



Risk of Musculoskeletal Complications in Cancer Patients Treated with Nivolumab

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Abstract

Object: We performed a meta-analysis of the risk of selected musculoskeletal toxicities associated with the PD-1 inhibitor Nivolumab versus other drugs.

Methods: Several databases were searched. We assess the relevant articles and relative risks (RRs) with 95% confidence intervals (95% CIs) were estimated regarding the risk of arthralgia, asthenia, myalgia and extremity pain and Nivolumab versus control. Heterogeneity, sensitivity analysis and publication bias of the included studies were also analyzed.

Results: There were 5 eligible studies, including 2220 patients that were considered in the present meta-analysis. The RRs of arthralgia, asthenia, myalgia and extremity pain were 1.116 (95% CI: 0.669, 1.860; p=0.675), 0.846 (95% CI: 0.657, 1.090; p=0.197), 0.658 (95% CI: 0.141, 3.062; p=0.593), 1.037 (95% CI: 0.647, 1.662; p=0.882), respectively.

Conclusion: Our results suggested that PD-1 inhibitor Nivolumab was not associated with an increased risk of musculoskeletal toxicities including arthralgia, asthenia, and myalgia and extremity pain compared with control.

Keywords: Musculoskeletal complications; Cancer patients; Nivolumab; Meta-analysis

Introduction

Immunotherapy has been considered to be one of the most important breakthroughs in cancer treatments in the last decade. Immune checkpoint inhibitors against 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 T-cells' cytokine secretion, function and proliferation 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 level of PD-1s have been tested, indicating that PD-1 inhibition might prevent cancer-correlated T-cells' exhaustion [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-L2 and PD-L1 [5]. In an amount of phase III studies regarding non-small cell lung cancer (NSCLC), renal cancer and melanoma, Nivolumab administration has shown survival benefit. Because of this, in 2015, US Food and Drug Administration (FDA) approved its marketing [6]. Different from

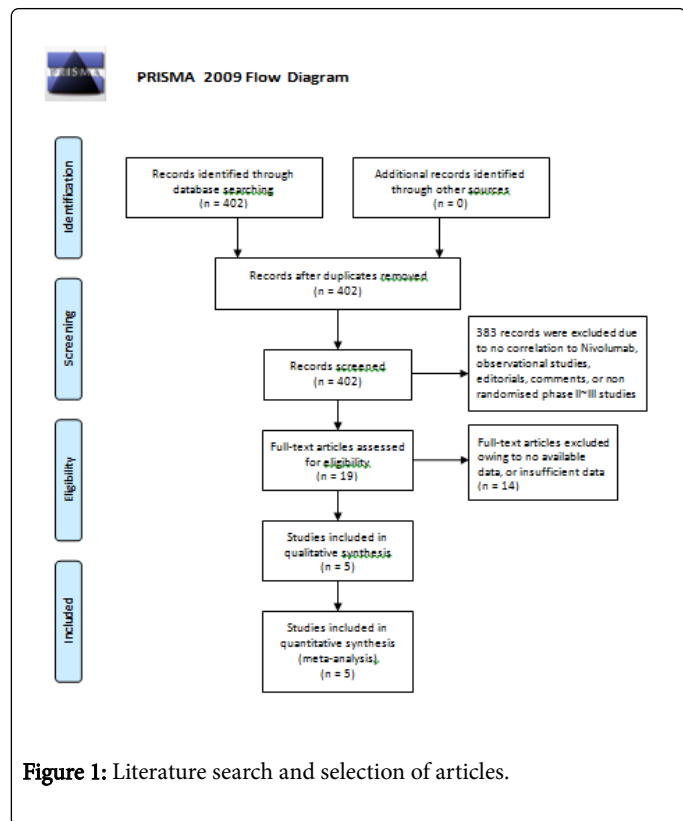
traditional antineoplastic chemotherapies, Nivolumab can potentially lead to some side-effects, such as gastrointestinal, hepatotoxic, orthopedic and mucocutaneous toxicities [7]. Nevertheless, large variations in the incidence of musculoskeletal adverse events among clinical trials such as asthenia, arthralgia, myalgia, et al still exist [8-10]. Until now, there is still no comprehensive review and analysis to synthesize those data, thus the overall musculoskeletal risks caused by Nivolumab needs to be further clarified. We conducted a meta-analysis of randomized clinical trials to determine the overall risk of musculoskeletal disorders in cancer patients treated with Nivolumab.

Material and Methods

Search strategy and study selection

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, two authors independently searched the database of Embase, PubMed, Chinese National Knowledge Infrastructure (CNKI), and Web of Knowledge (time:~September 1st, 2016) to enroll studies which met the criteria. The search term was "Nivolumab". Search results were limited to randomized clinical studies without language limitation. If there were duplicate literatures, only the most updated and complete ones were adopted. If there were disagreements between the two investigators, a discussion would be carried out or a third investigator would

intervene. Inclusion criteria and exclusion criteria have been listed in (Table 1). We also reviewed related references to find out other potentially eligible studies.



Data extraction and clinical endpoints

We extracted the data independently. We generally gathered the following data: author name, publication year, phase of the trial, total number of patients enrolled for analysis, number of events for musculoskeletal disorders (asthenia, arthralgia, myalgia and pain in extremity), and treatment arms. Jadad score scale was adopted to evaluate the methodological qualities of these literatures. 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 grade in the included clinical trials.

Number	Inclusion criteria
1	Randomized phase II and III studies in patients with solid tumors.
2	The outcome of the study include musculoskeletal toxicities like arthralgia, asthenia, myalgia and extremity pain
3	Participants received treatment with Nivolumab.
4	The relative risk (RR) with a 95% confidence interval (95% CI) of the risk of selected musculoskeletal toxicities 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.
Number	Inclusion criteria

1	Phase I trials were excluded.
2	The treatments in experimental groups should not include other drugs.

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

Data synthesis

Differences were expressed as RRs with 95% CIs. The Labbe plot, I² test and Cochran's Q-test (Table 2) were all conducted to estimate the heterogeneity among the studies [11,12]. In case no evidence of statistical heterogeneity was detected, we chose to use a fixed-effects model. Otherwise, Laird's and DerSimonian's random-effects model would be adopted. To access the stability of the pooled values, we also performed sensitivity analyses (explanation in Table 2) [12]. Potential publication bias was assessed by contour-enhanced funnel plots [13] (Table 2). Since only 5 studies were included, meta-regression analyses were not performed. P<0.05 was deemed as statistical significance. The statistical analysis was done through Review Manager 5.3 (The Cochrane Collaboration, Oxford, UK) and STATA 13.0 (StataCorp LP, College Station, TX, USA) software.

Statistic 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 three 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

Table 2: The statistical methods used in this meta-analysis and there explanation.

Results

Search results and characteristics of the studies

The article search process was performed as presented in (Figure 1). A total of 5 articles involving 2220 patients eventually met the

inclusion criteria [8-10,14,15]. All the 5 studies were written in English and were randomized phase III trials. Four studies were done in the US [8-10,14] and 1 in France [15]. Their baseline characteristics including treatment arms, interventions and clinical indications are shown in (Table 3).

Study	Year	Country	Study type	Treatment arms	Indication	Arthralgia	Asthenia	Myalgia	Extremity pain
Robert	2014	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	12 (5.8%) versus 3 (1.5%)	21 (10.2%) versus 25 (12.2%)	9 (4.4%) versus 2 (1.0%)	6 (2.9%) versus 3 (1.5%)
Weber	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	14 (5.2%) versus 12 (11.7%)	-	-	-
Larkin	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	24 (7.7%) versus 19 (6.1)	-	-	-
Borghaei	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	46 (16%) versus 32 (12%)	58 (21%) versus 62 (23%)	18 (6%) versus 35 (13%)	27 (9%) versus 27 (10%)
Brahmer	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	7 (5%) versus 9 (7%)	13 (10%) versus 18 (14%)	2 (2%) versus 13 (10%)	-

CTLA-4: Cytotoxic T Lymphocyte Antigen-4; NSCLC: Non-Small Cell Lung Cancer; BRAF: B-Raf.

Table 3: Baseline characteristics of included studies comparing Nivolumab to other drugs.

Quality of the included studies

(Table 4) shows various items of the Jadad scale for all included literatures, including blindings, randomizations and accounts of included patients in addition to the overall score [16].

Study	Year	Country	Study type	Randomization	Blinding	An account of all patients	Overall score
Robert	2014	France	Phase III	2	2	1	5
Weber	2015	USA	Phase III	2	0	1	3
Larkin	2015	USA	Phase III	2	2	1	5
Borghaei	2015	USA	Phase III	2	0	1	3
Brahmer	2015	USA	Phase III	2	0	1	3

Table 4: Jadad quality assessment of the included studies.

Meta-analysis regarding nivolumab and musculoskeletal toxicities

Arthralgia was reported in all 5 studies and it ranged from 11 to 51%; asthenia and myalgia were reported in 3 out of the 5 studies and they ranged from 3 to 32% and 3 to 32%, respectively; Extremity pain was reported in 2 out of the 5 studies and it ranged from 1 to 16%. A meta-analysis of the OR of all-grade adverse events was performed on the included randomized trials. Take arthralgia as an example. From the Labbe figure (Figure 2A), we can see the points did not present as a linear distribution, which can be taken as evidence of heterogeneity among these studies ($Q=10.16$, $d.f.=4$, $I^2=95.8\%$, $p=0.038$). Consequently, we summarized the data with a random effects model. As revealed in (Figure 3A), the forest plot demonstrated that Nivolumab administration did not increase the risk of arthralgia (RR 1.116, 95% CI 0.669, 1.860; $p=0.675$). We also tested the correlation between the risk of arthralgia, asthenia, myalgia and extremity pain and Nivolumab versus other drugs on the according effect models. The results also suggest no significant differences (asthenia: RR 0.846, 95% CI 0.657, 1.090; $p=0.197$; myalgia: RR 0.658, 95% CI 0.141, 3.062; $p=0.593$; extremity pain: RR 1.037, 95% CI 0.647, 1.662; $p=0.882$) as shown in (Figures 3B-3D).

Sensitivity analysis and publication bias

To access if a single literature can affect the final RRs, each individual study was removed one time and re-pool the data. The analysis results demonstrated that the pooled RRs were not affected by deleting every single study (Figures 2D-2F). 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 no publication bias in the study (Figures 2G-2I). 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 couldn't confirm if there are any additional potential risk factors correlated to developments of musculoskeletal toxicities.

Discussion

To the best of our knowledge, this is the most updated meta-analysis to provide an evaluation of selected musculoskeletal toxicities including arthralgia, asthenia, myalgia and extremity pain in patients with solid tumors receiving Nivolumab. Our analysis of data from 5 III randomized controlled trials did not demonstrate any increased or decreased risks of these musculoskeletal disorders with Nivolumab treatment compared with control. Normally, T-cells has the capacity to attack cancer cells; meanwhile, T-cells have to be regulated properly through certain inhibitory checkpoints to be controlled not to attack normal cells and normal tissues [17]. According to this theory, inhibiting these checkpoints is likely to activate T-cells and lead them to stronger anticancer responses [18]. At the moment, PD-1 as an inhibitory receptor, is one of the most fashionable and hottest research directions in the cancer immunotherapy field [2]. Its antagonist Nivolumab has been developed as a US-FDA approved anticancer drug for melanomas, which is based on the findings of a mount of Phase II~III studies [6]. Moreover, Nivolumab has been evaluated for its effects on anti- gastrointestinal cancer, prostate cancer and lung cancer.

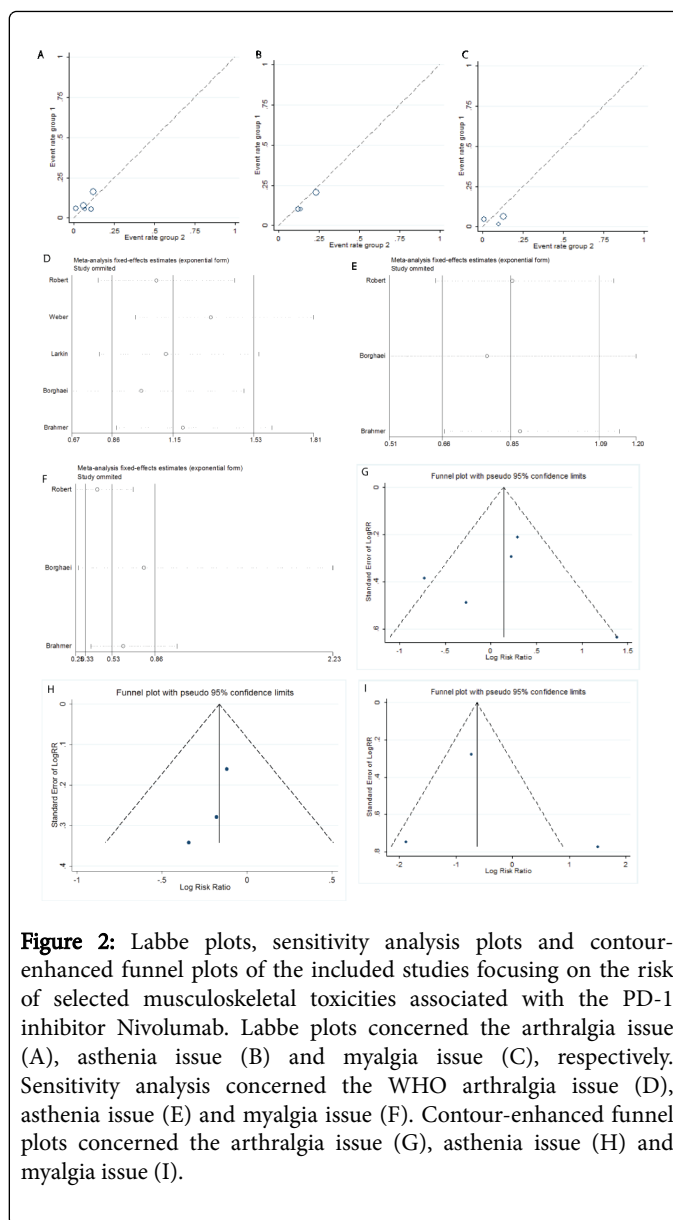


Figure 2: Labbe plots, sensitivity analysis plots and contour-enhanced funnel plots of the included studies focusing on the risk of selected musculoskeletal toxicities associated with the PD-1 inhibitor Nivolumab. Labbe plots concerned the arthralgia issue (A), asthenia issue (B) and myalgia issue (C), respectively. Sensitivity analysis concerned the WHO arthralgia issue (D), asthenia issue (E) and myalgia issue (F). Contour-enhanced funnel plots concerned the arthralgia issue (G), asthenia issue (H) and myalgia issue (I).

The number of literatures in relation to Nivolumab each year show a general tendency to increase over time. A timeline of the related publications is available as (Figure 4). On the basis of a world map with the global distribution of Nivolumab-related publications based on the analysis of their geolocational data, the countries that the publications are from are mainly concentrated in Europe, North America and East Asia (Figure 5). 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.

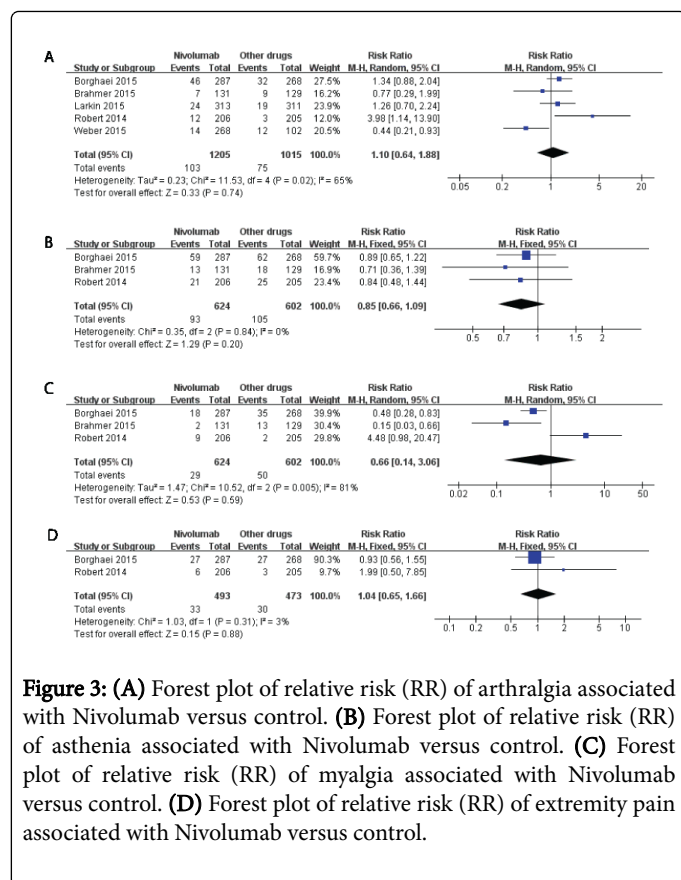


Figure 3: (A) Forest plot of relative risk (RR) of arthralgia associated with Nivolumab versus control. (B) Forest plot of relative risk (RR) of asthenia associated with Nivolumab versus control. (C) Forest plot of relative risk (RR) of myalgia associated with Nivolumab versus control. (D) Forest plot of relative risk (RR) of extremity pain associated with Nivolumab versus control.

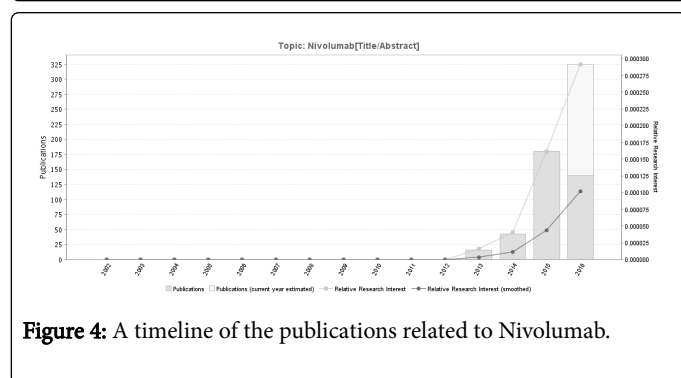


Figure 4: A timeline of the publications related to Nivolumab.

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 area where studies are perceived to be missing are areas of high statistical significance, then publication bias isn't the cause of funnel asymmetry [19]. In the present meta-analysis, the funnel plot indicated no publication bias.

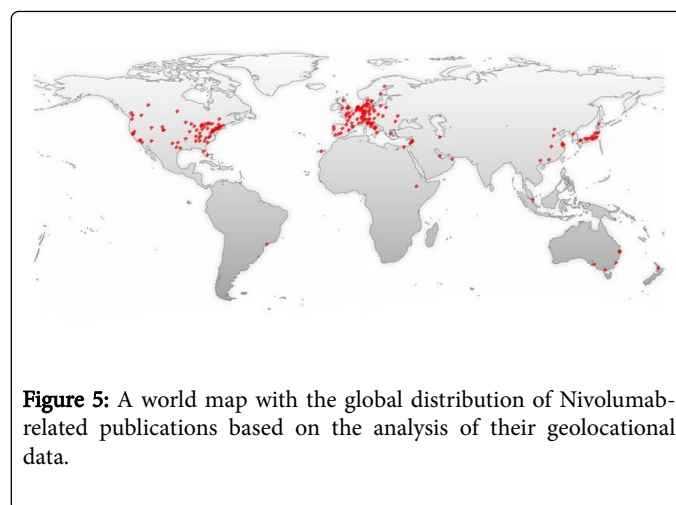


Figure 5: A world map with the global distribution of Nivolumab-related publications based on the analysis of their geolocalational data.

The musculoskeletal adverse effects have been regarded as an emerging reason for treatment discontinuation or interruption in some studies. Although hematological toxicities are not common, at present no effective methods have been developed to predict high-risk patients, hence careful monitoring of laboratory and clinical parameters being necessary. Hematological toxicities have been reported also in a number of other targeted anticancer therapeutics and have been linked to noncompliance with many of them [7-10,14,15]. Therefore, we combined Wanfang, PubMed, Google Scholar, Embase, Sinomed and CNKI databases to analyze the correlation between the risk of arthralgia, asthenia, myalgia and extremity pain and Nivolumab versus other drugs systematically. The results of our study demonstrated that in comparison with controls, Nivolumab did not significantly increased the risk of selected musculoskeletal toxicities (arthralgia: RR 1.116, 95% CI 0.669, 1.860; p=0.675; asthenia: RR 0.846, 95% CI 0.657, 1.090; p=0.197; myalgia: RR 0.658, 95% CI 0.141, 3.062; p=0.593; extremity pain: RR 1.037, 95% CI 0.647, 1.662; p=0.882).

Conclusions

Summarily, our analysis supported that PD-1 inhibitor Nivolumab did not cause an increased or decreased risks of musculoskeletal toxicities including arthralgia, asthenia, myalgia and extremity pain in patients with solid tumors compared with control. These outcomes indicated that in term of musculoskeletal side effects, Nivolumab is safe.

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