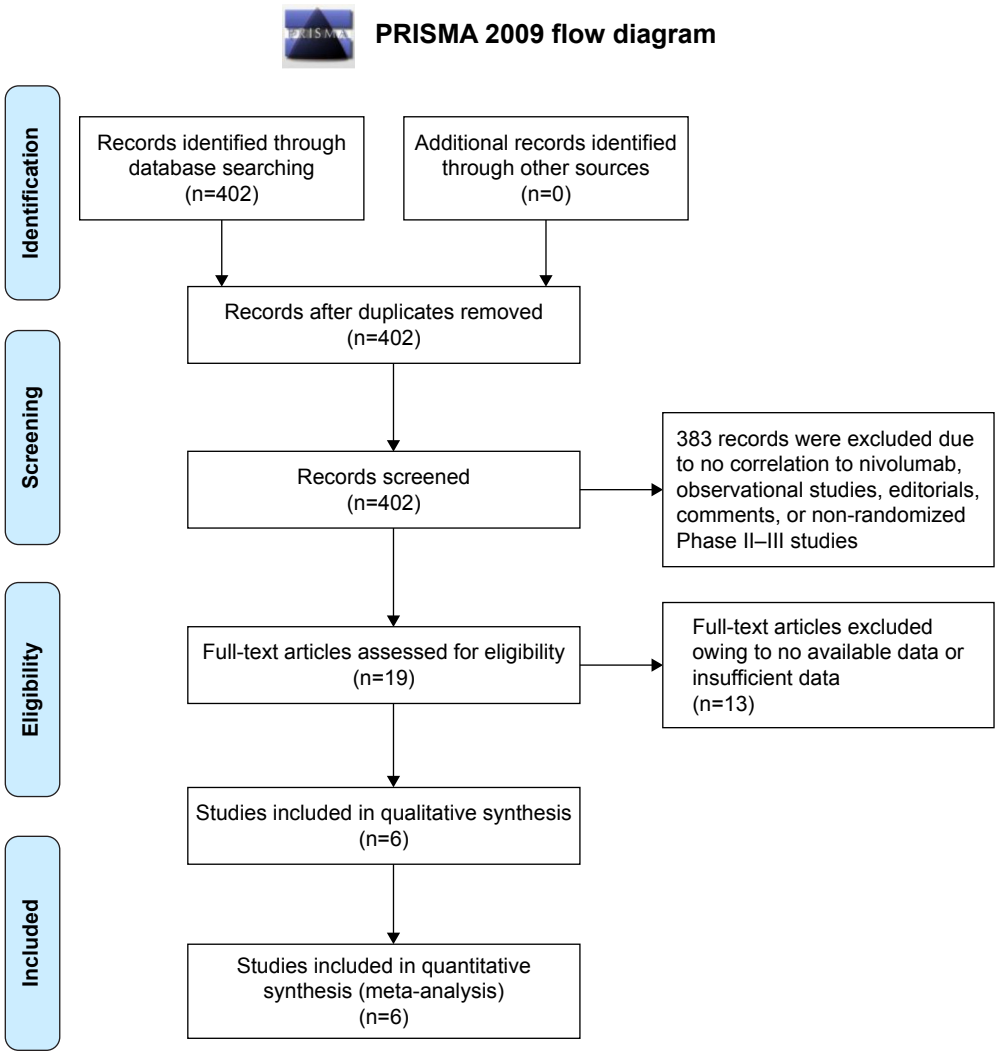


Figure 1 Literature search and selection of articles.
Note: Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. Creative Commons license and disclaimer available from: http://creativecommons.org/licenses/by/4.0/legalcode.[20]
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews.

95% CI 0.232, 0.730; *P*=0.002; Figure 3E; peripheral neuropathy: RR 0.192, 95% CI 0.039, 0.935; *P*=0.041; Figure 3G).

Sensitivity analysis and publication bias

To assess whether a single study could affect the final RRs, each individual study was removed one time and the data were re-pooled. The analysis results demonstrated that the pooled RRs were not affected by deleting every single study (Figure 2G–K). The contour-enhanced funnel plots were employed to reveal the publication bias, showing that the studies had missing areas for high statistical significance (in the right-hand side of the plot), indicating that there was no publication bias in the study (Figure 2L–P).

Table 4 Jadad quality assessment of the included studies

Study	Year	Country	Study type	Randomization	Blinding	An account of all patients	Overall score
Robert et al[12]	2015	France	Phase III	2	2	1	5
Weber et al[13]	2015	USA	Phase III	2	0	1	3
Larkin et al[10]	2015	USA	Phase III	2	2	1	5
Borghaei et al[8]	2015	USA	Phase III	2	0	1	3
Brahmer et al[9]	2015	USA	Phase III	2	0	1	3
Motzer et al[11]	2015	USA	Phase III	2	0	1	3

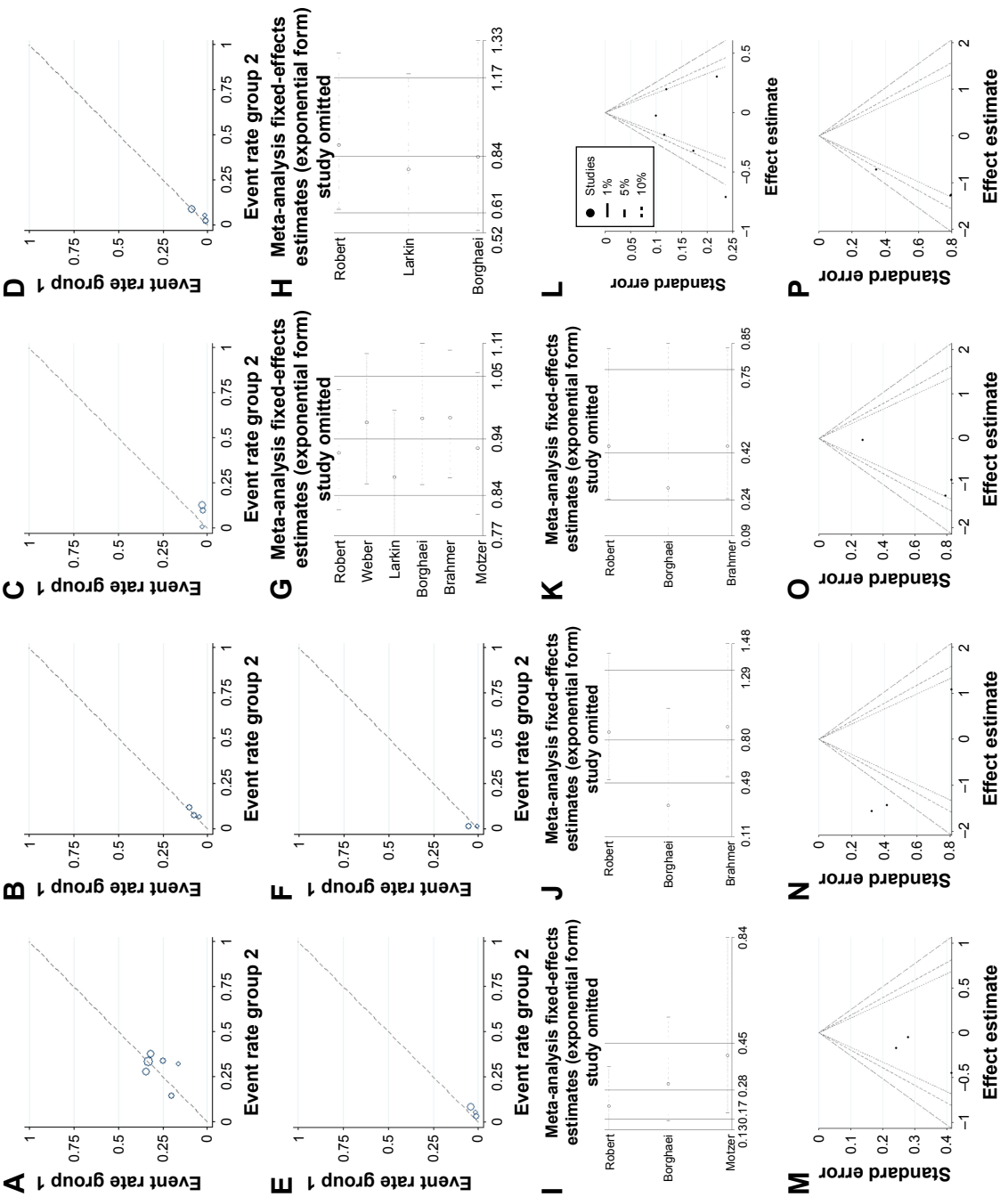
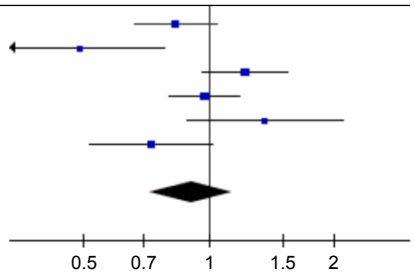


Figure 2 Labbe plots, sensitivity analysis plots and contour-enhanced funnel plots of the included studies focusing on the risk of selected neurotoxicity associated with the PD-1 inhibitor nivolumab.
Notes: Labbe plots concerned fatigue (**A**), headache (**B**), dysgeusia (**C**), vertigo (**D**), paresthesia (**E**) and anxiety or malaise (**F**), respectively. Sensitivity analysis concerned fatigue (**G**), headache (**H**), dysgeusia (**I**), vertigo (**J**) and paresthesia (**K**). Contour-enhanced funnel plots concerned fatigue (**L**), headache (**M**), dysgeusia (**N**), vertigo (**O**) and paresthesia (**P**). Sensitivity analysis was performed using the one-at-a-time method (**G**–**K**).
Abbreviation: PD-1, programmed death-1.

A Forest plot of relative risk (RR) of fatigue associated with nivolumab versus control

Study or subgroup	Nivolumab Events	Total	Control Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI
Borghaei et al[8]	91	287	102	268	19.5	0.83 (0.66, 1.05)
Brahmer et al[9]	21	131	42	129	12.0	0.49 (0.31, 0.78)
Larkin et al[10]	107	313	87	311	19.2	1.22 (0.97, 1.55)
Motzer et al[11]	134	406	134	397	20.6	0.98 (0.80, 1.19)
Robert et al[12]	41	206	30	205	13.0	1.36 (0.89, 2.09)
Weber et al[13]	67	268	35	102	15.7	0.73 (0.52, 1.02)
Total (95% CI)		**1,611**		**1,412**	**100**	**0.91 (0.72, 1.14)**
Total events	461		430			

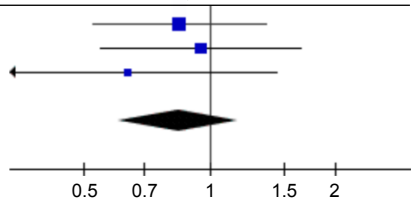
Heterogeneity: τ^2=0.05; χ^2=18.47, *df*=5 (*P*=0.002); I^2=73%
Test for overall effect: *Z*=0.84 (*P*=0.40)



B Forest plot of relative risk (RR) of headache associated with nivolumab versus control

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight (%)	Risk ratio M–H, fixed, 95% CI
Borghaei et al[8]	29	287	32	268	46.5	0.85 (0.53, 1.36)
Larkin et al[10]	23	313	24	311	33.8	0.95 (0.55, 1.65)
Robert et al[12]	9	206	14	205	19.7	0.64 (0.28, 1.44)
Total (95% CI)		**806**		**784**	**100**	**0.84 (0.61, 1.17)**
Total events	61		70			

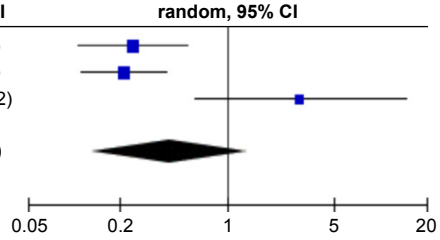
Heterogeneity: χ^2=0.63, *df*=2 (*P*=0.73); I^2=0%
Test for overall effect: *Z*=1.03 (*P*=0.30)



C Forest plot of relative risk (RR) of dysguesia associated with nivolumab versus control

Study or subgroup	Nivolumab Events	Total	Control Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI
Borghaei et al[8]	7	287	27	268	36.5	0.24 (0.11, 0.55)
Motzer et al[11]	11	406	51	397	39.2	0.21 (0.11, 0.40)
Robert et al[12]	6	206	2	205	24.3	2.99 (0.61, 14.62)
Total (95% CI)		**899**		**870**	**100**	**0.42 (0.13, 1.36)**
Total events	24		80			

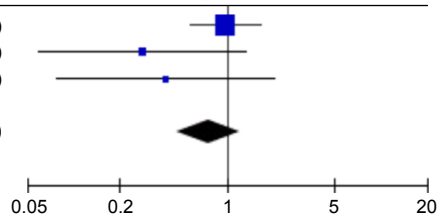
Heterogeneity: τ^2=0.80; χ^2=9.42, *df*=2 (*P*=0.009); I^2=79%
Test for overall effect: *Z*=1.45 (*P*=0.15)



D Forest plot of relative risk (RR) of vertigo associated with nivolumab versus control

Study or subgroup	Nivolumab Events	Total	Control Events	Total	Weight (%)	Risk ratio M–H, fixed, 95% CI
Borghaei et al[8]	25	287	24	268	67.3	0.97 (0.57, 1.66)
Brahmer et al[9]	2	131	7	129	19.1	0.28 (0.06, 1.33)
Robert et al[12]	2	206	5	205	13.6	0.40 (0.08, 2.03)
Total (95% CI)		**624**		**602**	**100**	**0.76 (0.48, 1.22)**
Total events	29		36			

Heterogeneity: χ^2=2.99, *df*=2 (*P*=0.22); I^2=33%
Test for overall effect: *Z*=1.13 (*P*=0.26)



E Forest plot of relative risk (RR) of paresthesia associated with nivolumab versus control

Study or subgroup	Nivolumab Events	Total	Control Events	Total	Weight (%)	Risk ratio M–H, fixed, 95% CI
Borghaei et al[8]	12	287	23	268	62.8	0.49 (0.25, 0.96)
Brahmer et al[9]	2	131	7	129	18.6	0.28 (0.06, 1.33)
Robert et al[12]	2	206	7	205	18.5	0.28 (0.06, 1.35)
Total (95% CI)		**624**		**602**	**100**	**0.41 (0.23, 0.73)**
Total events	16		37			

Heterogeneity: χ^2=0.68, *df*=2 (*P*=0.71); I^2=0%
Test for overall effect: *Z*=3.03 (*P*=0.002)

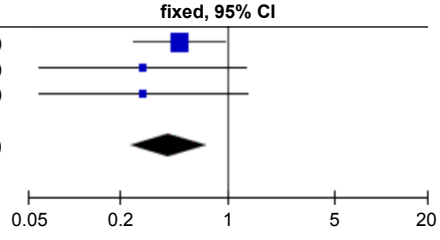


Figure 3 (*Continued*)

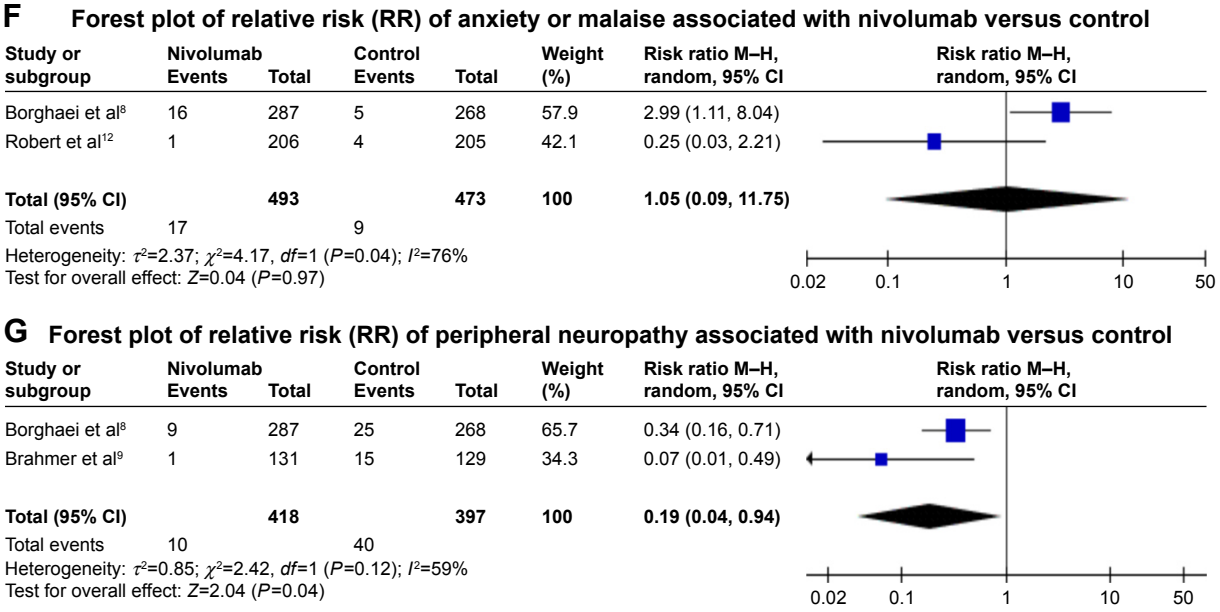


Figure 3 Forest plots (individual and pooled effects with 95% CI) regarding the risk of selected neurotoxicity of fatigue (**A**, random-effects model), headache (**B**, fixed-effects model), dysgeusia (**C**, random-effects model), vertigo (**D**, fixed-effects model), paresthesia (**E**, fixed-effects model), anxiety or malaise (**F**, random-effects model) and peripheral neuropathy (**G**, random-effects model) associated with nivolumab versus controls.
Abbreviations: RR, risk ratio; CI, confidence interval; *df*, degree of freedom; M–H, Mantel–Haenszel.

Discussion

In the light of our present knowledge, this analysis is the most updated one to provide an evaluation of the neurotoxicities, including fatigue, headache, dysgeusia, vertigo, paresthesia, anxiety or malaise and peripheral neuropathy, in cancer patients treated with nivolumab. This meta-analysis summarized 6 Phase III randomized clinical trials, demonstrating that nivolumab did not cause increased or decreased risks of fatigue, headache, dysgeusia, vertigo and anxiety or malaise and was associated with decreased risks of paresthesia and peripheral neuropathy as compared with controls.

Normally, T-cells have the capacity to attack cancer cells; meanwhile, T-cells have to be regulated properly through certain inhibitory checkpoints to be controlled to not attack normal cells and normal tissues.[17] According to this theory, inhibiting these checkpoints is likely to activate T-cells and lead them to have stronger anticancer responses.[18] Currently, PD-1, as an inhibitory receptor, is one of the most topical, and its antagonist nivolumab has been developed as a US FDA-approved anticancer drug for melanomas, which is based on the findings of a mound of Phase II–III studies.[6] Moreover, nivolumab has also been evaluated for its effects on anti-gastrointestinal cancer, prostate cancer and lung cancer. According to the National Cancer Institute (NCI), nivolumab is approved to be used alone or with other drugs to treat: 1) classical Hodgkin's lymphoma that has gotten worse after an autologous stem cell transplant and treatment with brentuximab vedotin; 2) melanoma that cannot be removed by surgery or that has metastasized (spread to other parts of the body); 3) NSCLC that has metastasized. It is used in patients whose disease got worse during or after treatment with platinum chemotherapy; and 4) renal cell carcinoma (a type of kidney cancer) that is advanced. It is used in patients who have already received angiogenesis inhibitor therapy. Pembrolizumab is another drug that has been recently approved by the US FDA. Formerly known as MK-3475 or lambrolizumab, it is a high affinity humanized IgG4 monoclonal antibody targeting PD-1, having been approved to treat: 1) melanoma that cannot be removed by surgery or that has metastasized (spread to other parts of the body); 2) NSCLC that has metastasized and 3) squamous cell carcinoma of the head and neck that has metastasized or recurred (come back) in patients whose disease got worse during or after treatment with platinum chemotherapy. With respect to the differential activity of nivolumab and pembrolizumab, the former is a fully human IgG4 PD-1 immune checkpoint inhibitor antibody.

The nervous system adverse effects have been regarded as an emerging reason for treatment discontinuation or interruption in some studies. Although neurotoxicities are not common, at present, no effective methods have been developed to predict high-risk patients, necessitating careful monitoring of laboratory and clinical parameters. Neurotoxicities have also been reported in a number of other targeted anticancer therapeutics and have been linked to noncompliance with many of them.[8–13] In light of this, we combined PubMed, Google

Scholar, Embase and CNKI databases to systematically analyze the correlations between the risks of fatigue, headache, dysgeusia, vertigo, paresthesia, anxiety or malaise and peripheral neuropathy and nivolumab. The results of our study demonstrated that when compared with controls, nivolumab did not statistically increase the risks of selected neurotoxicity of paresthesia and peripheral neuropathy. Therefore, although clinicians should be attentive to the side effects of nivolumab, in terms of nervous system side effects, nivolumab is safe.

On a contour-enhanced funnel plot, contours of statistical significance are overlaid on the funnel plot. Adding contours of statistical significance facilitates the assessment of whether the areas where studies exist are areas of statistical significance and whether the areas where studies are potentially missing correspond to areas of low statistical significance. Generally, if studies appear to be missing in areas of low statistical significance, then it is very possible that the asymmetry is due to publication bias. Conversely, if the areas where studies are perceived to be missing are areas of high statistical significance, then publication bias is not the cause of funnel asymmetry.[19] In our meta-analysis, the funnel plot indicated no publication bias.

The results of our study should be interpreted with caution because the meta-analysis is at a study level, thus limiting variables at patient levels might not be worked out. So, we could not confirm if there are any additional potential risk factors correlated to developments of neurotoxicities.

Conclusion

Our analysis supported that the PD-1 inhibitor nivolumab did not cause increased or decreased risks of fatigue, headache, dysgeusia, vertigo and anxiety or malaise and was associated with decreased risks of paresthesia and peripheral neuropathy as compared with controls. These outcomes indicated that in terms of nervous system side effects, nivolumab is safe.

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Disclosure

The authors report no conflicts of interest in this work.

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