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ORIGINAL ARTICLE

Anti-PD-1/PD-L1 Therapy as a Promising Option for Non-Small Cell Lung Cancer: a Single arm Meta-Analysis

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Abstract Anti-PD-1/PD-L1 antibodies showed satisfactory efficacy in treating non-small-cell lung cancer. We conducted this meta-analysis to explore the advantage subtypes and best therapeutic modalities of Anti-PD-1/PD-L1 therapy on NSCLC. A quantitative meta-analysis was performed through a systematic search in PubMed, Web of Science, and the Cochrane Library. The pooled ORR, 6-month progression-free survival rate ($PFSR_{6m}$), and 1-year overall survival rate (OSR_{1y}) were calculated and compared. 15 trials were included in this meta-analysis. Our analyses demonstrated the pooled ORR of 1st line and 2nd or more line anti-PD-1/PD-L1 therapy were 36.5 % (21.9–51.0 %) and 17.0 % (14.3–19.7 %), respectively. While the difference was significant ($Z = 3.31$, $p < 0.001$). The pooled ORR for non-squamous and squamous cell lung cancer were 18.5 % (16.0–21.1 %) and 17.9 % (14.4–21.5 %), respectively. The difference was not significant ($Z = 0.27$, $p = 0.791$). The pooled ORR for PD-L1 positive and negative patients were 29.6 % (21.6–37.6 %) and 13.5 % (10.6–16.3 %), respectively. The difference was significant ($Z = 4.39$, $p < 0.001$). The $PFSR_{6m}$ for PD-L1 positive and negative NSCLC were 50.0 % (40.5–62.3 %) and 27.0 % (19.2–34.7 %). The difference was significant ($Z = 3.72$, $p < 0.001$). The OSR_{1y} for PD-L1 positive and negative NSCLC were 66.8 % (44.8 %-88.9 %) and 54.0 % (32.6–75.3 %). The difference was not significant ($Z = 0.77$, $p = 0.441$). Anti-PD-1/PD-L1 antibody can serve as a promising treatment option for NSCLC. Patients with positive PD-L1 expression may benefit more from anti-PD-1/PD-L1 therapy. 1st-line anti-PD-1/PD-L1 therapy can be chosen as the best modality. Squamous cell lung cancer also benefit from anti-PD-1/PD-L1 therapy.

Keywords PD-1 · PD-L1 · Non-small cell lung cancer · Checkpoint inhibitor · Meta-analysis

Abbreviations

AEs	Adverse events
irAEs	Immune-related adverse events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
NOS	Newcastle-Ottawa Scale
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
OSR1y	1-year overall survival rate
PD-1	Programmed death receptor 1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PFS	Progression free survival
PFSR6m	6-month progression-free survival rate
sq	Squamous cell lung cancer

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Introduction

For many decades, lung cancer has been the most common cancer and the leading cause of cancer death worldwide. [1] Surgery, chemotherapy and radiotherapy are the three primary treatment modalities for non-small cell lung cancer (NSCLC). Great advances have been made in treatment of specific genotype NSCLC; however, there are still large proportion of lung cancer without drugable targets of which squamous lung cancer account for a great percentage.

The host immune system has been long thought to play great role in antitumor response. While the intrinsic mechanism is complicated and not well understood. Tumor specific T cells was expected to exert strong antitumor effect, however, less successful was seen in targeting T cells. [2] Tumor develops immune resistance by multiple mechanisms. [3] Co-inhibitory receptors and their pathways termed immune checkpoints being the major mechanisms of immune resistance dampen functions of T-cell in the tumor microenvironment. [4] The most important co-inhibitory receptors recently found are cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death receptor 1 (PD-1). Recent progress in anti-CTLA-4 and anti-PD-1 as well as its ligand (PD-L1) has accelerated understanding the function of tumor's surrounding immune microenvironment. CTLA-4 inhibitors, the first clinically used immune checkpoints inhibitors, have been applied in treatment of several tumors. [5–8].

However, frequent immune-related adverse events (irAEs) limit the use of CTLA-4 inhibitors. [9] New checkpoint inhibitors targeting PD-1 and PD-L1 showed more tumor-specific activity as well as fewer irAEs compared to CTLA-4 inhibitors. PD-1 negatively regulates and limits T-cell activity at variety of stages by interacting with its two ligands PD-L1 and PD-L2. [10–12] High expression of PD-L1 was found in approximately 50 % of NSCLC, both in adenocarcinomas and squamous cell carcinomas, and may contribute to poor prognosis. [13] A series of phase II studies [14, 15] on NSCLC confirmed the efficacy of PD-1/PD-L1 inhibitors. While most of these trials were designed as single arm and non-comparable forms, benefits on specific subtypes of NSCLC were unknown. Therefore, we conducted this quantitative meta-analysis to explore the advantage subtypes of Anti-PD-1/PD-L1 therapy on NSCLC.

Materials and Methods

Publication Search

We searched PubMed, Web of Science, and the Cochrane Library from 1966 to Jul. 29, 2015. We also reviewed records at American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), the world Conference of Lung cancer (WCLC). The search strategy used both MeSH terms and free-text words to increase sensitivity. The following search terms were used: "pembrolizumab/lambrolizumab/Keytruda/MK-3475/PEMBRO", "MPDL-3280A", "MEDI-4736", "Nivolumab/ONO-4538/BMS-936,558/MDX-1106/Opdivo", "AMP-224","BMS-936,559/MDX-1105″, and "pidilizumab/CT-011″, and "lung cancer/carcinoma". The study was approved by the Ethics Committee of Hangzhou First People's Hospital.

Inclusion and Exclusion Criteria

Inclusion criteria are the followings: (1) Articles investigating anti-PD-1/PD-L1 antibody on NSCLC patients; (2) Studies reporting any of the following information: overall response rate (ORR), overall survival (OS), and progression free survival (PFS). Exclusion criteria are the following: (1) letters, editorials, expert opinions, case reports and reviews; (2) Studies without usable data; (3) duplicate publications.

Data Extraction

Two investigators independently extracted data from the eligible studies, and disagreements were resolved by discussion with a third investigator. For each studies, the following information was recorded: the first author, year of publication, number of patients, ORR, PFS, and OS.

Quality Control

Most of the included studies were single arm or non-controlled studies. Therefore, we choose the Newcastle-Ottawa Scale (NOS) for assessing the quality [16]. Assessment scores of 0–3, 4–6, and 7–9 were evaluated as poor, fair, and good studies, respectively. Any discrepancies were resolved by consensus.

Statistical Analysis

The pooled ORR, 6-month progression-free survival rate ($PFSR_{6m}$), and 1-year overall survival rate (OSR_{1y}) were OpenMeta[Analyst] (Tufts medical center, Boston, Massachusetts, USA). The heterogeneity of the data was evaluated by chi-square Q test and I^2 statistic. For the Q test, a p value less than 0.05 indicated significant heterogeneity; for the I^2 statistics, an I^2 value greater than 50 % was considered significant heterogeneity. For comparing different settings, the following formulas

were used. Statistical significance was defined as a p value less than 0.05.

$$Z = \frac{lnRR_A - lnRR_B}{\sqrt{\text{variance of } lnRR_A + \text{variance of } lnRR_B}};$$

$$\text{variance of lnRR} = \left[\frac{\ln(\text{upper } CI) - \ln(\text{lower } CI)}{2 \times Z \text{ score } for \text{ upper } CI \text{ boundary}}\right]^2$$

Results

Characteristics of Included Studies

As shown in Fig. 1, the electronic search yielded 396 records. After screening titles and abstracts, 74 full-text articles were assessed for eligibility. Finally, a total of 15 articles were included in meta-analysis. [14, 15, 17–29] Among these 15 studies, eight reported the efficacy and toxicities of nivolumab in treating advanced NSCLC, three reported that of pembrolizumab, and four reported that of MPDL3280A. 6 of 15 studies were assessed as good by NOS score system, nine were fair. Details were summarized in Table 1.

15 studies reported overall response rate (ORR) after anti-PD-1/PD-L1 treatments for NSCLC. The ORR across the studies varied from 10.2 to 66.7 % (median ORR was 20.0 %). The random-effects model was adopted as the significant heterogeneity (I^2 = 79.6 %, p < 0.001). Analysis showed a pooled ORR was 21.1 % (95%CI 16.9 %, 25.3 %) (Fig. S1). As the significant heterogeneity of ORR across the studies existed, we further investigated potential sources of heterogeneity by meta-regression and subgroup analyses.

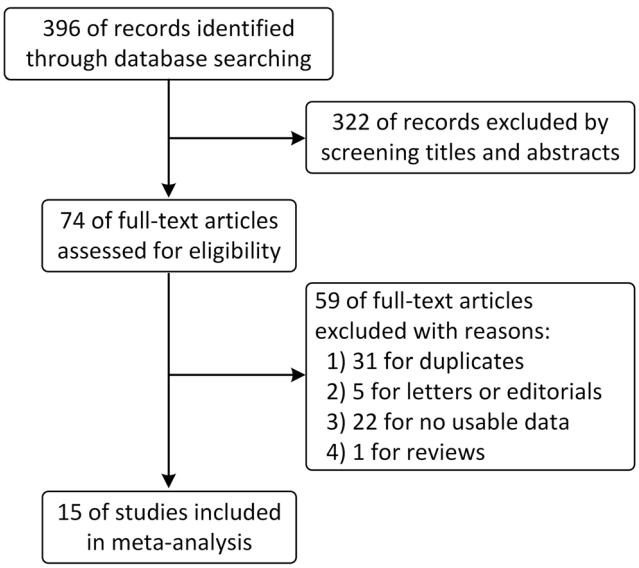

Fig. 1 The flow diagram of this meta-analysis

Meta-Regression and Subgroup Analyses

We choose three factors (lines of prior therapy, pathology type, and PD-L1 expression) for meta-regression analysis. The results showed lines of prior therapy (1 L vs. ≥2 L therapy, p < 0.001) and PD-L1 expression (positive vs. negative, p < 0.001) contributed to heterogeneity of ORR, while pathology type (Non-Squamous vs. squamous cell lung cancer, p = 0.781) did not influence ORR.

1st Line Versus 2nd or More Line Therapy

Five studies included usable data of ORR for 1st line (1 L) anti-PD-1/PD-L1 therapy. The pooled ORR was 36.5 % (95%CI 21.9 %, 51.0 %) (Fig. 2a), while the significant heterogeneity existed (I^2 = 84.6 %, p < 0.001). 12 studies included usable data of ORR for second or more line (≥2 L) anti-PD-1/PD-L1 therapy. The pooled ORR was 17.0 % (95%CI 14.3 %, 19.7 %) with significant heterogeneity (I^2 = 47.3 %, p = 0.035) (Fig. 2b). The difference of ORR between 1 L and ≥2 L therapy was significant (Z = 3.31, p < 0.001).

Non-Squamous Versus Squamous Cell Lung Cancer

Six studies reported ORRs of non-squamous cell lung cancer. The pooled ORR was 18.5 % (95%CI 16.0 %, 21.1 %) with small heterogeneity (I^2 = 0 %, p = 0.752) (Fig. 3a). Seven studies reported ORRs of squamous cell lung cancer. The pooled ORR was 17.9 % (95%CI 14.4 %, 21.5 %) with small heterogeneity (I^2 = 1.4 %, p = 0.413) (Fig. 3b). The ORR of non-squamous and squamous cell lung cancer was similar (Z = 0.27, p = 0.791).

PD-L1 Positive Versus Negative

Eight studies reported ORRs of PD-L1 positive lung cancer. The random-effect model was adopted as the significant heterogeneity (I^2 = 57.6 %, p = 0.021). The pooled ORR for PD-L1 positive was 29.6 % (95%CI 21.6 %, 37.6 %) (Fig. 4a). Seven studies reported ORRs of PD-L1 negative lung cancer. The pooled ORR for PD-L1 negative was 13.5 % (95%CI 10.6 %, 16.3 %) with small heterogeneity (I^2 = 0 %, p = 0.807) (Fig. 4b). Anti-PD-1/PD-L1 therapy achieved a higher ORR in PD-L1 positive NSCLC patients (Z = 4.39, p < 0.001).

PFS and OS

Eight studies with a total of 976 patients reported results of 6-month PFS rate ($PFSR_{6m}$). The $PFSR_{6m}$ across the studies varied from 18.5 to 42.0 % (median $PFSR_{6m}$ was 34.0 %). The summary $PFSR_{6m}$ was 32.1 % (95%CI 25.6 %, 38.6 %) (Figure S2A), with significant heterogeneity (I^2 = 83.6 %,

Table 1 Characteristics of 15 included studies

First author	Year	Total	Interventions	Prior therapy	NSCLC	NOS score	Ref
Spira	2015	287	MPDL3280A vs. Docetaxel	≥1	All	7	[17]
Spigel	2015	138	MPDL3280A	None/≥2	All	6	[18]
Rizvi	2015	117	Nivolumab	≥2	sq	7	[15]
Paz-Ares	2015	582	Nivolumab vs. Docetaxel	≥1	non-sq	8	[19]
Patnaik	2015	17	Pembrolizumab + Ipilimumab	≤2	All	4	[20]
Papadimitrakopoulou	2015	44	Pembrolizumab + PDC	None	All	5	[21]
Nishio	2015	111	Nivolumab	≥1	All	6	[22]
Liu	2015	37	MPDL3280A + PDC	None	All	5	[23]
Horn	2015	88	MPDL3280A	≥1	All	6	[24]
Gettinger	2015	129	Nivolumab	≥1	All	7	[25]
Gettinger	2015	52	Nivolumab	None	All	6	[26]
Garon	2015	495	Pembrolizumab	None/≥1	All	7	[27]
Brahmer	2015	135	Nivolumab vs. Doctaxel	≥1	sq	8	[28]
Bauer	2015	51	Nivolumab	≥1	All	4	[29]
Brahmer	2012	75	Nivolumab	≥1	All	5	[14]

PDC Platinum-Based Doublet Chemotherapy, *≥1* more than one line therapy, *≥2* more than two lines therapy, *≤2* more than two lines therapy, *All* both squamous and non-squamous cell lung cancer, *sq* squamous cell lung cancer, *non-sq* non-squamous cell lung cancer, *NOS* Newcastle-Ottawa Scale, *Ref* reference citation

$p < 0.001$). Six studies reported results of one-year OS rate (OSR_{1y}). The OSR_{1y} across the studies varied from 41.0 % to 81.8 % (median OSR_{1y} was 50.7 %). The summary OSR_{1y} was 51.4 % (95%CI 40.5 %, 62.3 %) (Figure S2B), with high heterogeneity ($I^2 = 92.81$ %, $p < 0.001$). As lack of sufficient data of PFS and OS, we only undertook subgroup analysis on

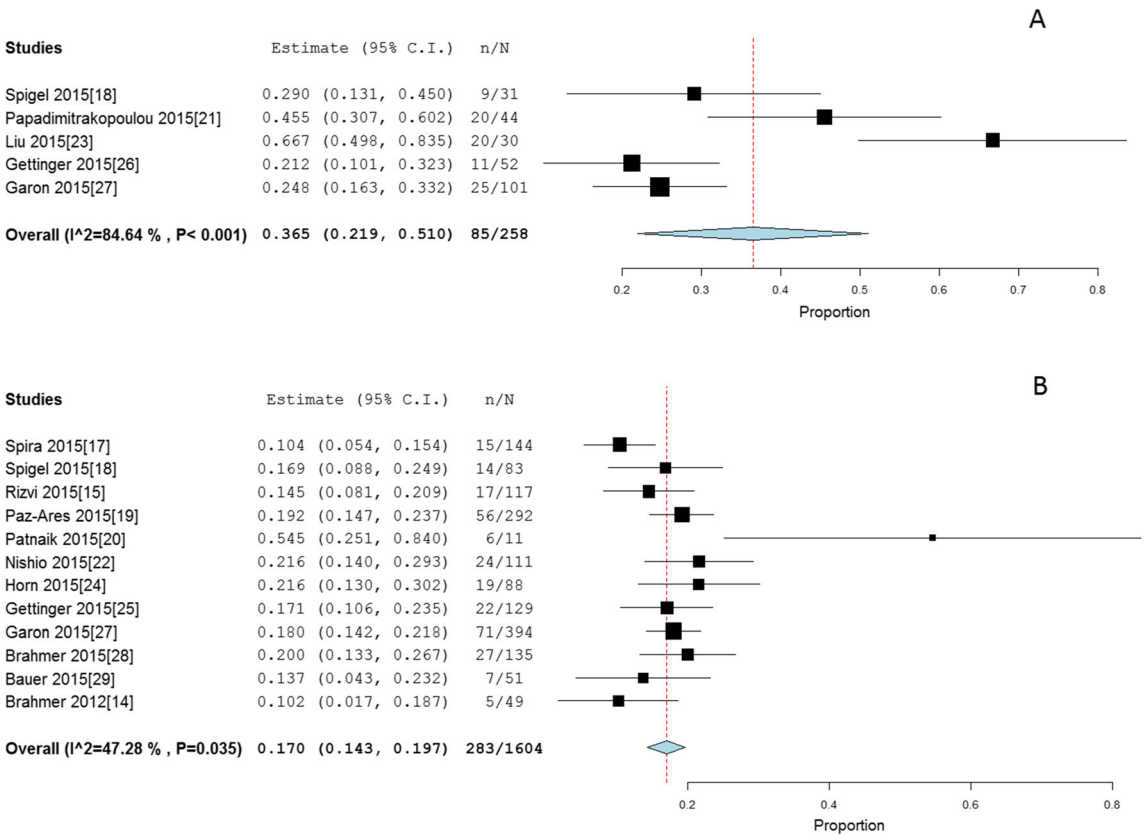

Fig. 2 Summary ORR for 1st line (**a**) and 2nd or more line studies (**b**)

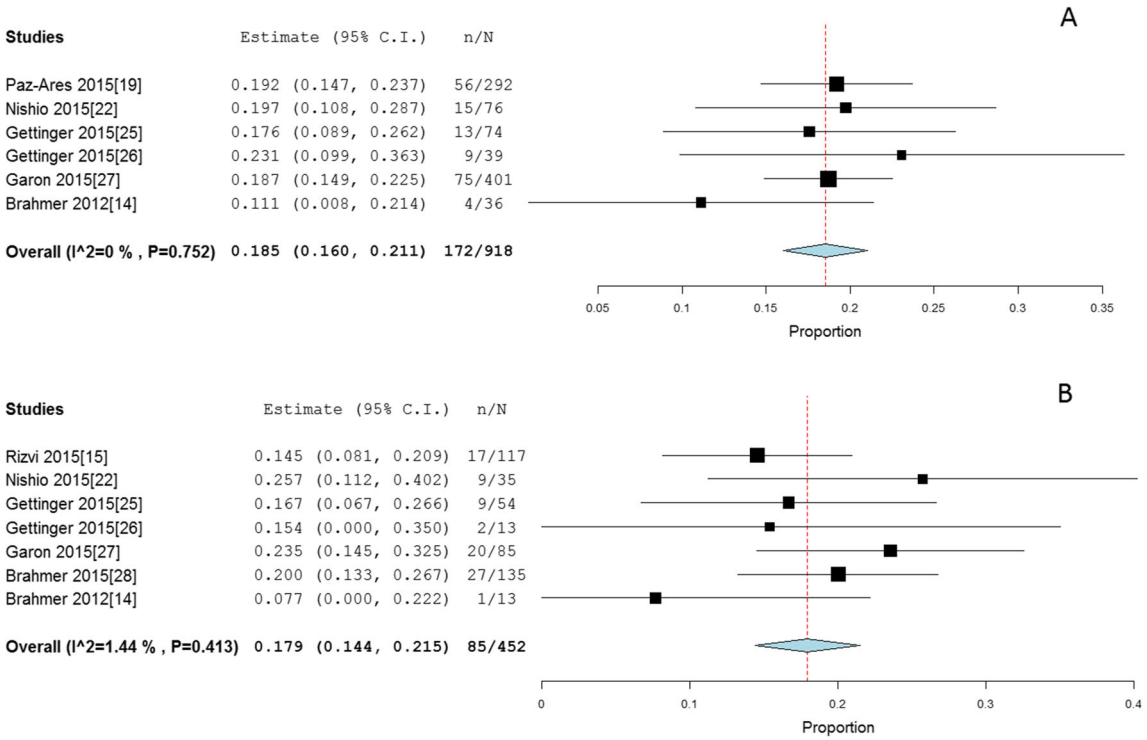

Fig. 3 Summary ORR for squamous (**a**) and non-squamous cell lung cancer (**b**)

PD-L1 positive and negative NSCLC. Meta-regression showed PD-L1 expression was correlation with PFS ($p < 0.001$) but not OS ($p = 0.350$). Four studies reported results of $PFSR_{6m}$ for PD-L1 positive NSCLC. The summary $PFSR_{6m}$ was 50.0 % (95%CI 43.3 %, 56.6 %) (Fig. 5a), with small heterogeneity ($I^2 = 0$ %, $p = 0.617$). Four studies reported results of $PFSR_{6m}$ for PD-L1 negative NSCLC. The summary $PFSR_{6m}$ was 27.0 % (95%CI 19.2 %, 34.7 %) (Fig. 5b),

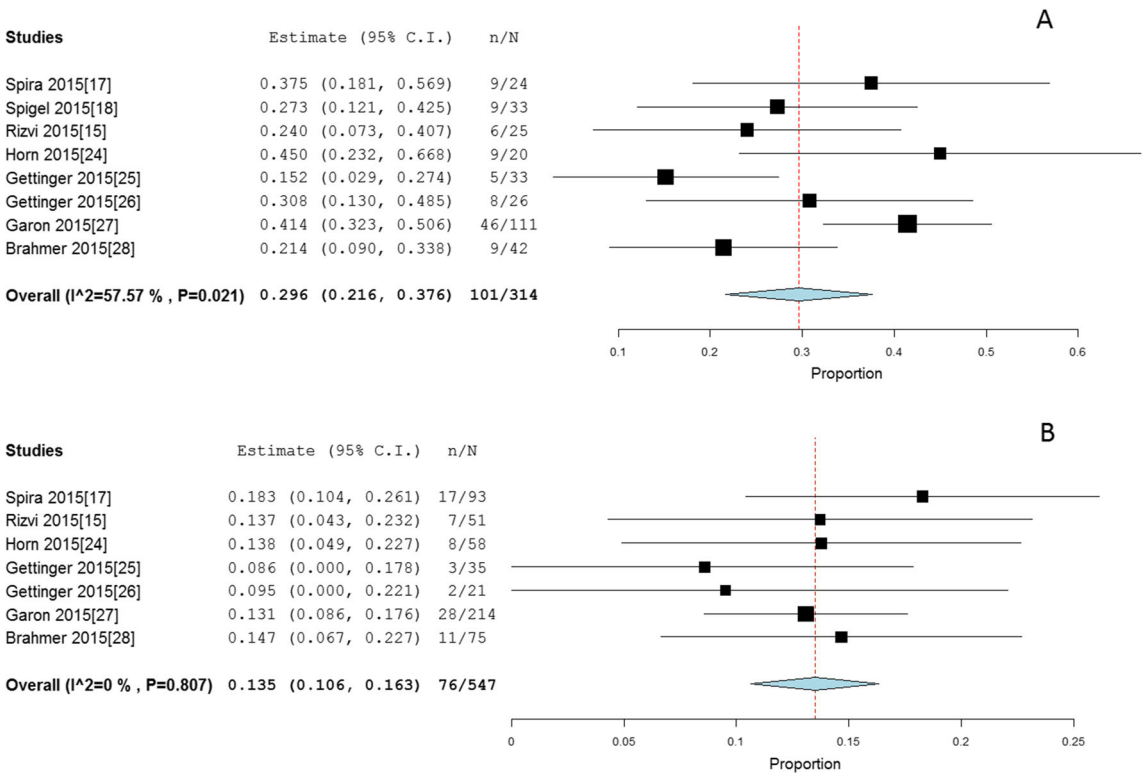

Fig. 4 Summary ORR for PD-L1 positive (**a**) and negative lung cancer (**b**)

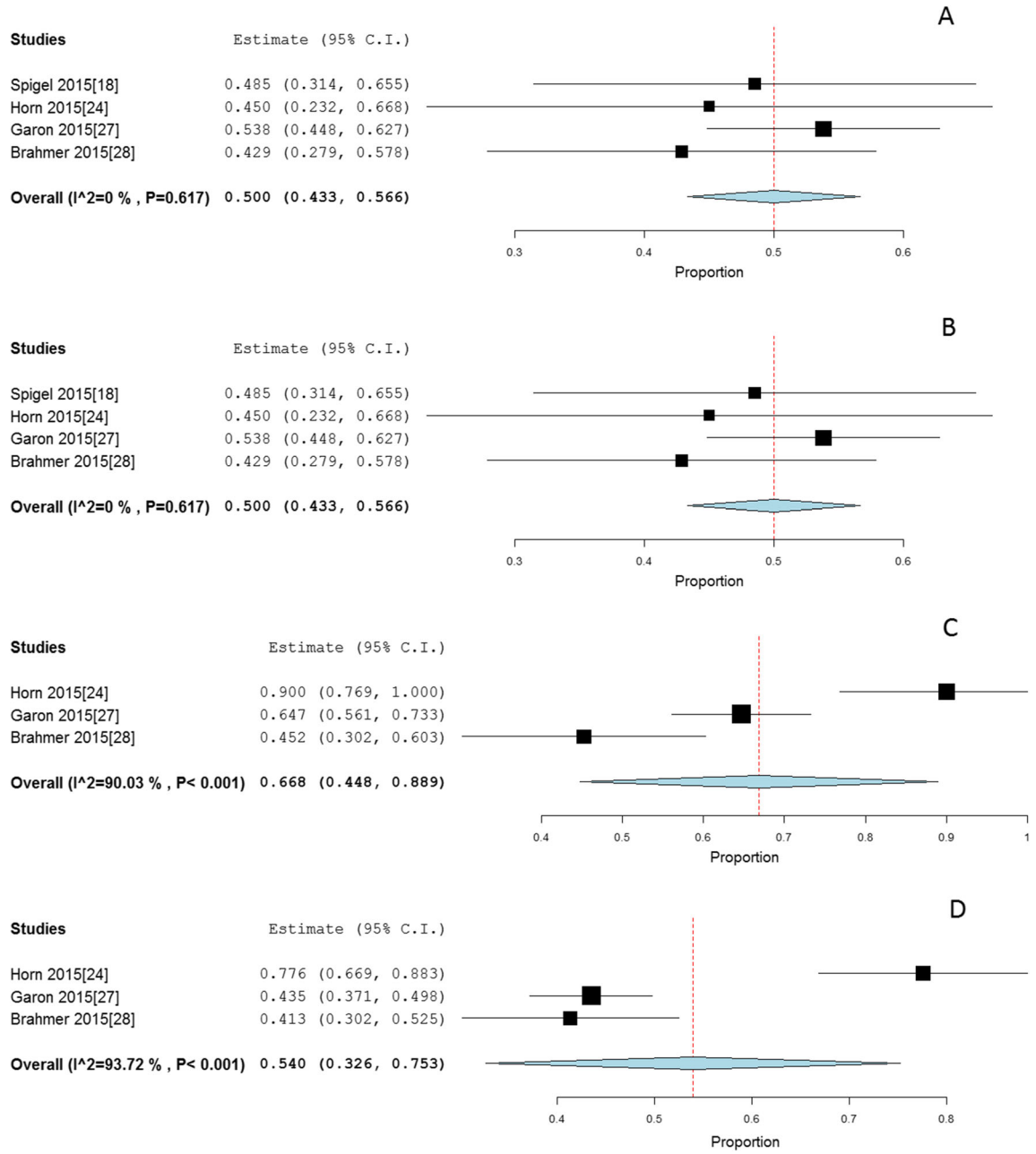

Fig. 5 Summary 6-month PFS for PD-L1 positive (**a**) and negative NSCLC (**b**), 1-year OS for PD-L1 positive (**c**) and negative NSCLC (**d**)

with big heterogeneity (I^2 = 66.7 %, p = 0.029). Anti-PD-1/PD-L1 therapy achieved a superior PFS in PD-L1 positive NSCLC patients (Z = 3.72, $p < 0.001$). Three studies reported results of OSR_{1y} for PD-L1 positive NSCLC. The summary OSR_{1y} was 66.8 % (95%CI 44.8 %, 88.9 %) (Fig. 5c), with high heterogeneity (I^2 = 90.0 %, $p < 0.001$). Three studies reported results of OSR_{1y} for PD-L1 negative NSCLC. The summary OSR_{1y} was 54.0 % (95%CI 32.6 %, 75.3 %) (Fig. 5d), with high heterogeneity (I^2 = 93.7 %, $p < 0.001$). Anti-PD-1/PD-L1 therapy achieved similar OS in both PD-L1 positive and negative NSCLC patients (Z = 0.77, p = 0.441).

Discussion

Activated T cells, B cells and myeloid cells express PD-1. When PD-1 binds to its ligands PD-L1 or PD-L2, it induces inhibition and exhaustion of T cells. Tumor cells "smartly" utilize this approach to protect itself from immune elimination by high expressing PD-L1. PD-1 also binds to PD-L2, while the function of PD-L2 is unknown. To date, there are several drugs targeting this pathway, including Nivolumab (BMS-936,558), pembrolizumab (MK-3475), AMP-224, and pidilizumab (CT-011) targeting PD-1, and MPDL-3280A, MEDI-4736, and BMS-936,559 (MDX-1105) targeting PD-

L1. Nivolumab is the first approved anti-PD-1 drug, and showed great OS and PFS improvement in previous untreated melanoma as compared with dacarbazine. [30] Success in melanoma triggers enormous incentive to investigate anti-PD-1/PD-L1 drugs on NSCLC as well as other tumors. In this article, we will focus on NSCLC. A series of studies has investigate anti-PD-1/PD-L1 drugs on NSCLC, however, most of these studies are designed as phase I or phase II trials. Therefore, it is necessary to summarize current data to help future studies.

In this studies, we found the ORR across the studies varied from 10.2 to 66.7 % with great heterogeneity. Different designing types may contribute to this heterogeneity. We hence undertook meta-regression and subgroup analyses. Meta-regression analysis demonstrated lines of prior therapy and PD-L1 expression had a significant correlation with ORR. Squamous cell lung cancer was supposed to associate with poor efficacy to chemotherapy or tyrosine kinase inhibitors. While for anti-PD-1/PD-L1 therapy, we did not observe that difference between squamous and non-squamous cell lung cancer. The pooled ORR for non-squamous and squamous cell lung cancer were 18.5 and 17.9 %, respectively. In other words, anti-PD-1/PD-L1 therapy may be not limited by lung cancer cell type. First-line of Platinum-based chemotherapy for advanced or metastasis NSCLC have an ORR of 25 to 35 %. [31] A recent randomized phase III study compared nivolumab with docetaxel as 2nd line therapy in patients with squamous cell lung cancer. [28] It showed ORR, OS, and PFS treated with nivolumab were significantly better than docetaxel. Our study showed 1st line anti-PD-1/PD-L1 therapy achieved an ORR of 36.5 %. This result was encouraging because anti-PD-1/PD-L1 achieved similar ORR compared with platinum-based therapy for advanced or metastasis NSCLC. PD-L1 expression level of tumor cells is supposed to be a promising predictor, and Wang *et al.* found NSCLC patients with positive PD-L1 expression exhibited poor OS. [32] A meta-analysis conducted by Zhang *et al.* also found Epithelial-originated cancer patients with positive expression of PD-L1 on tumor tissues were associated with significantly poorer OS when compared to those with negative expression of PD-L1. [33] This can be explained by inhibitory effect of PD-1 binding to PD-L1. Our result showed anti-PD-1/PD-L1 drugs rendered a more potent efficacy to PD-L1 positive patients. This was in accordance with previous studies. [34, 35] However, a recent phase III study found in squamous cell lung cancer, the efficacy of nivolumab did not correlate with PD-L1 expression. In our study, the pooled ORR for PD-L1 positive and negative lung cancer patients were 29.6 and 13.5 %, respectively. Anti-PD-1/PD-L1 therapy achieved a better ORR in PD-L1 positive patients ($Z = 3.49$, $p < 0.001$). Additionally, we compared PFS and OS with different settings. Due to lack of sufficient data, only $PFSR_{6m}$ and OSR_{1y} for PD-L1 positive and negative NSCLC were compared. We found difference between $PFSR_{6m}$ for PD-L1 positive and negative NSCLC was significant (50.0 % vs. 27.0, $p < 0.001$), while not significant for OSR_{1y} (66.8 % vs. 54.0 %, $p = 0.441$). Although we did not access safety of anti-PD-1/PD-L1 in this study, Jia *et al.* [36] conducted a meta-analysis evaluation safety of anti-PD-1/PD-L1 antibody for NSCLC and demonstrated it had a tolerable adverse-effect profile.

Nevertheless, there are several limitations in the study. Most of the included articles article were non-comparable studies and part of them had small sample size. Additionally, the definition of PD-L1 positive differed in these studies. Furthermore, single arm meta-analysis was not maturation compared with traditional pair-wise meta-analysis.

In **conclusion**, we thought it was timely and necessary to conduct this meta-analysis. Anti-PD-1/PD-L1 antibody can serve as a promising treatment option for NSCLC. Patients with positive PD-L1 expression may benefit more from anti-PD-1/PD-L1 therapy. 1st-line anti-PD-1/PD-L1 therapy can be chosen as the best modality. Squamous cell lung cancer also benefit from anti-PD-1/PD-L1 therapy.

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Compliance with Ethical Standards

Conflict of Interest All authors declare that there is no conflict of interests.

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