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Review Article

The efficacy of nivolumab for the treatment of advanced non-small cell lung cancer: a systematic review and meta-analysis of clinical trials

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Abstract: The aim of this study was to reevaluate the therapeutic effects of nivolumab for advanced non-small cell lung cancer (NSCLC) at a standard dose (3 mg/kg) in terms of the short-term response and long-term survival using a meta-analysis. Electronic databases were searched for eligible literature. Data for the objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS) were extracted. The outcomes were synthesized based on a random effects model. Subgroup analyses were proposed. Eight studies involving 400 advanced NSCLC patients using nivolumab monotherapy were eligible. Overall, the ORR was 21.3% (95% CI 17.0%-26.4%), while the DCR was 39.9% (95% CI 26.5%-55.1%). Additionally, the rates of 6-month PFS, 1-year PFS, 6-month OS and 1-year OS were 34.5% (95% CI 27.6%-42.1%), 22.3% (95% CI 17.8%-27.4%), 63.6% (95% CI 57.8%-68.9%) and 49.8% (95% CI 38.5%-61.1%), respectively. Subgroup analyses demonstrated that the ORR and DCR in Phase 1 trials were greater than those in Phase 2 and 3 trials. In addition, the ORR and DCR in patients with squamous cell carcinoma (SQCC) were lower than those in patients with non-SQCC. PD-1 ligand 1 (PD-L1)-positive patients were associated with a numerically higher ORR compared with PD-L1-negative patients, but this difference was not significant (OR 1.702, 95% CI 0.891-3.253). In conclusion, nivolumab exhibited a favorable efficacy for the treatment of patients with advanced NSCLC both in short-term responses and long-term survival.

Keywords: Nivolumab, PD-L1, non-small cell lung cancer, response, survival, meta-analysis

Introduction

Non-small cell lung cancer (NSCLC) was accounts for 85-90% of all lung cancers, it contains two major subtypes, non-squamous cell (mainly adenocarcinoma) and squamous cell carcinomas [1, 2]. Patients with NSCLC often diagnosed at an advanced stage, an unresectable stage with a high mortality rate, so it is very important to improve the effective and safety of NSCLC treatment. Recent years, immune checkpoint inhibitors have been applied in different malignancies, and the nivolumab has recently been shown to has a therapeutic effect in the patients of NSCLC [3, 4].

Nivolumab (also known as ONO-4538, BMS-936558, or MDX1106) is a humanized monoclonal antibody that targets programmed death-1 (PD-1). It was developed by Ono Pharmaceutical and Medarex (later acquired by Bristol-Myers Squibb) and marketed as Opdivo for cancer immunotherapy [5]. By binding to PD-1 on tumor-infiltrating lymphocytes (TILs), this antibody can block the recognition of PD-1 by its ligand 1 (PD-L1) on tumor cells, allowing T-cells to maintain their antitumor properties and ability to mediate tumor cell death [6-9].

Nivolumab has demonstrated surprising clinical responses in some advanced and metastatic solid tumors [10, 11]. Moreover, it is approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with unresectable or metastatic melanoma who no longer respond to other drugs [12-14]. Research has shown that nivolumab-based therapy prolongs PFS during the treatment of advanced melanoma and causes fewer adverse effects [15, 16]. In addition, nivolumab was the first PD-1 inhibitor to be approved for use in advanced squamous cell carcinoma

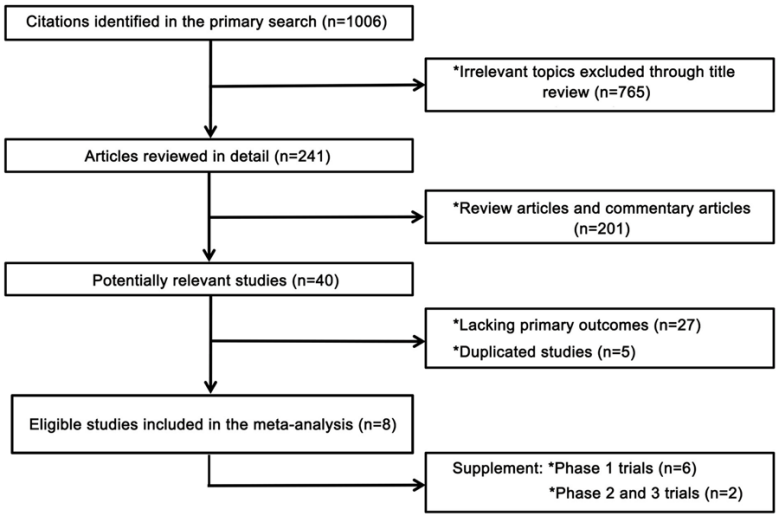

Figure 1. Flow chart of the article selection process.

(SQCC), a subtype of non-small cell lung cancer (NSCLC) that was previously treated with platinum-based chemotherapy [3, 17, 18]. The pivotal CheckMate 017 revealed that patients with squamous NSCLC receiving nivolumab have a significantly better OS, PFS and ORR compared with those receiving docetaxel [18]. As different histological types of lung cancer, the ORR was prolonged in both squamous and non-squamous cell lung cancer with the administration of anit-PD-1/PD-L1 therapy [18-20]. However, because of the different study designs and sample sizes, the ORR varied across the studies, and consequently the relationship between PD-L1 expression levels in tumor cells and the efficacy of nivolumab has remained controversial [20, 21].

To date, a series of clinical trials (including phase 2 and 3 trials) investigating nivolumab for the treatment of advanced NSCLC have been completed. Thus, it is time to summarize all of the clinical trial results obtained to date. We performed a meta-analysis by incorporating all published clinical trials to evaluate the therapeutic effect of nivolumab for the treatment of advanced NSCLC in terms of short-term responses and long-term survival.

Methods

Literature search

This meta-analysis followed the PRISMA statement for reporting systematic reviews, as recommended by the Cochrane Collaboration [22]. Two authors independently performed a comprehensive systematic search for published articles or abstracts in PubMed, EMBASE, SCOPUS, the Cochrane library and the ASCO meeting library from the time of inception to August 2015. The searches were limited to human studies and utilized a combination of the terms "nivolumab", "ONO-4538", "BMS-936558", "MDX1106", "lung" and "NSCLC". Relevant reference lists and reviews were also manually reviewed. There were no language restrictions.

Inclusion and exclusion criteria

All clinical trials exploring the efficacy of nivolumab for the treatment of advanced NSCLC were considered potentially eligible for inclusion in this meta-analysis. Studies meeting the following criteria were eligible: 1) clinical trials reporting the therapeutic effect of nivolumab for advanced NSCLC; 2) nivolumab mono-therapy without the combination of platinum-based doublet chemotherapy or other target therapies; 3) a nivolumab dose of 3 mg/kg every 2 weeks until progression or the occurrence of an unacceptable toxic effect; 4) at least one clinical outcome referred to as a short-term response and long-term survival. Studies that failed to meet the inclusion criteria were excluded from the analysis.

Outcome measures, data extraction and quality assessment

The primary outcome for this meta-analysis was the objective response rate (ORR), which was available for all included articles. Other outcomes were the disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). Data for PFS and OS were extracted as the 6-month and 1-year PFS/OS rates. Data for the lead author, trial type, treatment line, follow up, tumor subtype, PD-L1 status, ORR, DCR, PFS and OS were extracted by two investigators independently. Three reviewers used a modified Newcastle-Ottawa (NOS) scale to assess the quality of all included studies, NOS contains eight items and each

Table 1. Main characteristics of the selected studies for single-arm meta-analyses

Lead author (y)	Trial	Treatment line	Follow-up (mo)	Tumor	Patient (N)	ORR (%)	DCR (%)	PFS rate		OS rate	
								6 mo	1 y	6 mo	1 y
Brahmer 2012	Phase 1	≥ 2	NA	NSCLC	18	5/18 (27.78)	NA	NA	NA	NA	NA
Topalian 2012	Phase 1	≥ 2	≥ 12	NSCLC	19	6/19 (31.58)	8/19 (42.11)	8/19 (42.11)	NA	NA	NA
				SQCC	6	3/6 (50.00)	3/6 (50.00)	3/6 (50.00)	NA	NA	NA
				Non-SQCC	13	3/13 (23.08)	5/13 (38.46)	5/13 (38.46)	NA	NA	NA
Brahmer 2013	Phase 1	≥ 2	≥ 12	NSCLC	33	9/33 (27.27)	NA	NA	NA	NA	NA
				SQCC	15	4/15 (26.67)	NA	NA	NA	NA	NA
				Non-SQCC	18	5/18 (27.78)	NA	NA	NA	NA	NA
Gettinger and Rizvi 2014	Phase 1	1	≥ 12	NSCLC	20	6/20 (30.00)	NA	NA	NA	NA	15/20 (75.00)
				SQCC	9	2/9 (22.22)	NA	NA	NA	NA	NA
				Non-SQCC	11	4/11 (36.36)	NA	NA	NA	NA	NA
Rizvi 2014	Phase 1	≥ 2	≥ 6	NSCLC	21	2/21 (9.52)	10/21 (47.62)	NA	NA	NA	NA
				SQCC	8	0/8 (0.00)	4/8 (50.00)	NA	NA	NA	NA
				Non-SQCC	13	2/13 (15.38)	6/13 (46.15)	NA	NA	NA	NA
Rizvi 2015	Phase 2	≥ 2	≥ 11	SQCC	117	17/117 (14.53)	30/117 (25.64)	31/117 (25.90)	24/117 (20.00)	72/117 (61.54)	48/117 (41.03)
Brahmer 2015	Phase 3	≥ 2	≥ 11	SQCC	135	27/135 (20.00)	66/135 (48.89)	50/135 (37.04)	29/135 (21.48)	85/135 (62.96)	57/135 (42.22)
Gettinger 2015	Phase 1	≥ 2	≥ 32	NSCLC	37	9/37 (24.32)	NA	15/37 (40.54)	11/37 (29.73)	27/37 (72.97)	21/37 (56.76)
				SQCC	18	4/18 (22.22)	NA	7/18 (38.89)	5/18 (27.78)	NA	9/18 (50.00)
				Non-SQCC	19	5/19 (26.32)	NA	8/19 (42.11)	6/19 (31.58)	NA	12/19 (63.16)

Abbreviations: DCR=disease control rate; NA=not available; NSCLC=non-small-cell lung cancer; SQCC=squamous cell carcinoma; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

Table 2. Characteristics of the studies included in the two-arm meta-analysis

Lead author (y)	Trial	Treatment line	Follow-up (mo)	Tumor	PD-L1 status[a] (N)	ORR (%)	DCR(%)	Median PFS, mo (95% CI)	Median OS, mo (95% CI)
Gettinger and Rizvi 2014	Phase 1	1	≥ 12	NSCLC	PD-L1(+) (N=10)	5/10 (50.00)	NA	11.4	NA
					PD-L1(-) (N=7)	0/7(0)	NA	9.0	NA
Rizvi 2015	Phase 2	≥ 2	≥ 11	SQCC	PD-L1(+) (N=25)	6/25 (24.00)	12/25 (48.00)	NA	NA
					PD-L1(-) (N=51)	7/51 (13.73)	17/51 (33.33)	NA	NA
Brahmer 2015	Phase 3	≥ 2	≥ 11	SQCC	PD-L1(+) (N=42)	9/42 (21.43)	NA	4.8	10
					PD-L1(-) (N=75)	11/75 (14.67)	NA	2.2	8.5
Gettinger 2015	Phase 1	≥ 2	≥ 32	NSCLC	PD-L1(+) (N=33)	5/33 (15.15)	NA	3.3 (1.8, 7.5)	7.8 (5.6, 21.7)
					PD-L1(-) (N=35)	5/35 (14.29)	NA	1.8 (1.7, 2.3)	10.5 (5.2, 14.8)

[a]Positivity is defined as tumor cell membrane staining at any intensity with ≥5% PD-L1 expression in a minimum number of 100 evaluable cells using an automated immunohistochemistry assay (Dako North America, Carpinteria, CA). Abbreviations: CI=confidence interval; DCR=disease control rate; NA=not available; NSCLC=non-small-cell lung cancer; SQCC=squamous cell carcinoma; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PD-L1=programmed cell death 1 ligand 1; PD-L1 (+)=PD-L1-positive.

item provide a series of response options. A star system was used in the assessment of study quality, range from zero to nine stars [23]. In our research, only those articles with a NOS of 6 or greater were included. Discrepancies were discussed by all investigators to reach consensus.

Statistical analysis and publication bias

Data for ORR, DCR, PFS and OS were pooled statistically using the event rates. In addition, data for ORR stratified by PD-L1 status were pooled as odds ratios (ORs) with 95% confidence intervals (CIs). A subgroup analysis was conducted according to the clinical trial category and tumor subtype. All calculations were performed using MetaAnalyst Beta 3.13 (Tufts Medical Center). Heterogeneity across the incorporated studies was assessed by the inconsistency statistic (I^2), I^2>50% was considered substantial heterogeneity and random effects model was used. While if I^2<50%, fixed effects model was used. Publication bias was evaluated using funnel plots and the Begg test [24].

Results

Characteristics of eligible studies

A total of 1006 records were initially selected by database searches according to the search strategy, and eight studies [3, 18, 25-31] focusing on the therapeutic effect of nivolumab in advanced NSCLC (the study by *Rizvi NA in 2014* [21] represents sequential research from Gettinger SN in 2014 [30], and thus should be considered the same data) were ultimately included in the analysis. **Figure 1** shows the selection process for the eligible studies. Four hundred advanced NSCLC patients received nivolumab immunotherapy, and most had undergone prior treatments. **Table 1** summarizes the characteristics of the eight studies included in the meta-analysis. A total of 278 tumor samples from these studies were tested for PD-L1 expression (110/168 cases for PD-L1 positive/negative). Additional data for clinical response or survival stratified by PD-L1 status are shown in **Table 2**.

Meta-analysis of the efficacy of nivolumab in terms of ORR, DCR, PFS and OS

First, we evaluated the short-term response of nivolumab in advanced NSCLC. Overall, the ORR in the whole population treated with nivolumab was 21.3% (95% CI: 17.0% to 26.4%, I^2=13.2%, **Figure 2A**), while the DCR was 39.9% (95% CI: 26.5% to 55.1%, I^2=44.3%, **Figure 2B**). Additional analysis of pooled data for survival revealed that the rate of 6-month PFS, 1-year PFS, 6-month OS and 1-year OS were 34.5% (95% CI: 27.6% to 42.1%, I^2=26.6%, **Figure 2C**), 22.3% (95% CI: 17.8% to 27.4%, I^2=0%, **Figure 2D**), 63.6% (95% CI: 57.8% to 68.9%, I^2=0%, **Figure 2E**) and 49.8% (95% CI: 38.5% to 61.1%, I^2=40.6%, **Figure 2F**), respectively. These indexes had a low heterogeneity in this analysis.

Subgroup and sensitivity analyses and publication bias

When stratifying the studies according to trial types, we observed that the ORR and DCR were 25.9% (95% CI: 19.4% to 33.8%, I^2=0%) and 45.0% (95% CI: 30.5% to 60.4%, I^2=0%) in Phase 1 trials, which were greater than those

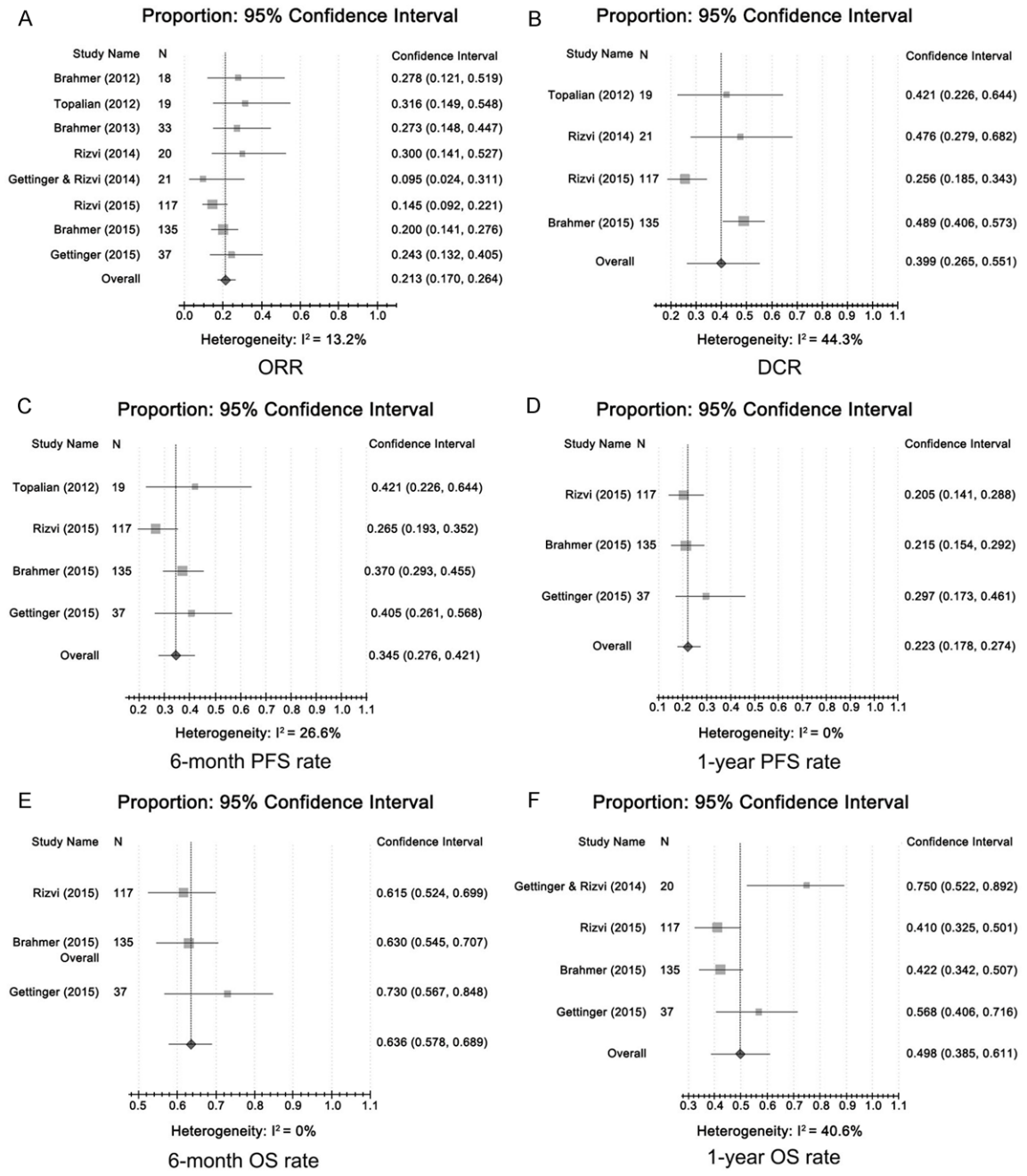

Figure 2. Single-arm meta-analysis of the efficacy of nivolumab. (A: ORR; B: DCR; C: 6-month PFS rate; D: 1-year PFS rate; E: 6-month OS rate; F: 1-year OS rate). Abbreviations: DCR=disease control rate; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

in Phase 2 and 3 trials (17.5%, 95% CI: 12.7% to 23.6%, I^2=18.4%; 36.7%, 95% CI: 17.6% to 61.1%, I^2=48.1%), and their heterogeneity were low. Additionally, when stratifying patients according to tumor subtype, the ORR and DCR were 19.3% (95% CI: 14.8% to 24.7%) and 40.6% (95% CI: 24.7% to 58.7%) in SQCC patients, which were smaller than those in non-SQCC patients (26.2%, 95% CI: 17.3% to 37.6% and 42.4%, 95% CI: 25.2% to 61.6%) (**Table 3**).

The subgroup analyses were not available for PFS or OS due to limited survival data. We also performed a two-arm meta-analysis to evaluate the association between PD-L1 expression and the clinical response of nivolumab

Table 3. Subgroup results for the single-arm meta-analyses

Subgroup items	No. of studies	No. of patients	Rate (95% CI) (%)	I^2 (%)
ORR				
Phase 1 trials	6	148	25.9 (19.4-33.8)	0
Phase 2 and 3 trials	2	252	17.5 (12.7-23.6)	18.4
SQCC	7	308	19.3 (14.8-24.7)	5.8
Non-SQCC	5	74	26.2 (17.3-37.6)	0
DCR				
Phase 1 trials	2	40	45.0 (30.5-60.4)	0
Phase 2 and 3 trials	2	252	36.7 (17.6-61.1)	48.1
SQCC	4	266	40.6 (24.7-58.7)	44.3
Non-SQCC	2	26	42.4 (25.2-61.6)	0

Abbreviations: CI=confidence interval; DCR=disease control rate; ORR=objective response rate.

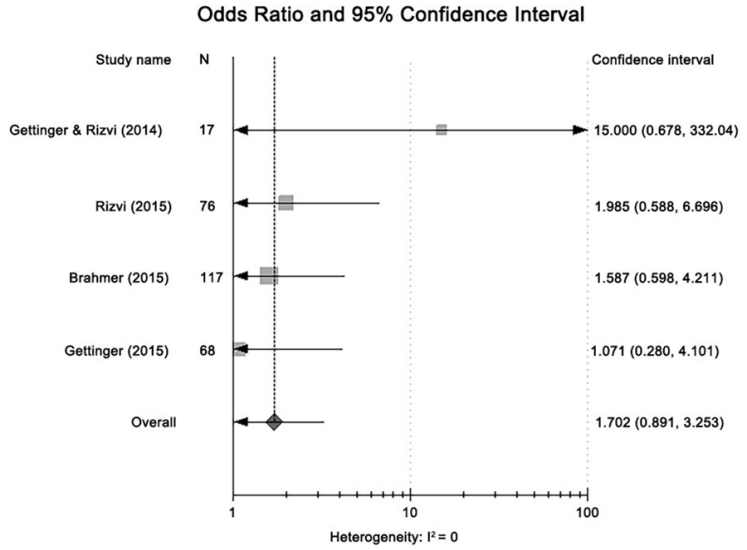

Figure 3. Two-arm meta-analysis of PD-L1-positive versus PD-L1-negative patients in terms of the objective response rate with nivolumab treatment. Abbreviations: PD-L1=programmed cell death 1 ligand 1.

(only in terms of ORR due to a lack of DCR and survival data). PD-L1-positive patients were associated with a numerically higher ORR compared with PD-L1 negative patients, but this difference was not significant and with a low heterogeneity (OR 1.702, 95% CI: 0.891 to 3.253, I^2=0%, **Figure 3**). Begg tests revealed no significant publication bias (P=0.734>0.05).

Discussion

Since patients with a NSCLC at the advanced stage often limited in the treatment options, it is very necessary to explore effective therapeutic method for advanced NSCLC [2, 32]. Immunotherapy is opening new perspectives for treatment of lung cancer, giving new effective options for advanced NSCLC [33].

A previous meta-analysis evaluated the efficacy of anti-PD-1 antibody for the treatment of NSCLC based on the results from limited phase 1 trials [34]. However, the above meta-analysis took very little consideration of the possible influence of the efficacy of the combination treatment effects of nivolumab with other drug and the drug dose of nivolumab. Additionally, no subgroup analysis stratified by tumor subtype and PD-L1 status was performed. Moreover, pooled survival data were not shown. With the advent of the results of the phase 2 trial from *Rizvi NA* [18] and the phase 3 trial from *Brahmer J* [3] in 2015, the FDA approved nivolumab, an anti-PD-1 immune checkpoint inhibitor, for the treatment of squamous non-small cell lung cancer. Thus, a summary of the trials to evaluate the therapeutic effect of a standard dose (3 mg/kg) of nivolumab for advanced NSCLC in terms of the short-term response and long-term survival was overdue. Subgroup analyses by clinical trial category tumor subtype and PD-L1 status were also needed. A meta-analysis incorporating all of the available data from correlative studies (including phase 2 and 3 trials) is an effective strategy to examine the current evidence.

We found that the ORR and DCR in NSCLC with nivolumab treatment were 21.3% and 39.9% and the rate of 6-month PFS, 1-year PFS, 6-month OS and 1-year OS were 34.5%, 22.3%, 63.6% and 49.8%, respectively. In accordance with previous studies demonstrating that nivolumab treatment resulted in a generally prolonged ORR, PFE and OS, we found that nivolumab was effective in patients with advanced NSCLC [35]. These results revealed

some patients who survived for a long time even with tumor progression, as assessed by the Response Evaluation Criteria In Solid Tumors (RECIST) standard. These findings provided important support for the implementation of new judgment criteria for tumor progression in cancer immunotherapy, such as nivolumab.

Subgroup analyses showed that the ORR and DCR in Phase 1 trials were greater than those in Phase 2 and 3 trials. Expansion of the sample size made the latter more convincing. Additionally, the ORR and DCR in SQCC patients were smaller than those in non-SQCC patients. Recent studies have demonstrated that the activation of some driver mutations, such as epidermal growth factor receptor (EGFR) and echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK), can induce PD-L1 expression [36, 37]. It is already known that mutations in EGFR mutation and the EML4-ALK fusion gene mostly occur in adenocarcinoma of NSCLC [38].

As a result, there may be more PD-L1-positive patients with adenocarcinoma of NSCLC (non-SQCC) compared with SQCC. We also found that, compared with PD-L1-negative patients, PD-L1-positive patients were associated with a numerically higher ORR. This finding has also been demonstrated by other groups. Velcheti et al [39] and Zhu et al [16] both found that PD-L1 expression rendered greater efficacy to PD-L1-positive patients. Taken together, this evidence might explain why non-SQCC patients received a greater benefit from nivolumab than those with SQCC due to a potentially higher proportion of PD-L1-positive non-SQCC patients. Additional clinical trials are needed to clarify whether nivolumab could be an effective therapeutic choice for non-SQCC patients after first-line treatment.

This is the first meta-analysis incorporating phase 2 and 3 trials to evaluate the efficacy of nivolumab at a standard dose for the treatment of advanced NSCLC based on subgroup analyses of the short-term response and long-term survival. However, some limitations must be acknowledged. First, some Phase 1 trials failed to provide data for PFS and OS, which limited our subgroup analyses. Second, the sample size of patients with known PD-L1 status was too small to generate conclusions regarding the association between PD-L1 expression and the response to nivolumab. Third, some clinical data were extracted from subgroup data of clinical trials, which might compromise the level of evidence. In addition, almost all of the eligible trials reported second-line results, and thus the efficacy of first-line nivolumab treatment should be re-evaluated in the future when more first-line trial results are available. Further studies are warranted to confirm the present findings.

In conclusion, this meta-analysis investigated the efficacy of nivolumab for the treatment of patients with advanced or metastatic NSCLC. Nivolumab showed favorable outcomes both in the short-term response and long-term survival.

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Disclosure of conflict of interest

None.

Authors' contribution

Jun-Ming Yung and Jiao Luo conceived and designed the study and critically revised the manuscript. Ming Bao and Yue-Jiang Pan are responsible for the collection and assembly of data and the data analysis and interpretation. Ran Wang, Sheng-Long Li and Jie Liang assessed all included studies according to NOS. All authors wrote and approved the final manuscript.

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