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Predictive effect of PD-L1 expression for immune checkpoint inhibitor (PD-1/PD-L1 inhibitors) treatment for non-small cell lung cancer: A meta-analysis

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ABSTRACT

Background: Programmed death-ligand-1 (PD-L1) is a well-known predictive biomarker in non-small cell lung cancer (NSCLC) patients, however, its accuracy remains controversial. Here, we investigated the correlation between PD-L1 expression level and efficacy of its inhibitors, and hence assessed the predictive effect of PD-L1 expression.

Methods: Studies that evaluated the efficacy of programmed death-1 (PD-1)/ PD-L1 inhibitors in advanced NSCLC patients according to tumor PD-L1 expression levels were searched for on Medline, Cochrane Library, and Embase. The pooled risk ratio (RR) and 95% confidence intervals (95% CIs) were calculated for the objective response rate (ORR) with overall survival (OS) and progression-free survival (PFS) were measured in terms of hazard ratio (HR) and the corresponding 95% CIs.

Results: 1432 NSCLC patients from six randomized controlled trials (RCTs) were included and three PD-1/PD-L1 inhibitors (atezolizumab, nivolumab, and pembrolizumab) were used to treat the patients. A significantly higher ORR was observed in the high PD-L1 expression group compared to the low expression group (0.35 [95% CI, 0.30–0.40] vs 0.11 [95% CI, 0.09–0.14]). The results of the subgroup analysis, grouped by the type of drugs and antibodies which assess immune checkpoint inhibitors were identical with the pooled result. However, our study showed that PD-L1 expression was neither prognostic nor predictive of overall survival (OS) or progression-free survival (PFS) in patients treated with PD-1/PD-L1 inhibitors compared to chemotherapy.

Conclusions: PD-L1 can be a predictive biomarker for ORR. Nevertheless, PD-L1 expression is not a good predictive tool for OS and PFS.

1. Introduction

Lung cancer is the most commonly diagnosed cancer and the main cause of death associated with cancer. Additionally, non-small cell lung cancer (NSCLC) accounts for a large percentage of lung cancer [1]. In addition to chemotherapy, radiotherapy, and targeted therapy, immunotherapy has also become a significant treatment strategy for NSCLC recently. The emergence of immune checkpoint inhibitors (ICIs) has increased the number of therapies available for treatment [2].

Immune checkpoints are cell surface receptors expressed by immune cells, which are composed of a group of molecules that can be both co-stimulatory and co-inhibitory. The best-known immune checkpoints are the cytotoxic T-lymphocyte protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1/PD-L1) [3–6]. PD-1 is an immunosuppressive transmembrane protein expressed on the surface of T cells which has two ligands PD-L1 and PD-L2, respectively [2,4–6]. In the tumor microenvironment, tumor cells are able to express immune checkpoint proteins PD-L1 or PD-L2 which bind to the immune checkpoint receptor PD-1 on the surface of activated T-cells, resulting in tyrosine phosphorylation of the intracellular domain of PD-1 and recruitment of

Abbreviations: PD-L1, programmed death-ligand-1; PD-1, programmed cell death protein 1; NSCLC, non-small cell lung cancer; RR, risk ratio; 95% CI, 95% confidence interval; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; RCT, randomized controlled trial; CTLA-4, cytotoxic T-lymphocyte protein 4; ICI, immune checkpoint inhibitor; FDA, food and drug administration; PRISMA, preferred reporting items for systematic reviews and meta-analyses; IHC, immunohistochemistry; bTMB, blood-based tumor mutational burden

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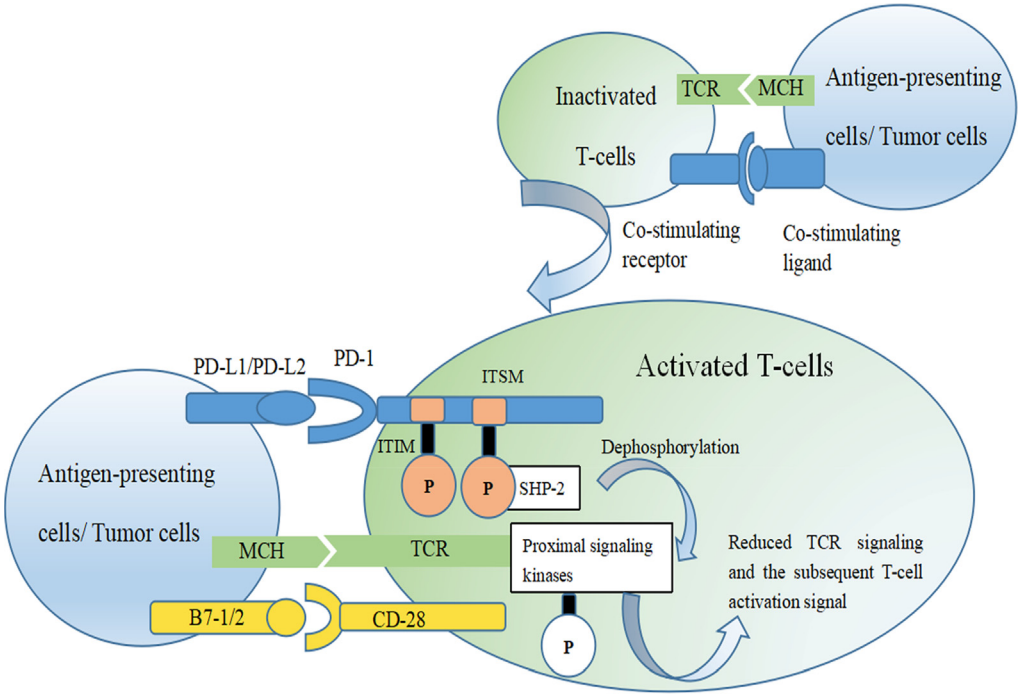

Fig. 1. PD-1 signaling pathway inhibits TCR signaling. Tumor cells express PD-L1 or PD-L2 which bind to PD-1 on the surface of activated T-cells, resulting in tyrosine phosphorylation of the the intracellular immunoreceptors tyrosine-based switch motif (ITSM) and tyrosinebased inhibitory motif (ITIM) of PD-1 and recruitment of tyrosine phosphatase SHP2, to reduce the phosphorylation of proteins involved in the TCR signaling pathway and the subsequent T-cell activation signal.

tyrosine phosphatase SHP2, to reduce the phosphorylation of proteins involved in the TCR signaling pathway and the subsequent T-cell activation signal (Fig. 1). Consequently, on inhibition of immune checkpoints by ICIs restores T-cell immune response against cancer cells [4–6].

Since 2011, the FDA-approved therapeutic antibodies such as ipilimumab, nivolumab, pembrolizumab, atezolizumab which have resulted in a major breakthrough in the treatment of various cancers [7]. Among the ICIs available for NSCLC patients, pembrolizumab was approved by the US Food and Drug Administration (FDA) as a first-line treatment for advanced patients whose tumor presents ≥ 50% of PD-L1 positive tumor cells and the second- or higher-line treatment in patients with PD-L1 ≥ 1%. Nivolumab and atezolizumab have been approved by FDA as second- or higher-line treatments regardless of PD-L1 expression for advanced NSCLC patients [8]. There are many completed clinical trials and ongoing clinical trials exploring the effectiveness and safety of PD-1/PD-L1 inhibitors. As such, tumor PD-L1 expression has been suggested as a potential predictive biomarker; however, controversial and different views have also been reported.

Hence, we conducted a meta-analysis of randomized controlled trials (RCTs) and evaluated the pooled efficacy of ICIs in advanced NSCLC patients to provide an overview of the relationship between PD-L1 expression status and response of patients to treatment, and therefore to explore the feasibility of PD-L1 expression as a predictive marker of PD-1/ PD-L1 inhibitor immunotherapy.

2. Methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and presented based on the Cochrane Handbook for Systematic Reviews of Interventions.

2.1. Search strategy

We conducted an exhaustive literature search of PubMed, EMBASE and Cochrane Library for RCTs that compared the ORR in high PD-L1 expression group and low PD-L1 expression group. The search terms included “PD-L1”, “PD-1 inhibitor”, “PD-L1 biomarker”, “CTLA-4 inhibitor”, “immune checkpoint inhibitor”, “atezolizumab”, “nivolumab”, “duralumin”, “avelumab”, “pembrolizumab” and “lung neoplasms”. The detailed search strategy is Table A.1. We did not limit the search to any language or date of publication of the paper. The literature search was last updated on July 31, 2019. Two reviewers (B.-B. Z. and Y.L.) independently searched all the titles, and the abstracts and references of relevant studies were also reviewed for applicable literature.

2.2. Selection criteria

Trials were selected and excluded based on the PICOS principle, as follows: (1) Participants: Only NSCLC patients would be included. Patients who had previously received chemotherapy, radiation therapy or surgical treatment were acceptable but those who had been treated with systemic immunosuppressive therapy or had an active autoimmune disease were excluded. Patient selection should have allowed for division into two groups (high and low) on the basis of PD-L1 expression level. (2) Interventions: Interventions of ICI (atezolizumab, nivolumab, durvalumab, avelumab, and pembrolizumab) monotherapy would be included. If radiotherapy was used as an intervention in the trial then, it would be excluded. (3) Comparisons: ORR, OS and PFS were observed in the high PD-L1 expression group in comparison to the low PD-L1 expression group. (4) Outcomes: ORR, OS and PFS of NSCLC patients should be reported. (5) Study design: RCTs were eligible. Cohort studies, case-control studies, case reports, retrospective studies, systematic reviews, and meta-analyses were excluded. And some ongoing trials that have not yet published their results or the experimental results which we could not be obtained were not within our scope.

2.3. Data extraction

Two reviewers (B.-B. Z. and Y.L.) independently performed data extraction from the qualified studies. Differences were resolved through discussion. For each study, the following information was extracted: first author’s name, year of publication, trial phase, type of immune checkpoint inhibitor, number of patients, immune checkpoint inhibitor dose, cut-off points of PD-L1 expression, type of antibodies assessing immune checkpoint inhibitor, type of cells assessing PD-L1 level,

Table 1
Characteristics of the included studies.

Study	Year	Design	Drug	Molecule	Number of patients	Dose	Cut-off	Antibody	Sample	Histology	Response assessment
Fehrenbacher [9]	2018	Randomized phase III study	Atezolizumab	PD-L1 inhibitor	607	1200 mg every 3 weeks	TC ≥ 50% or IC ≥ 10%	VENTANA SP142	Tumor and infiltrating cells	Non-squamous or squamous	RECIST v1.1
Hui [10]	2017	International, randomized, open-label, phase 1 study	Pembrolizumab	PD-1 inhibitor	91	2 mg/kg every 3 weeks or 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks	≥50%	Dako 22C3	Tumor	Adenosquamousor squamous or non-squamous	RECIST v1.1
Chatterjee arm1 [11]	2016	Randomized phase Ib trial	Pembrolizumab	PD-1 inhibitor	50	2 mg/kg every 3 weeks	≥50%	Dako 22C3	Tumor	Adenosquamousor squamous or non-squamous	RECIST v1.1
Chatterjee arm2 [11]	2016	Randomized phase Ib trial	Pembrolizumab	PD-1 inhibitor	109	10 mg/kg every 3 weeks	≥50%	Dako 22C3	Tumor	Adenosquamousor squamous or non-squamous	RECIST v1.1
Chatterjee arm3 [11]	2016	Randomized phase Ib trial	Pembrolizumab	PD-1 inhibitor	83	10 mg/kg every 2 weeks	≥50%	Dako 22C3	Tumor	Adenosquamousor squamous or non-squamous	RECIST v1.1
Fehrenbacher [12]	2016	Multicentre, randomised, open-label phase 2 trial	Atezolizumab	PD-L1 inhibitor	144	1200 mg every 3 weeks	TC ≥ 50% or IC ≥ 10%	VENTANA SP142	Tumor and infiltrating cells	Non-squamous or squamous	RECIST v1.1
Brahmer [13]	2015	Randomised phase 3 study	Nivolumab	PD-1 inhibitor	117	3 mg/kg every 2 weeks	≥5%	Dako clone 28–8	Tumor	Squamous	RECIST v1.1
Borghaei [14]	2015	Randomised phase 3 study	Nivolumab	PD-1 inhibitor	231	3 mg/kg every 2 weeks	≥5%	Dako clone 28–8	Tumor	Non-squamous	RECIST v1.1

histology, standard of response assessment (Table 1).

2.4. PD-L1 expression analysis

In each study, tumoral PD-L1 expression was measured by different test antibodies and different immunohistochemistry (IHC) cut-off points. The nivolumab trial used the IHC antibody clone 28–8; in the pembrolizumab trial, the test used a clone 22C3 antibody and the atezolizumab trial used the SP142 clone [15]. Hence, in this meta-analysis, we set cut-off points as TC ≥ 50% or IC ≥ 10%, 5% and 50% for atezolizumab, pembrolizumab and nivolumab trials, respectively. If PD-L1 expression was less than the cut-off point, we defined it as part of the low expression group; if PD-L1 expression was no less than the cut-off point, we considered it as part of the high expression group.

2.5. Quality assessment

The Cochrane risk-of-bias criteria were utilized by two researchers (Y. L. and B .-B. Z.) to independently assess the methodological quality of the included RCTs, which included seven items: randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other biases (and any important concerns about bias not covered in the other domains in the tool) [16] (Table 2).

2.6. Statistical analysis

Statistical analyses were conducted using Stata 12.0. risk ratio (RR) and the corresponding 95% CIs for ORR were extracted from the included articles and the efficacy of PD-1 inhibitors versus chemotherapy was measured by HR for OS and PFS, with their corresponding 95% CIs. $P < 0.05$ was considered to be statistically significant. I-square value < 50% was treated as low-level heterogeneity, and > 50% was considered as high-level heterogeneity [17]. A fixed-model was used if the I-square was not over 50%. If the I-square value was over 50%, we used a random-model, subgroup analyses, meta-regression or sensitivity analyses. Stata 12.0 was also used to process original data in each study.

3. Results

3.1. Selection of studies

Fig. 2 represents the whole process of literature selection. In total, 14,172 results were obtained from the searches in the Pub Med, Cochrane Library, and Embase databases. Of these results, 3101 studies were excluded as duplicates. After the title and abstract screening, we found 283 studies were excluded as no available clinical outcomes; thus, 163 possibly eligible studies needed a full-text review. Eventually, we included 1432 patients from six RCTs according to inclusion criteria: three-phase III trials, one phase II trial and two-phase I trials [9–14].

3.2. Characteristics of included studies

In summary, three different drugs were analyzed, including atezolizumab, nivolumab, and pembrolizumab. PD-L1 expression and the ORR of patients were reported by all eligible studies. Only four eligible studies mentioned OS and PFS according to PD-L1 expression. Table 1 depicted the main characteristics of the included trials and the cut-off point of each study in this analysis.

3.3. PD-L1 expression level and ORR

All included studies reported the ORR. The ORR (95% CI) in PD-L1 high expression group and PD-L1 low expression group was 0.52

Table 2
Quality assessment by the Cochrane collaboration's tool.

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Fehrenbacher, 2018 [9]	Low risk	High risk	High risk	High risk	Low risk	Unclear risk	Unclear risk
Hui, 2017 [10]	High risk	Unclear risk	High risk	High risk	Low risk	Unclear risk	Unclear risk
Chatterjee, 2016 [11]	Unclear risk	Unclear risk	High risk	High risk	Unclear risk	Unclear risk	Unclear risk
Fehrenbacher, 2016 [12]	Low risk	High risk	High risk	High risk	Low risk	Unclear risk	Unclear risk
Brahmer, 2015 [13]	Unclear risk	Unclear risk	High risk	High risk	High risk	Unclear risk	Unclear risk
Borghaei, 2015 [14]	Unclear risk	Unclear risk	High risk	High risk	High risk	Unclear risk	Unclear risk

(0.33–0.71) and 0.14 (0.05–0.23) in Hui (2017) [10], 0.30 (0.11–0.49) and 0.25 (0.09–0.41) in Chatterjee (2016) arm 1 [11], 0.48 (0.33–0.63) and 0.10 (0.03–0.17) in Chatterjee (2016) arm 2 [11], 0.39 (0.22–0.56) and 0.13 (0.04–0.22) in Chatterjee (2016) arm 3 [11], 0.38 (0.19–0.57) and 0.09 (0.04–0.14) in Fehrenbacher (2016) [12], 0.21 (0.09–0.33) and 0.15 (0.07–0.23) in Brahmer (2015) [13], 0.36 (0.26–0.46) and 0.10 (0.05–0.15) in Borghaei (2015) [14], respectively. ORR (95% CI) was 0.31 (0.22–0.41) in PD-L1 the high expression group in Fehrenbacher (2018) [9]. Since we could not obtain the original data for PD-L1 low expression group from the study by Fehrenbacher et al. [9] in 2018, we did not include this data in the PD-L1 low expression group. First, the heterogeneity of the analysis of ORR was measured. The I-square value was 41.9% and 0.0% in the PD-L1 high expression group and the PD-L1 low expression group respectively, consequently we applied a fixed effect analysis model. The pooled ORR was significantly higher in the PD-L1 high expression group than in the PD-L1 low expression group (0.35 [95% CI, 0.30–0.40] vs 0.11[95% CI, 0.09–0.14]); thus, higher PD-L1 expression was associated with increased ORR on treatment with PD-1/ PD-L1 inhibitors which indicated that PD-L1 expression can be considered as an ORR biomarker in NSCLC patients. (Fig. 3)

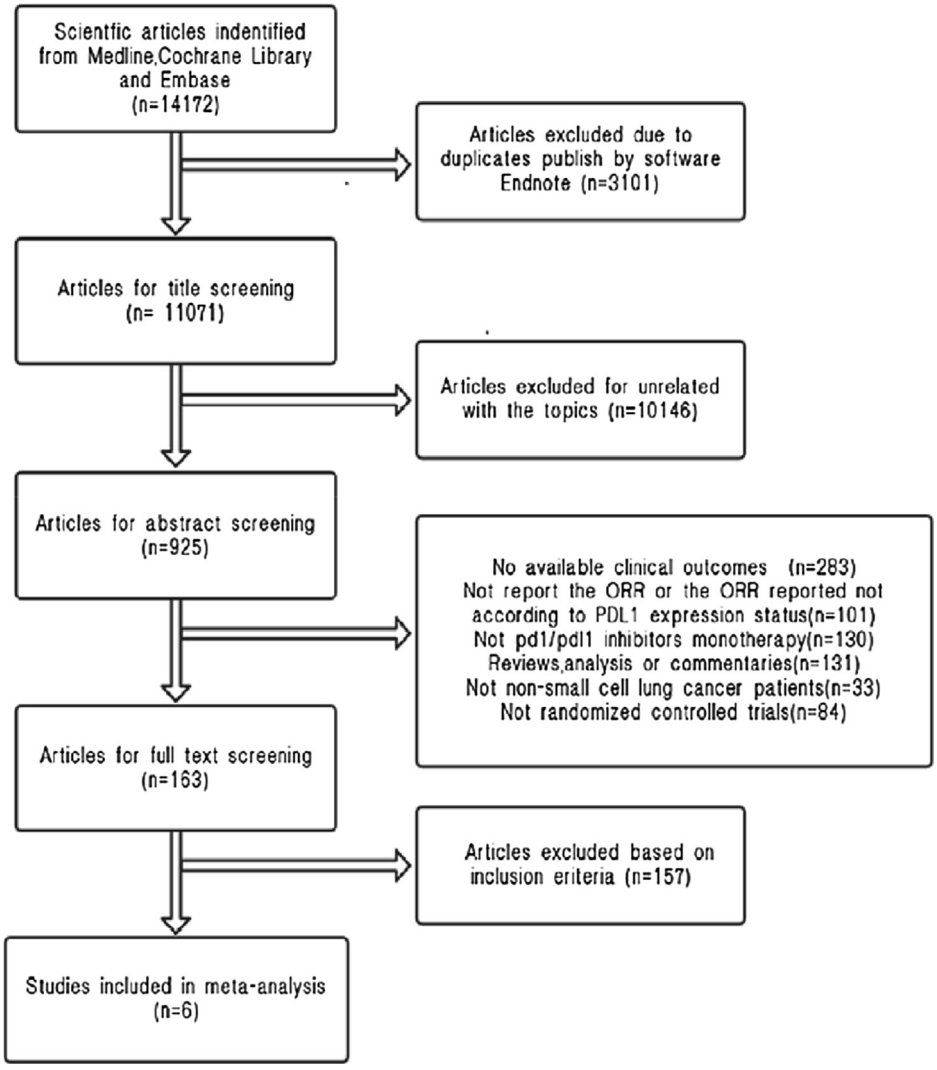

Fig. 2. Study selection process of this meta-analysis.

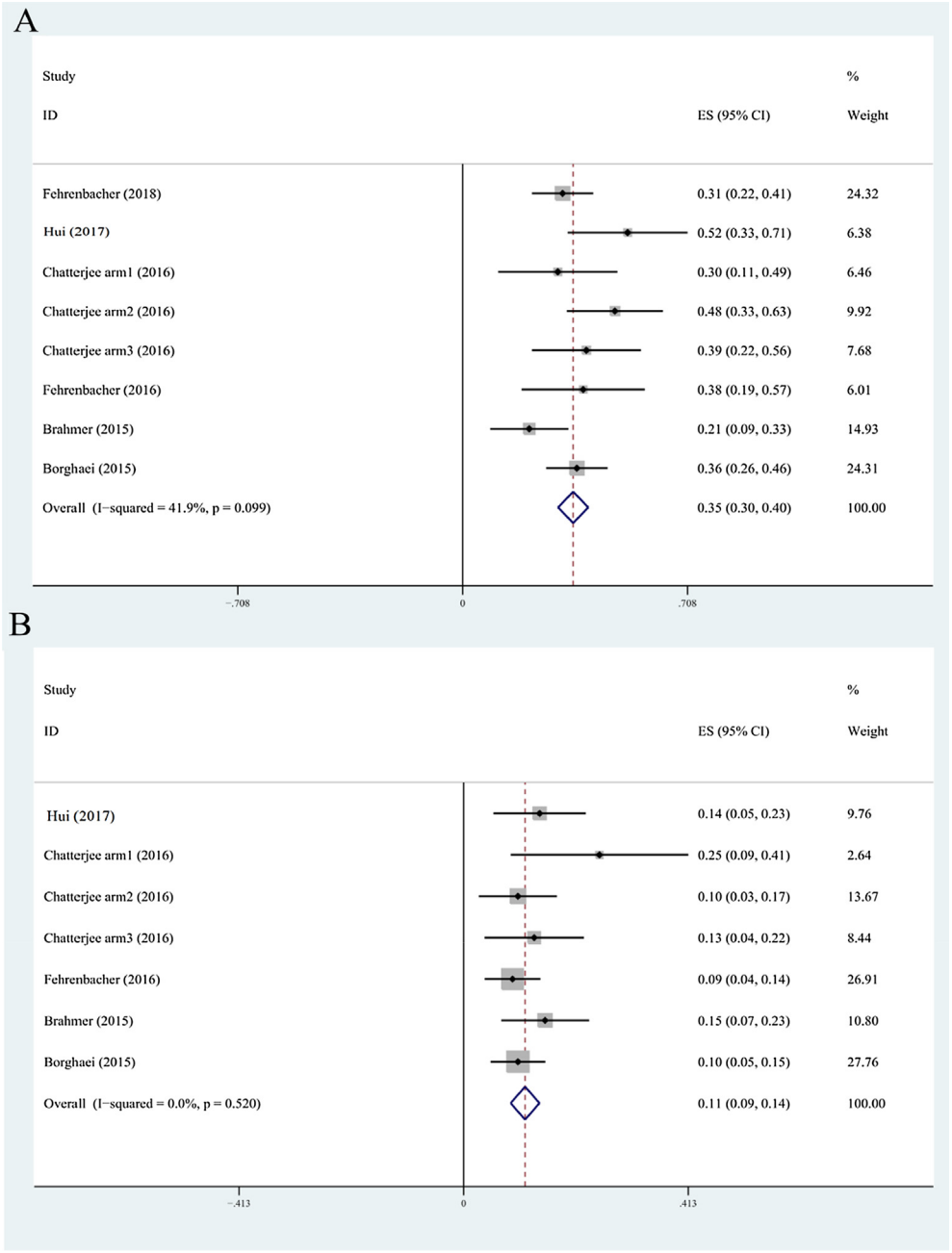

Fig. 3. Forest plots of objective response rate (ORR) in PD-L1 high expression group vs in PD-L1 low expression group. (A) Objective response rate (ORR) in PD-L1 high expression group; (B) Objective response rate (ORR) in PD-L1 low expression group.

3.4. Type of drugs or antibodies which assess immune checkpoint inhibitor and ORR

There were two studies using atezolizumab [9,12], four studies using pembrolizumab [10,11] and two studies using nivolumab (13,14). For pembrolizumab trials, ORR was 0.43 (95% CI, 0.34–0.51) in the PD-L1 high expression group which was higher than in the PD-L1 low expression group (0.13[95% CI, 0.08–0.18]). For nivolumab trials, ORR was 0.30 (95% CI, 0.23–0.38) and 0.11 (95% CI, 0.07–0.16) in the PD-L1 high expression group and PD-L1 low expression group, respectively. ORR was 0.33 (95% CI, 0.24–0.41) in the PD-L1 high expression group and 0.09 (95% CI, 0.04–0.14) in the PD-L1 low expression group in atezolizumab trials. (Fig. 4) As expected, higher ORR was observed in the high PD-L1 expression group than in the low PD-L1 expression group, which was in accordance with the pooled result. Each drug uses a specific antibody to measure the PD-L1 expression level. Hence, the result of subgroup analysis according to the type of antibodies which assess immune checkpoint inhibitor concentration was identical to the result of subgroup analysis for the type of drugs. (Fig. 5)

3.5. PD-L1 expression level and OS

Only four studies reported OS data. The OS (95% CI) of PD-1 inhibitor monotherapy versus chemotherapy in PD-L1 high expression group and PD-L1 low expression group was 0.53 (0.31–0.89) and 0.7 (0.47–1.02) in Brahmer (2015) [13], 0.43 (0.3–0.63) and 1.01(0.77–1.34) in Borghaei (2015) [14]. OS (95% CI) was 0.45 (0.3–0.68) and 0.49 (0.22–1.07) in the PD-L1 high expression group in Fehrenbacher (2018) [9] and Fehrenbacher (2016) [12], respectively. Since we could not obtain the original data of PD-L1 low expression

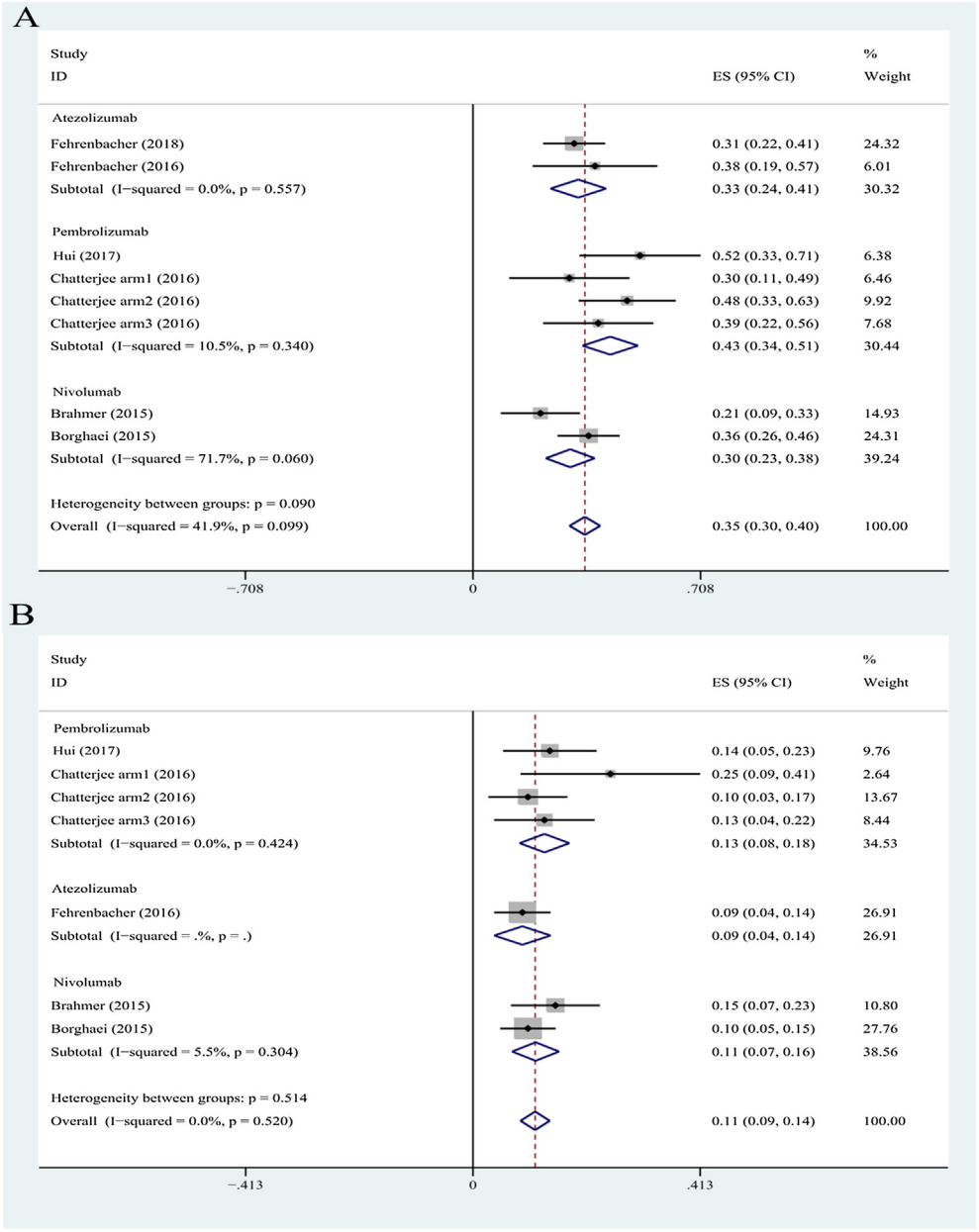

Fig. 4. Subgroups of objective response rate (ORR) for type of drugs in PD-L1 high expression group vs in PD-L1 low expression group. (A) Objective response rate (ORR) for type of drugs in PD-L1 high expression group; (B) Objective response rate (ORR) for type of drugs in PD-L1 low expression group.

group from the studies wrote by Fehrenbacher et al. [9] in 2018 or Fehrenbacher et al. [12] in 2016, we did not include these data in PD-L1 low expression group. The heterogeneity result with the I-square value was 0.0% and 56.1% in the PD-L1 high expression group and PD-L1 low expression group, respectively. The pooled OS was 0.46 (95% CI, 0.36–0.58) and 0.86 (95% CI, 0.60–1.23) in the PD-L1 high expression group and PD-L1 low expression group, respectively, which indicated that higher PD-L1 expression may not be associated with increased OS on treatment with PD-1/ PD-L1 inhibitors compared with chemotherapy (Fig. 6).

3.6. PD-L1 expression level and PFS

In Brahmer (2015) [13], the PFS (95% CI) of PD-1 inhibitor monotherapy versus chemotherapy in the PD-L1 high expression group and PD-L1 low expression group was 0.54 (0.32–0.9) and 0.75 (0.52–1.08), respectively; meanwhile in Borghaei (2015) [14], it was 0.54 (0.39–0.76) and 1.31 (1.01–1.71), respectively. Like OS, the original data of PFS in PD-L1 low expression group from the studies by Fehrenbacher et al. [9] in 2018 or Fehrenbacher et al. [12] in 2016 could not be obtained by us. Consequently, we only included PFS (95% CI) in the PD-L1 high expression group in Fehrenbacher (2018) [9] and Fehrenbacher (2016) [12] which was 0.59 (0.41–0.84) and 0.60 (0.31–1.16), respectively. The pooled result of PFS (95% CI) in the high PD-L1 expression group compared with low PD-L1 expression group (0.56 [95% CI, 0.46–0.69] vs 1.01 [95% CI, 0.58–1.74]) with I-square value of 0.0% and 83%, respectively, reflected that PD-L1 expression is not a good predictive tool for PFS. (Fig. 7)

4. Discussion

The appearance of ICIs has brought about a great breakthrough in the treatment of NSCLC patients [18]. However, whether to recommend ICIs to NSCLC patients still remains a major question for clinicians. It is

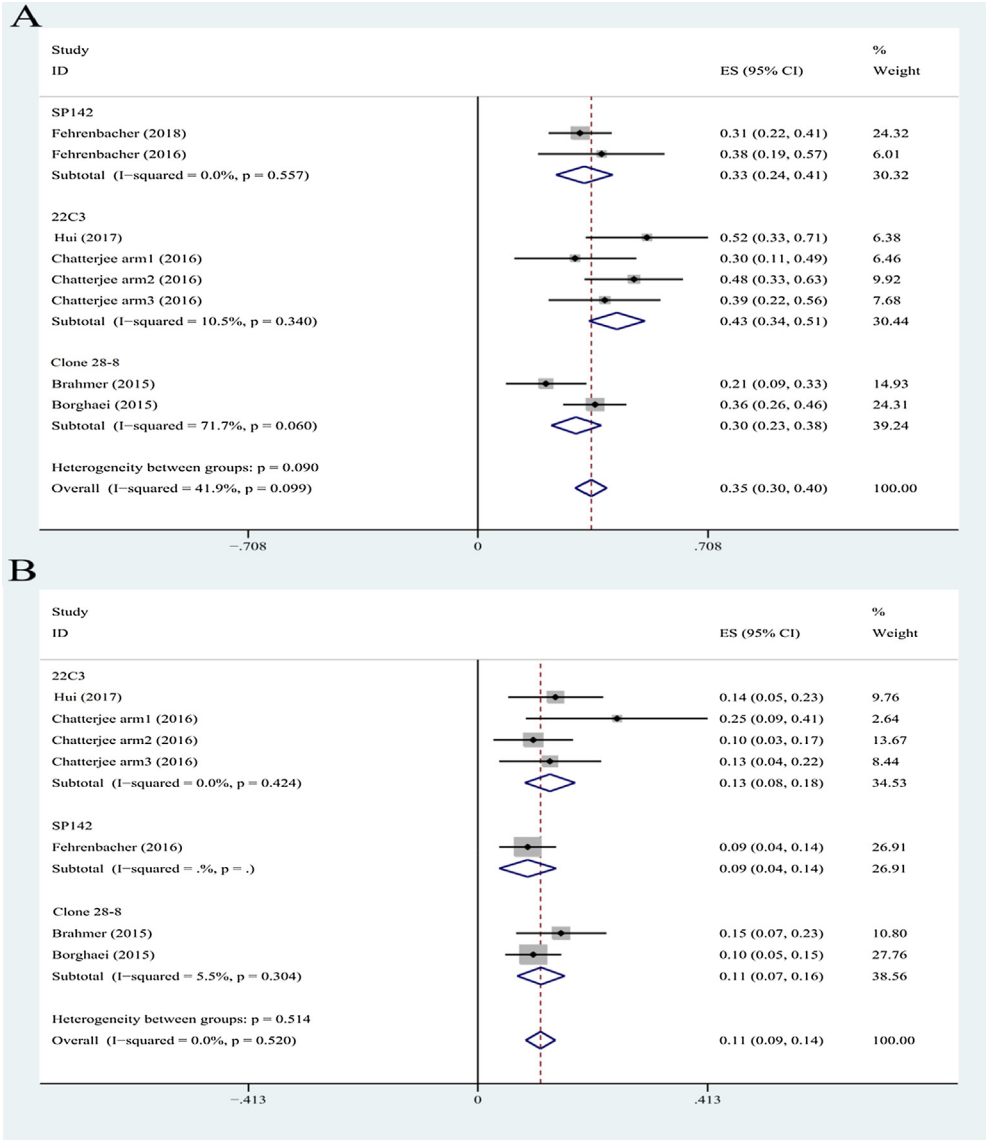

Fig. 5. Subgroup of objective response rate (ORR) for type of antibodies assessing immune checkpoint inhibitor in PD-L1 high expression group vs in PD-L1 low expression group. (A) Objective response rate (ORR) for type of antibodies assessing immune checkpoint inhibitor in PD-L1 high expression group; (B) Objective response rate (ORR) for type of antibodies assessing immune checkpoint inhibitor in PD-L1 low expression group.

also a complex decision-making for patients to choose whether to receive ICIs or not on the basis of curative effect and economic burden. In this case, we explored the relationship between PD-L1 expression and ORR, OS and PFS, and assessed whether PD-L1 can predict survival efficacy. This systematic meta-analysis of six randomized clinical trials indicated that PD-L1 can be considered as a biomarker of objective response rate for NSCLC patients. An enormously better effect was noticed in the PD-L1 high expression group than in the PD-L1 low expression group. Nevertheless, PD-L1 expression was neither prognostic nor predictive of OS and PFS.

The result of this study is consistent with other published articles in some respects. Aguiar et al. included 14 studies in a network meta-analysis and reported that the ORR was 27.6% among 931 PD-L1 positive patients meanwhile the ORR was 12.1% among 1084 PD-L1 negative patients. And in PD-L1 positive patients, the ORR was statistically remarkably higher (RR: 2.19; 95% CI: 1.63–2.94; $p < 0.01$) which indicated that PD-L1 expression was a predictive biomarker for response [19]. In another pooled analysis of nivolumab treated advanced non-small-cell lung cancer, the ORR was also higher in 237 PD-L1 positive patients than in 339 PD-L1 negative patients (27% vs 13%) [20]. However, higher PD-L1 expression was not linked with higher OS and PFS in our study.

Nevertheless, the randomized, open-label, international, phase 3 study by Brahmer et al. in advanced squamous-cell non–small cell lung cancer patients who were treated with nivolumab or docetaxel revealed that the remarkable benefit of using nivolumab was observed regardless of PD-L1 expression level and the PD-L1 expression was neither prognostic nor predictive of any of the efficacy endpoints. The interaction P-value of nivolumab monotherapy was 0.9364, 0.2908 and 0.6411 according to the prespecified PD-L1 expression levels 1%, 5%, and 10%, respectively [13]. In this situation, exploring predictive biomarkers of response to PD-1/PD-L1 inhibitor agents in lung cancer has been a popular field. Bocanegra et al. through reporting two clinical cases and studying 32 cases of NSCLC patients indicated that quantification of systemic PD-L1+ myeloid cell subsets could be served as a simple biomarker for patients even if PD-L1 expression could not be measured through biopsies [21]. Meanwhile, blood-based tumor mutational burden (bTMB) and tumor inflammation are suggested to be reliable predictors of immunotherapy efficacy in NSCLC patients [22,23]. Finding better predictive biomarkers is the call of the hour and could

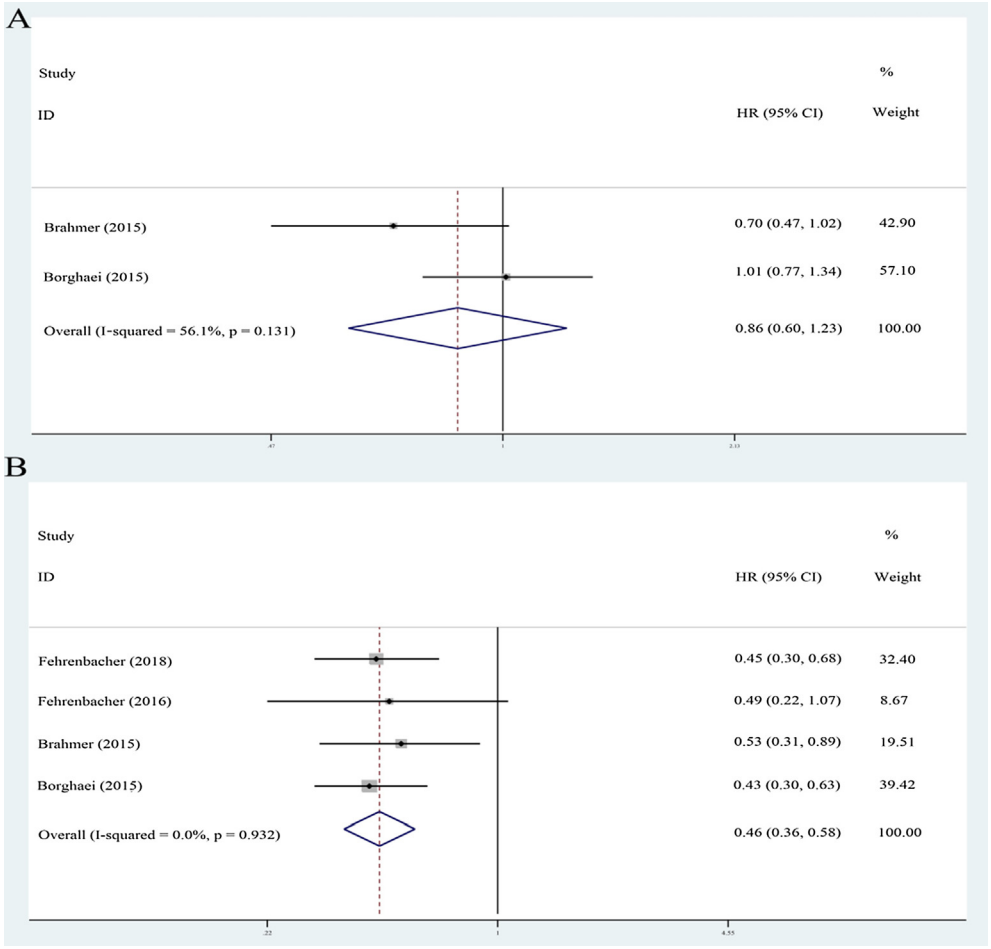

Fig. 6. Forest plots of overall survival (OS) in PD-L1 low expression group vs in PD-L1 high expression group. (A) Overall survival (OS) in PD-L1 low expression group; (B) Overall survival (OS) in PD-L1 high expression group.

lead to a breakthrough in therapy.

In this study, we confirmed that PD-L1 expression can be a potential biomarker for higher ORR in the PD-L1 high expression group but not a good predictive biomarker for OS and PFS. Though some articles have analyzed ORR, OS, and PFS in NSCLC patients who were treated with PD-1/PD-L1 inhibitors, our study has several accomplishments. First, we included the latest published literature on RCTs. Second, Tartarone et al. included seven studies in a meta-analysis and indicated that PD-1/PD-L1 inhibitors showed very robust efficacy over docetaxel when considering the overall survival, while in terms of progression-free survival the therapy with PD-1/PD-L1 inhibitors was slightly favored. This meta-analysis also reported that anti-PD-1 inhibitors given a more significant benefit than anti-PD-L1 inhibitors in terms of OS and PFS; however, excluding the KEYNOTE 010 trial that enrolled only PD-L1 positive patients, the subgroup difference remains only in terms of progression-free survival, which indicated that PD-L1 expression levels may affect the efficacy in PD-1/PD-L1 inhibitors treatment [24]. Thus, we analyzed the ORR, OS, and PFS according to different PD-L1 expression levels and divided them into high and low PD-L1 expression groups to explore the influence of PD-L1 expression level in our study. Third, we included not only non-squamous but also squamous tumors which increases the reliability of our study. Additionally, we conducted different and generally approved cut-off points of different PD-1 /PD-L1 inhibitors as grouping standards which increased the accuracy of this study. Different staining platforms and antibodies are used to measure PD-L1 expression level in different ICIs trails meanwhile type of cells (tumor or immune cells) in which PD-L1 levels were assessed is also different. PD-L1 IHC assays 22C3 DAKO and 28–8 DAKO assess PD-L1 expression in tumor cells while Ventana SP142 assay assesses levels in tumor and infiltrating cells [25]. Hence, 1%, 5%, 10% or 50% cut-off points are used in IHC assays 22C3 DAKO and 28–8 DAKO to stratification. PD-L1 expression on PD-L1 ≥ 50% of tumor cells or ≥ 10% of immune cells in the atezolizumab trials served as “TC3 or IC3” while PD-L1 on < 1% of tumor cells and < 1% of immune cells are considered as “TC0 and IC0” [26]. Therefore, we are in need of development of more accurate and concordant detection technology for assessment of PD-L1 levels.

Certainly, our study has some potential disadvantages similar to other meta-analyses. Only six randomized clinical trials that investigated the efficacy of PD-1/PD-L1 inhibitors were included in this meta-analysis, which is one of our limitations, therefore did not assess the publication bias in this study. Results of some ongoing trials, such as NCT02352948, NCT02581943, NCT02409342, NCT02273375 and NCT03091491, have not been published or the original data in these ongoing trials could not be obtained by us, and hence we did not include these trials. Our study only included three immune checkpoint inhibitors which cannot represent all kinds of PD-1/PD-L1 inhibitors. Only two articles reported the one-year OS rate, so we did not conduct the analysis of the same. High heterogeneity in PD-L1 low expression group in the analysis of OS and PFS is another problem, which may be caused by the small sample size in the PD-L1 low expression group. Thus, more randomized controlled trials should be analyzed to establish and report these clinical results. The source and timing for sample collection, the size of tissue samples, and the accuracy of different PD-L1 IHC assays remain as issues. The BP2 study summarized that PD-L1 IHC assay Ventana SP142 represents lower sensitivity to assess PD-L1

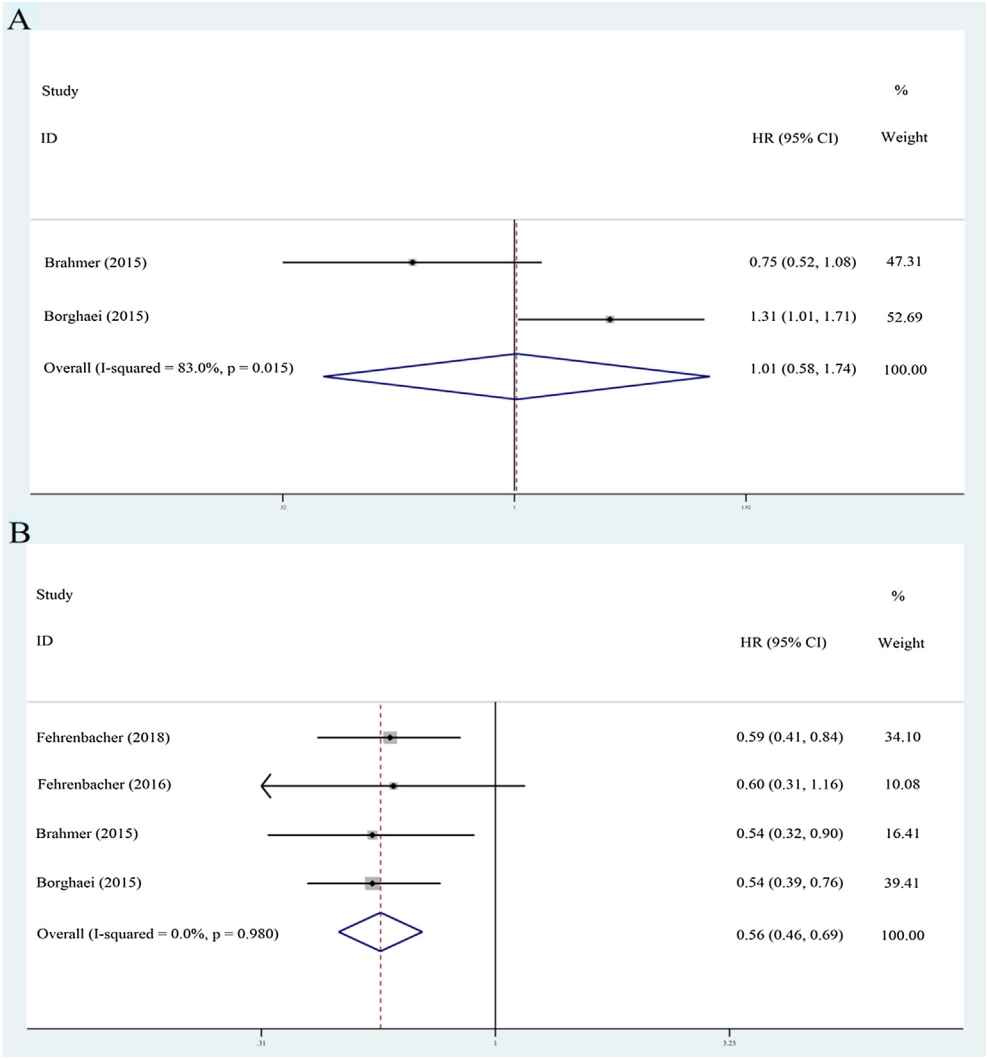

Fig. 7. Forest plots of progression-free survival (PFS) in PD-L1 low expression group vs in PD-L1 high expression group. (A) Progression-free survival (PFS) in PD-L1 low expression group; (B) Progression-free survival (PFS) in PD-L1 high expression group.

expression on tumor cells than IHC assays 22C3 DAKO and 28–8 DAKO, while 22C3 DAKO and 28–8 DAKO assays have comparable sensitivity [25]. Consequently, more research must be carried out to mitigate these issues. The ORR was the only outcome that we summarized and some articles have reported that higher PD-L1 levels were likely to correlate with better OS in advanced NSCLC patients [27,28]. Therefore, more studies are required to explore potential biomarkers.

In addition, a study suggested that EGFR TKIs played an important role in delaying disease progression in elderly patients with advanced NSCLC [29] and another study indicated that patients with lung cancer had genetic mutations which may also influence the curative effect [30]. The studies indicated that that the same treatment had different effects on different populations. For there was no separate available data from elderly patients or some population, we did not analyze it. Thus, further studies are needed on the efficacy of immune checkpoint inhibitor treatment in specific populations. And the safety of ICIs needs to be considered though ICIs take great effect. The review conduted by Zhu et al. exhibited that no enough evidence could suggest survival benefit from adding immunotherapy (excluding checkpoint inhibitors) to surgery or radiotherapy for NSCLC patents (stages I to III) [31]. And studies explored by Akamatsu et al. [32], Baldini et al. [33] and Sun et al. [34] indicated that the use of ICIs needed to be considered carefully for immune-related adverse events were common in NSCLC patents who were treated with ICIs.

Moreover, the network meta-analysis studied by Dafni et al. [35] included 12 phase-III studies with 9236 metastatic NSCLC patients indicated that significant PFS benefit was found in the PD-L1-high patients treated with the combination of chemotherapy with - atezolizumab or pembrolizumab and the meta analysis studied by Kim et al. [36] exhibited that pembrolizumab plus chemotherapy has a better PFS than pembrolizumab monotherapy for patients with NSCLC with PD-L1 TPS ≥ 50%, which indicated that PD-L1 status may be a predictive biomarker in PD-1/PD-L1 inhibitors treatment combined with chemotherapy or other therapies for PFS, differing with our conclusion that PD-L1 expression level was neither prognostic nor predictive of PFS. The articles written by Zeng et al. also indicated that ICIs plus chemotherapy increased cost effectiveness for previously untreated metastatic NSCLC patients [37]. Consequently, more studies are required to explore the predictive efficacy of PD-L1 expression level.

5. Conclusions

PD-L1 expression is a predictive biomarker for ORR for PD-1/PD-L1 inhibitors in advanced NSCLC patients; on the contrary, it is neither prognostic nor predictive of OS and PFS in advanced NSCLC patients who were treated with PD-1/ PD-L1 inhibitors compared with chemotherapy.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Author contributions

Binbin Zhang and Yi Liu analyzed the data and wrote the first draft. Ran Wang and Sijing Zhou designed the study, proofread and revised the submission. Huihui Jiang directed the statistical analyses of the data. Ke Zhu retrieved documents and extracted data. All authors discussed the results and approved the final manuscript.

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Appendix A. Supplementary data

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References

[1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA: A Can. J. Clin. 68 (6) (2018) 394–424.
[2] N.F. Pistamaltzian, V. Georgoulias, A. Kotsakis, The role of immune checkpoint inhibitors in advanced non-small cell lung cancer, Expert Rev. Respirat. Med. 13 (5) (2019) 435–447.
[3] S. Pesce, M. Greppi, F. Grossi, G. Del Zotto, L. Moretta, S. Sivori, et al., PD/1-PD-Ls checkpoint: insight on the potential role of NK cells, Front. Immunol. 10 (2019) 1242.
[4] L. Xia, Y. Liu, Y. Wang, PD-1/PD-L1 blockade therapy in advanced non-small-cell lung cancer: current status and future directions, Oncologist 24 (Suppl 1) (2019) S31–S41.
[5] da Silva JL, Dos Santos ALS, Nunes NCC, de Moraes Lino da Silva F, Ferreira CGM, de Melo AC. Cancer immunotherapy: the art of targeting the tumor immune microenvironment. Can Chemoth Pharmacol 2019;84(2):227–40.
[6] X. Li, C. Shao, Y. Shi, W. Han, Lessons learned from the blockade of immune checkpoints in cancer immunotherapy, J. Hematol. Oncol. 11 (1) (2018) 31.
[7] Lee HT, Lee SH,Heo YS. Molecular Interactions of Antibody Drugs Targeting PD-1, PD-L1, and CTLA-4 in Immuno-Oncology. Molecules (Basel, Switzerland). 2019;24(6).
[8] S. Lantuejoul, D. Damotte, V. Hofman, J. Adam, Programmed death ligand 1 immunohistochemistry in non-small cell lung carcinoma, J. Thoracic Disease 11 (Suppl 1) (2019) S89–s101.
[9] L. Fehrenbacher, J. von Pawel, K. Park, A. Rittmeyer, D.R. Gandara, S. Ponce Aix, et al., Updated efficacy analysis including secondary population results for OAK: a randomized phase III study of atezolizumab versus docetaxel in patients with previously treated advanced non-small cell lung cancer, J. Thoracic Oncol.: Off. Publ. Int. Assoc. Study Lung Can. 13 (8) (2018) 1156–1170.
[10] R. Hui, E.B. Garon, J.W. Goldman, N.B. Leighl, M.D. Hellmann, A. Patnaik, et al., Pembrolizumab as first-line therapy for patients with PD-L1-positive advanced non-small cell lung cancer: a phase 1 trial, Ann. Oncol: Off. J. Eur. Soc. Med. Oncol. 28 (4) (2017) 874–881.
[11] M. Chatterjee, D.C. Turner, E. Felip, H. Lena, F. Cappuzzo, L. Horn, et al., Systematic evaluation of pembrolizumab dosing in patients with advanced non-small-cell lung cancer, Ann Oncol.: Off. J. Eur. Soc. Med. Oncol. 27 (7) (2016) 1291–1298.
[12] L. Fehrenbacher, A. Spira, M. Ballinger, M. Kowanetz, J. Vansteenkiste, J. Mazieres, et al., Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial, Lancet (London, England). 387 (10030) (2016) 1837–1846.
[13] J. Brahmer, K.L. Reckamp, P. Baas, L. Crino, W.E. Eberhardt, E. Poddubskaya, et al., Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer, New Engl. J. Med. 373 (2) (2015) 123–135.
[14] H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, et al., Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer, New Engl. J. Med. 373 (17) (2015) 1627–1639.
[15] M. Hersom, J.T. Jorgensen, Companion and complementary diagnostics-focus on PD-l1 expression assays for PD-1/PD-L1 checkpoint inhibitors in non-small cell lung cancer, Therap Drug Monit 40 (1) (2018) 9–16.
[16] J.P. Higgins, D.G. Altman, P.C. Gotzsche, P. Juni, D. Moher, A.D. Oxman, et al., the cochrane collaboration's tool for assessing risk of bias in randomised trials, BMJ (Clinical research ed). 343 (2011) d5928.
[17] C.T. Smith, P.R. Williamson, A.G. Marson, An overview of methods and empirical comparison of aggregate data and individual patient data results for investigating heterogeneity in meta-analysis of time-to-event outcomes, J Eval Clin Pract. 11 (5) (2005) 468–478.
[18] K. Yoneda, N. Imanishi, Y. Ichiki, F. Tanaka, immune checkpoint inhibitors (ICIs) in non-small cell lung cancer (NSCLC), J UOEH. 40 (2) (2018) 173–189.
[19] P.N. Aguiar Jr., R.A. De Mello, P. Hall, H. Tadokoro, Lopes G. Lima, PD-L1 expression as a predictive biomarker in advanced non-small-cell lung cancer: updated survival data, Immunotherapy. 9 (6) (2017) 499–506.
[20] P.N. Aguiar Jr., I.L. Santoro, H. Tadokoro, Lopes G de Lima, B.A. Filardi, P. Oliveira, et al., A pooled analysis of nivolumab for the treatment of advanced non-small-cell lung cancer and the role of PD-L1 as a predictive biomarker, Immunotherapy. 8 (9) (2016) 1011–1019.
[21] A. Bocanegra, G. Fernandez-Hinojal, M. Zuazo-Ibarra, H. Arasanz, PD-L1 expression in systemic immune cell populations as a potential predictive biomarker of responses to PD-L1/PD-1 blockade therapy in lung Cancer, Int. J. Mol. Sci. 20 (7) (2019).
[22] D.R. Gandara, S.M. Paul, M. Kowanetz, E. Schleifman, W. Zou, Y. Li, et al., Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab, Nat. Med. 24 (9) (2018) 1441–1448.
[23] D.B. Doroshow, M.F. Sanmamed, K. Hastings, K. Politi, D.L. Rimm, L. Chen, et al., Immunotherapy in non-small cell lung cancer: facts and hopes, Clin. Can. Res.: Off. J. Am. Assoc. Can. Res. (2019).
[24] A. Tartarone, G. Roviello, R. Lerose, R. Roudi, M. Aieta, P. Zoppoli, Anti-PD-1 versus anti-PD-L1 therapy in patients with pretreated advanced non-small-cell lung cancer: a meta-analysis, Fut Oncol. (London, England). 15 (20) (2019) 2423–2433.
[25] M.S. Tsao, K.M. Kerr, M. Kockx, M.B. Beasley, A.C. Borczuk, J. Botling, et al., PD-L1 immunohistochemistry comparability study in real-life clinical samples: results of blueprint phase 2 project, J. Thoracic Oncol.: Off. Publ. Int. Assoc. Study Lung Can. 13 (9) (2018) 1302–1311.
[26] C. Teixido, N. Vilarino, R. Reyes, N. Reguart, PD-L1 expression testing in non-small cell lung cancer, Adv Med Oncol. 10 (2018).
[27] L. Festino, G. Botti, P. Lorigan, G.V. Masucci, J.D. Hipp, C.E. Horak, et al., Cancer treatment with anti-PD-1/PD-L1 agents: is PD-L1 expression a biomarker for patient selection? Drugs 76 (9) (2016) 925–945.
[28] Q. Zhao, R. Xie, Anti-PD-1/PD-L1 antibody therapy for pretreated advanced or metastatic nonsmall cell lung carcinomas and the correlation between PD-L1 expression and treatment effectiveness: an update meta-analysis of randomized clinical trials, BioMed Res. Int. 2018 (2018) 3820956.
[29] G. Roviello, L. Zanotti, M.R. Cappelletti, A. Gobbi, M. Dester, G. Paganini, et al., Are EGFR tyrosine kinase inhibitors effective in elderly patients with EGFR-mutated non-small cell lung cancer? Clin. Exp. Med. 18 (1) (2018) 15–20.
[30] Z. Fathi, S.A.J. Mousavi, R. Roudi, Distribution of KRAS, DDR2, and TP53 gene mutations in lung cancer: an analysis of Iranian patients, PloS one 13 (7) (2018) e0200633.
[31] J. Zhu, R. Li, E. Tiselius, R. Roudi, O. Teghararian, C. Suo, et al., Immunotherapy (excluding checkpoint inhibitors) for stage I to III non-small cell lung cancer treated with surgery or radiotherapy with curative intent, Cochrane Database Systemat. Rev. 12 (2017) Cd011300.
[32] H. Akamatsu, E. Murakami, J. Oyanagi, R. Shibaki, T. Kaki, E. Takase, et al., Immune-related adverse events by immune checkpoint inhibitors significantly predict durable efficacy even in responders with advanced non-small cell lung cancer, Oncol. (2019).
[33] E. Baldini, A. Lunghi, E. Cortesi, D. Turci, D. Signorelli, V. Stati, et al., Immune-related adverse events correlate with clinical outcomes in NSCLC patients treated with nivolumab: the Italian NSCLC expanded access program, Lung Can. (Amsterdam, Netherlands). 140 (2019) 59–64.
[34] X. Sun, R. Roudi, T. Dai, S. Chen, B. Fan, H. Li, et al., Immune-related adverse events associated with programmed cell death protein-1 and programmed cell death ligand 1 inhibitors for non-small cell lung cancer: a PRISMA systematic review and meta-analysis, BMC Can. 19 (1) (2019) 558.
[35] Dafni U, Tsourti Z, Vervita K,Peters S. Immune checkpoint inhibitors, alone or in combination with chemotherapy, as first-line treatment for advanced non-small cell lung cancer. A systematic review and network meta-analysis. Lung cancer (Amsterdam, Netherlands). 2019;134:127–40.
[36] R. Kim, B. Keam, S. Hahn, C.Y. Ock, M. Kim, T.M. Kim, et al., First-line pembrolizumab versus pembrolizumab plus chemotherapy versus chemotherapy alone in non-small-cell lung cancer: a systematic review and network meta-analysis, Clin. Lung Can. 20 (5) (2019), https://doi.org/10.1016/j.cllc.2019.05.009.
[37] X. Zeng, X. Wan, L. Peng, Y. Peng, F. Ma, Q. Liu, et al., Cost-effectiveness analysis of pembrolizumab plus chemotherapy for previously untreated metastatic non-small cell lung cancer in the USA, BMJ Open. 9 (12) (2019) e031019.