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Review Article

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PD-1/PD-L1 Antibody versus Gefitinib for Advanced Non-small Cell Lung Cancer: A Systematic Review and Network Meta-analysis of Randomized Control Trials

Babo Zhang[#], XianDa Wang[#], Shuaifei Ji*

School of Basic Medicine, Air Force Military Medical University, Xi'an, Shanxxi, China.

* Corresponding Author: 1135260399@qq.com. Mobile: +86 13720538722.

[#] Equal contributors.

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Abstract

PD-1/PD-L1 antibody and gefitinib have made much progress in treatment of advanced non-small cell lung cancer. Recent randomized control trials revealed that both of them exhibited effective outcomes after first-line treatment, especially compared to chemotherapy. However, it is unknown that what's the efficacy and safety between them due to lacking of direct evidences. Relevant randomized control trials were selected by searching electronic databases (PubMed, Embase, and Cochrane Library) and reference lists of related articles by hand. This study has been registered at International Prospective Register of Systematic Reviews (number CRD42018094297). According to Cochrane Handbook, two reviewers independently assessed eligibility and quality of the studies. The outcome measures were overall survival, progression-free survival, objective response rate and adverse events calculated through the fixed random effect model. PD-1/PD-L1 antibody could improve overall survival [HR=0.69(0.61-0.77), P=0.000] significantly over gefitinib, no matter of West Country, orient country and different PD-1/PD-L1 antibodies. While there was no significant difference between them in progression-free survival [HR=0.92(0.78-1.09), P=0.352] and objective response rate [HR=0.86(0.50-1.49), P=0.587]. Subgroup analysis suggested that PD-1/PD-L1 antibody could improve progression-free survival only for West Country [HR=0.83(0.71-0.96), P=0.010], and for objective response rate, similar results appeared only for orient country [HR=0.16(0.05-0.49), P=0.001] and atezolizumab [HR=0.50(0.27-0.94), P=0.031]. For incidence of adverse events, PD-1/PD-L1 antibody could reduce risk of nausea (all grades) [RR=0.65 (0.44-0.97), p=0.035], neutropenia (≥3 grade) [RR=0.30 (0.09-0.93), p=0.038], diarrhoea (all grades, ≥3 grade) [RR=0.26 (0.18-0.38), p=0.000, 0.23(0.08-0.67), p=0.007], rash (all grades) [RR=0.35 (0.14-0.84), p=0.019] and leukopenia (≥3 grade) [RR=0.19 (0.04-0.80), p=0.024] over gefitinib, but increase risk of fatigue (all grades) [RR=1.72 (1.18-2.49), p=0.004]. PD-1/PD-L1 monoclonal antibody is superior to gefitinib for overall survival for the after-first-line treatment of advanced NSCLC in general. Further considering survival and incidence of adverse events comprehensively, relative to gefitinib, PD-1/PD-L1 monoclonal antibody may be a better choice for advanced NSCLC.

Key words: PD-1/PD-L1 Antibody; Gefitinib; Non-small Cell lung Cancer; Meta-analysis

1. Introduction

There are approximately 1.6 million newly diagnosed lung cancer patients in the world each year, and its mortality rate ranks first among malignant tumor-related deaths (Sundar *et al.*, 2014). Non-small cell lung cancer (non-small cell lung cancer, NSCLC) accounts for 85% of lung cancer, and 70% of NSCLC patients approximately have reached the advanced stage when diagnosed. In the 21st century, epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have been explored for nearly 10 years, opening a new era of individualized treatment of non-small cell lung cancer. Gefitinib is the first marketed reversible EGFR-TKI for the treatment of locally advanced or metastatic NSCLC that have undergone chemotherapy or are unsuitable for chemotherapy. The efficacy of Gefitinib as a second and third line treatment for NSCLC has been validated in many clinical trials. The first generation of non-specific immunity has gradually progressed to specific target-based immunotherapy (Shimanovsky *et al.*, 2013). PD-1/PD-L1 antibody, immune checkpoint molecular-inhibitor has become a hot topic in the field of treating non-small cell lung cancer recent years (Rangachari *et al.*, 2013). Both PD-1

monoclonal antibodies (e.g. nivolumab, pembrolizumab) and PD-L1 monoclonal antibodies (e.g. atezolizumab) have been approved by the FDA for NSCLC (Gettinger *et al.*, 2015). As pop molecule-targeted drugs, gefitinib and PD-1/PD-L1 antibody have applied for advanced NSCLC and exhibited effective outcomes. Clinically, we may consider applying PD-1/PD-L1 antibody when NSCLC develops resistance to EGFR-TKIs (e.g. gefitinib). When it does not occur, we have no idea whether PD-1/PD-L1 antibody is more effective and safer than gefitinib. However, there is no direct comparison to reach a decisive conclusion so far. As a kind of special network meta-analysis, indirect comparison meta-analysis has been applied widely when direct evidences not enough, with excellent validity (Sormani, 2017; Kiefer *et al.*, 2015; Lim *et al.*, 2009). Therefore, to explore the difference of PD-1/PD-L1 antibody and gefitinib on treatment of advanced NSCLC, we conducted a systematic review and indirect meta-analysis between these two targeted drugs, expecting to provide clinical evidences.

2. Materials and Methods

2.1 Search Strategy

This systematic review and meta-analysis is reported in accordance with the Preferred Items for Systematic Reviews and Meta-analysis (PRISMA) Statement and was registered at International Prospective Register of Systematic Reviews (number CRD42018094297). Literature was retrieved by formal search of electronic databases (PubMed, Embase, and Cochrane Library) and trials registers on the Internet without date limitation. To achieve the maximum sensitivity of the search strategy, we used appropriated free text and thesaurus terms including “Non-small cell lung carcinoma”, “Gefitinib”, “programmed cell death protein-1”, “programmed cell death protein ligand-1”, “monoclonal antibody” and "docetaxel". We also search reference lists of related articles by hand to obtain more studies. All studies were limited to English language.

2.2 Study Selection

Inclusion criteria: (1) Gefitinib versus docetaxel; (2) PD-1/PD-L1 antibody versus docetaxel; (3) Patients with advanced non-small cell lung cancer; (5) Overall survival (OS) and/or Progression-free survival (PFS) was reported; (4) Randomized control trial. Exclusion criteria: (1) Review and meta-analysis; (2) Observational studies and letters; (3) Animal studies and basic research; (4) Radiotherapy, combination therapy and other therapy that didn’t meet the criteria; (5) About other antibodies (e.g. Bevacizumab) and other -tinibs (e.g. Sorafenib and erlotinib).

2.3 Data Abstraction and Quality Assessment

The extracted data were consisted of the follow items: the first author’s name, publication year, population (Ethnicity), methods, study design, matching criteria, sex, total number of cases and controls, age (years).

The quality assessment of the included trials was undertaken independently by two review authors (BB Z and XD W), following Cochrane Hanbook12 for assessing risk of bias. Seven main quality criteria were examined: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective outcome reporting (reporting bias); (7) other bias.

2.4 Statistical Analysis

We measured the treatment effect on dichotomous outcomes (e.g. Objective response rate and adverse events) and on time-to-event outcomes (e.g. overall survival and progression-free survival) by risk ratio (RR) with 95% confidence interval (CI) and hazard ratio (HR) with 95% CI, respectively. We used Review manager 5.3 and Stata14.0 software to perform the meta-analysis in the present study. We used adjusted indirect comparison meta-analysis to explore the differences between PD-1/PD-L1 antibody and Gefitinib in patients with advanced NSCLC due to insufficient direct data. We implemented subgroup analysis to explore the results of different population and antibodies. Sensitivity analysis about different PD-1/PD-L1 antibodies over

gefitinib was performed. The potential publication bias was investigated using Egger's test with limited to small size studies. Egger's test (P<0.05) was also considered to be representative of statistically significant publication bias. Heterogeneity among studies was assessed by I2 statistic. I2>50% indicated evidence of heterogeneity. All the comparisons were performed with random effects model.

3. Results

3.1 Characteristics of Individual Studies

We identified seven RCTs about PD-1/PD-L1 antibody Vs docetaxel (Brahmer *et al.*, 2015; Fehrenbacher *et al.*, 2016; Herbst *et al.*, 2016; Hida *et al.*, 2016; Rittmeyer *et al.*, 2017; Vokes *et al.*, 2018; Borghaei *et al.*, 2015) and six RCTs about gefitinib Vs docetaxel (Cufer *et al.*, 2006; Kim *et al.*, 2008; Lee *et al.*, 2010; Maruyama *et al.*, 2008; Morere *et al.*, 2010; Sun *et al.*, 2011) finally. Of the 13 eligible studies, 6 focused on American (Brahmer *et al.*, 2015; Fehrenbacher *et al.*, 2016; Herbst *et al.*, 2016; Vokes *et al.*, 2018; Borghaei *et al.*, 2015), 3 focused on European (Rittmeyer *et al.*, 2017; Cufer *et al.*, 2006; Morere *et al.*, 2010; Kim *et al.*, 2008; Sun *et al.*, 2011) and 4 for Asian (Hida *et al.*, 2016; Lee *et al.*, 2010; Maruyama *et al.*, 2008). One study is for first-line treatment for adverse events analysis merely (Morere *et al.*, 2010), and twelve studies are for second-line treatment for survival and adverse events analysis. Non-small cell lung cancer is mainly multiple, including squamous and non-squamous. Characteristics of included studies were shown in Table 1. Risk of bias summary and bias graph were shown in Fig. 1 and 2.

Table 1. Characteristics of include studies

Author	Country, year	Intervene/ Control (n)	Median age (years) (range)	Histology	Treatment arms
Borghaei et al	USA, 2015	292/290	61 (37-84)/64 (21-85)	NSQ	Nivolumab 3mg/kg q2w, DOX 75mg/m^2 q3w
Brahmer et al	USA, 2015	135/132	62 (39-85)/64 (42-84)	SQ	Nivolumab 3mg/kg q2w , DOX 75mg/m^2 q3w
Vokes et al	USA, 2018	427/427	NR	Multiple	Nivolumab 3mg/kg q2w, DOX 75mg/m^2 q3w
Fehrenbacher et al	USA, 2016	144/143	62 (42-82)/62 (36-84)	Multiple	Atezolizumab 1200mg q3w, DOX 75mg/m^2 q3w
Herbst et al	USA, 2016	344/343	63 (56-69)/62 (56-69)	Multiple	Pembrolizumab 2mg/kg q2w, DOX 75mg/m^2 q3w
		346/343	63 (56-69) /62 (56-69)	Multiple	Pembrolizumab 10mg/kg q2w, DOX 75mg/m^2 q3w
Rittmeyer et al	Germany, 2016	425/425	63 (33-82)/64 (34-85)	Multiple	Atezolizumab 1200mg q3w, DOX 75mg/m^2 q3w
Hida et al	Japan, 2018	36/28	63.5 (33-77)/58.5 (34-79)	Multiple	Atezolizumab 1200mg q3w, DOX 75mg/m^2 q3w
Cufer et al	UK, 2006	68/73	63 (34-85)/59.5 (29-83)	Multiple	Gefitinib 250mg/day, DOX 75mg/m^2 q3w
Kim et al	USA, 2008	733/733	61 (27-84)/60 (20-84)	Multiple	Gefitinib 250mg/day, DOX 75mg/m^2 q3w
Lee et al	Korea, 2010	82/79	57 (21-74)/58 (20-73)	Multiple	Gefitinib 250mg/day, DOX 75mg/m^2 q3w
Maruyama et al	Japan, 2008	245/244	NR	Multiple	Gefitinib 250mg/day, DOX 60mg/m^2 q3w
Morère et al*	France, 2010	43/42	70 (45-79) /71 (30-79)	Multiple	Gefitinib 250mg/day, DOX 75mg/m^2 q3w
Sun et al	China, 2011	107/115	NR	Multiple	Gefitinib 250mg/day, DOX 75mg/m^2 q3w

NR, no reported
NSQ, non-squamous non small cell lung cancer
SQ, squamous non small cell lung cancer
DOX, docetaxel
*First-line treatment

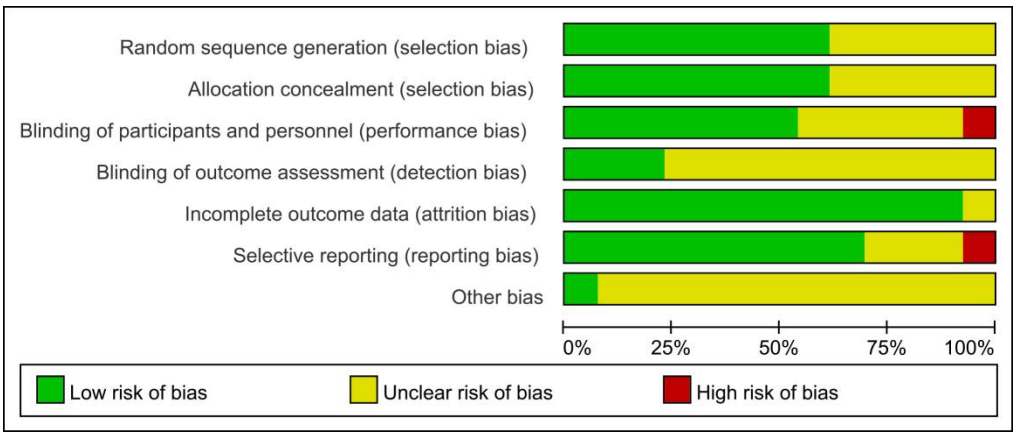

Fig. 1. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

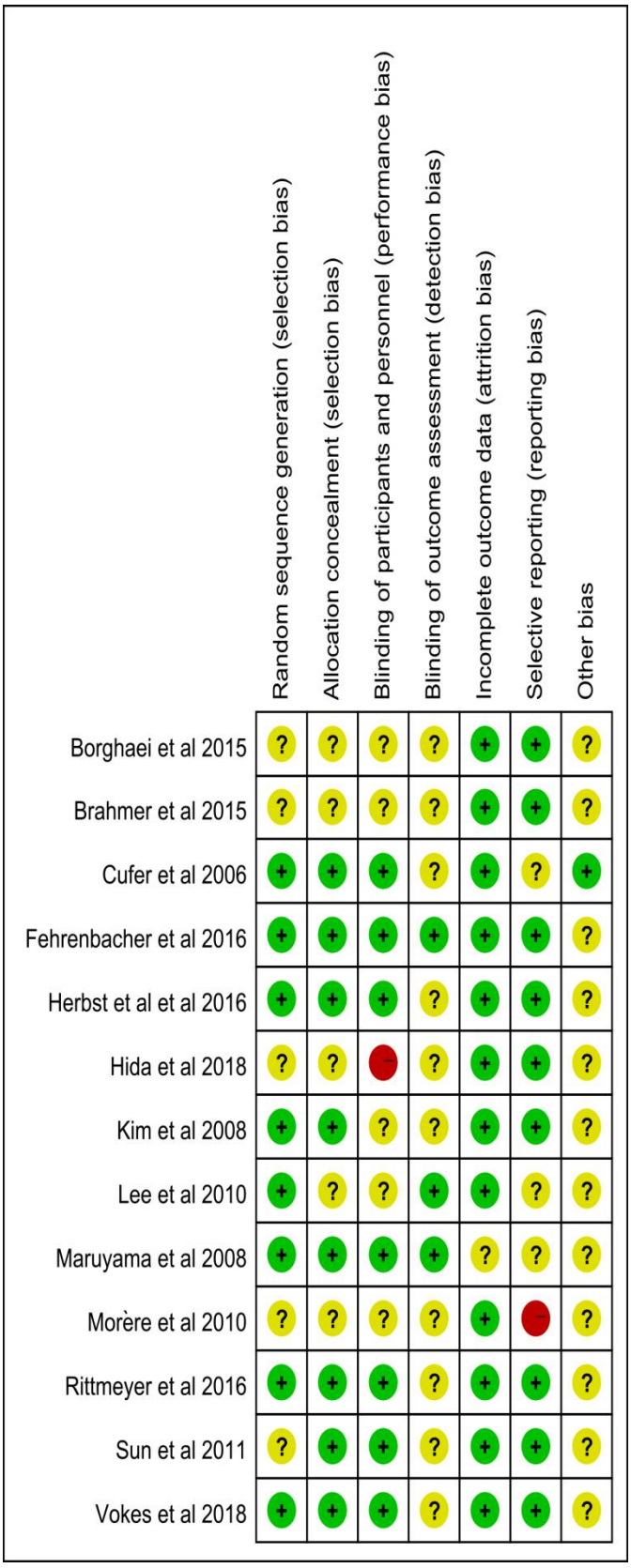

Fig. 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

3.2 Survival outcomes

For overall survival, the summary HRs of PD-1/PD-L1 antibody Vs docetaxel and gefitinib vs docetaxel were 0.70 (0.65-0.74, p<0.00001) and 1.02 (0.93-1.12, p=0.62), and indirect comparison meta-analysis showed there was significant difference for PD-1/PD-L1 antibody Vs gefitinib with advanced NSCLC [HR= 0.69(0.61-0.77), P=0.000]. For progression-free survival, the summary HRs were 0.86 (0.80-0.94, p=0.0005) for PD-1/PD-L1 antibody Vs docetaxel group and 0.93 (0.81-1.08, p=0.36) for gefitinib Vs docetaxel group, relative HR for PD-1/PD-L1 antibody Vs gefitinib was no statistical significance [HR=0.92 (0.78-1.09), p=0.352]. Likewise, objective response rate between PD-1/PD-L1 antibody and gefitinib was also no significant difference [RR=0.86 (0.50-1.49), p=0.587], with RR 1.46 (1.00-2.12, p=0.05) for PD-1/PD-L1 antibody vs docetaxel and 1.70 (1.14-2.54, p=0.009) for gefitinib Vs docetaxel. Direct evidences of PD-1/PD-L1 antibody vs docetaxel and gefitinib vs docetaxel were shown in Fig 3 and 4, relative results for survival outcomes were in Table 2.

3.3 Subgroup analysis for survival outcomes

We conducted subgroups analysis about different population and PD-1/PD-L1 antibodies. Not only west but Orient advanced NSCLC population, PD-1/PD-L1 antibody could improve overall survival over gefitinib [HR=0.68 (0.59-0.78), p=0.000, 0.70 (0.55-0.89), p=0.000]. Similarly, nivolumab, atezolizumab and pembrolizumab all could improve advanced NSCLC patients' overall survival over gefitinib. For progression-free survival, there exhibited significant difference in west country merely [HR=0.83 (0.71-0.96), p=0.010], and three antibodies were also similar to gefitinib. While, PD-1/PD-L1 antibody could improve objective response rate for Oriental population over gefitinib [RR=0.16 (0.05-0.49), p=0.001], but not for west country. In addition, only atezolizumab exhibited the improvement for objective response rate over gefitinib [RR=0.50 (0.27-0.94), p=0.031], other two antibodies not (Table 2).

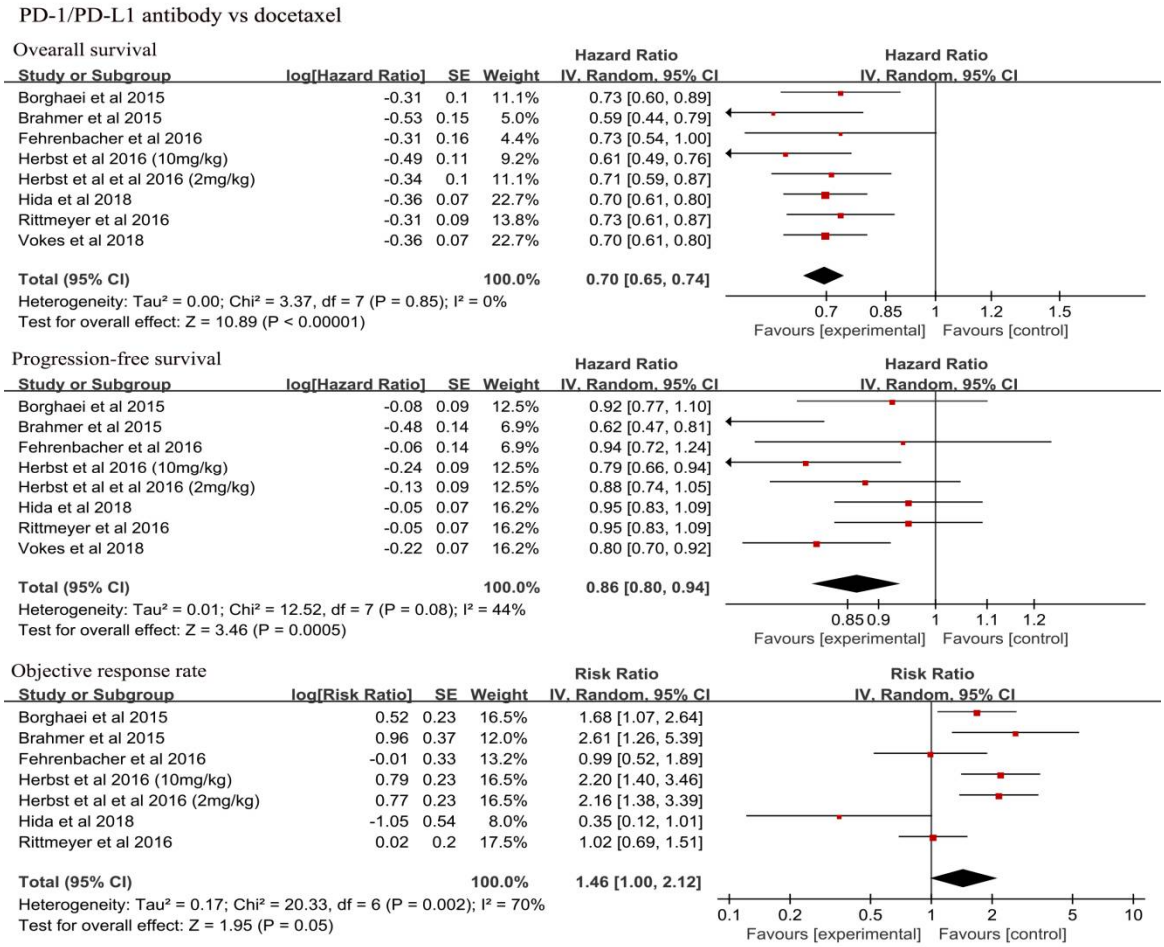

Fig. 3. Forrest plots for overall survival, progression-free survival and objective response rate comparing PD-1/PD-L1 antibody with docetaxel

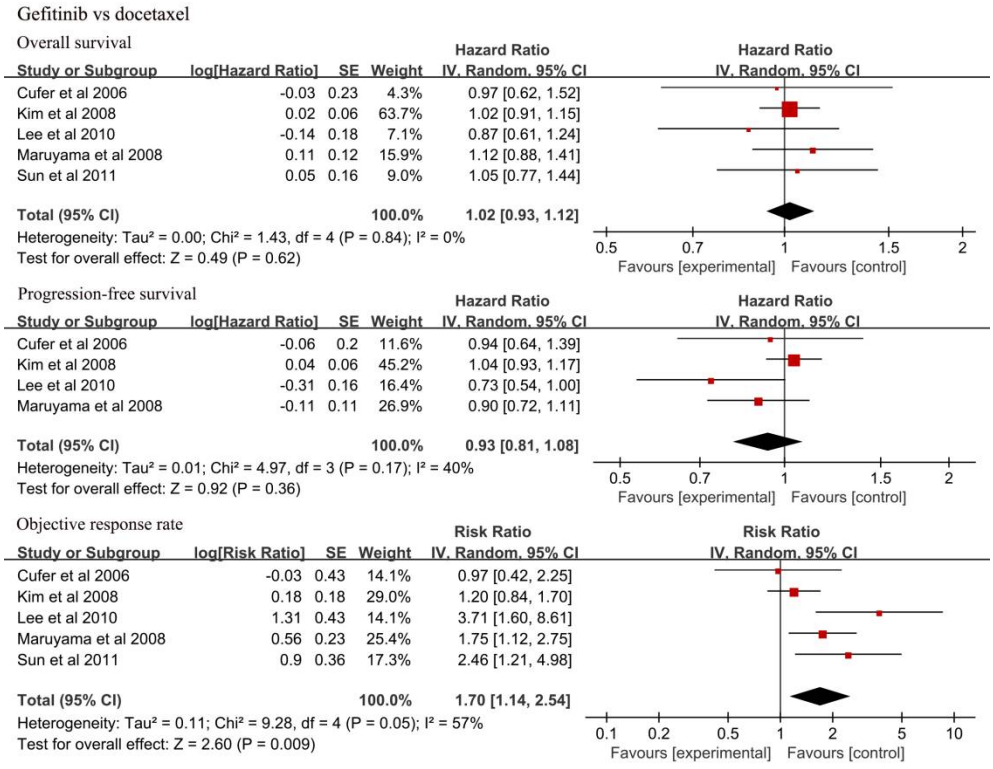

Fig. 4. Forrest plots for overall survival, progression-free survival and objective response rate comparing gefitinib with docetaxel

Table 2. Survival outcomes of PD-1/PD-L1 antibody Vs Gefitinib

Outcome	No. Of studies	Statistical method	Effect size (relative value)	P value
OS	8 vs 5	Hazard Ratio (Random, 95%CI)	**0.69 (0.61-0.77)**	**0.000**
PFS	8 vs 4	Hazard Ratio (Random, 95%CI)	0.92 (0.78-1.09)	0.352
ORR	7 vs 5	Risk Ratio (Random, 95%CI)	0.86 (0.50-1.49)	0.587
Subgroup (OS)				
West country	7 vs 2	Hazard Ratio (Random, 95%CI)	**0.68 (0.59-0.78)**	**0.000**
Orient country	1 vs 3	Hazard Ratio (Random, 95%CI)	**0.70 (0.55-0.89)**	**0.000**
Nivolumab vs Gefitinib	3 vs 5	Hazard Ratio (Random, 95%CI)	**0.68 (0.59-0.78)**	**0.000**
Atezolizumab vs Gefitinib	3 vs 5	Hazard Ratio (Random, 95%CI)	**0.72 (0.59-0.78)**	**0.000**
Pembrolizumab vs Gefitinib	2 vs 5	Hazard Ratio (Random, 95%CI)	**0.65 (0.55-0.77)**	**0.000**
Subgroup (PFS)				
West country	7 vs 2	Hazard Ratio (Random, 95%CI)	**0.83 (0.71-0.96)**	**0.010**
Orient country	1 vs 2	Hazard Ratio (Random, 95%CI)	1.13 (0.89-1.44)	0.324
Nivolumab vs Gefitinib	3 vs 4	Hazard Ratio (Random, 95%CI)	0.85 (0.67-1.08)	0.179
Atezolizumab vs Gefitinib	3 vs 4	Hazard Ratio (Random, 95%CI)	1.02 (0.86-1.22)	0.812
Pembrolizumab vs Gefitinib	2 vs 4	Hazard Ratio (Random, 95%CI)	0.89 (0.74-1.08)	0.242
Subgroup (ORR)				
West country	6 vs 2	Risk Ratio (Random, 95%CI)	1.41 (0.90-2.23)	0.137
Orient country	1 vs 3	Risk Ratio (Random, 95%CI)	**0.16 (0.05-0.49)**	**0.001**
Nivolumab vs Gefitinib	3 vs 5	Risk Ratio (Random, 95%CI)	1.12 (0.64-1.95)	0.696
Atezolizumab vs Gefitinib	3 vs 5	Risk Ratio (Random, 95%CI)	**0.50 (0.27-0.94)**	**0.031**
Pembrolizumab vs Gefitinib	2 vs 5	Risk Ratio (Random, 95%CI)	1.28 (0.76-2.13)	0.351

OS, overall survival
PFS, progression-free survival
ORR, objective response rate

Table 3. Risk of adverse events of PD-1/PD-L1 antibody Vs Gefitinib

Adverse events	No. Of studies	Statistical method	Effect size (relative value)	P value
Nausea (all grades)	5 vs 5	Risk Ratio (Random, 95%CI)	**0.65 (0.44-0.97)**	**0.035**
⩾3 grade	5 vs 5	Risk Ratio (Random, 95%CI)	1.83 (0.42-7.92)	0.419
Anaemia (all grades)	5 vs 3	Risk Ratio (Random, 95%CI)	0.53 (0.28-1.00)	0.05
⩾3 grade	5 vs 3	Risk Ratio (Random, 95%CI)	0.51 (0.14-1.82)	0.298
Neutropenia (all grades)	5 vs 4	Risk Ratio (Random, 95%CI)	0.33 (0.09-1.26)	0.106
⩾3 grade	5 vs 4	Risk Ratio (Random, 95%CI)	**0.30 (0.09-0.93)**	**0.038**
Diarrhoea (all grades)	5 vs 6	Risk Ratio (Random, 95%CI)	**0.26 (0.18-0.38)**	**0.000**
⩾3 grade	5 vs 6	Risk Ratio (Random, 95%CI)	**0.23 (0.08-0.67)**	**0.007**
Febrile neutropenia (all grades)	3 vs 4	Risk Ratio (Random, 95%CI)	0.14 (0.00-5.16)	0.287
⩾3 grade	3 vs 4	Risk Ratio (Random, 95%CI)	0.25 (0.01-9.52)	0.455
Rash (all grades)	4 vs 6	Risk Ratio (Random, 95%CI)	**0.35 (0.14-0.84)**	**0.019**
⩾3 grade	4 vs 6	Risk Ratio (Random, 95%CI)	0.48 (0.07-3.50)	0.470
Fatigue (all grades)	5 vs 3	Risk Ratio (Random, 95%CI)	**1.72 (1.18-2.49)**	**0.004**
⩾3 grade	5 vs 3	Risk Ratio (Random, 95%CI)	1.31 (0.22-7.65)	0.766
Leukopenia (all grades)	3 vs 1	Risk Ratio (Random, 95%CI)	1.08 (0.29-4.05)	1.087
⩾3 grade	3 vs 1	Risk Ratio (Random, 95%CI)	**0.19 (0.04-0.80)**	**0.024**

No. Of studies, PD-1/PD-L1 antibody vs Gefitinib

3.4 Risk of adverse events

As shown in Table 3, PD-1/PD-L1 antibody could reduce nausea (all grades) [RR=0.65 (0.44-0.97), p=0.035], neutropenia (≥3 grade) [RR=0.30 (0.09-0.93), p=0.038], diarrhoea (all grades, ≥3 grade) [RR=0.26 (0.18-0.38), p=0.000, 0.23(0.08-0.67), p=0.007], rash (all grades) [RR=0.35 (0.14-0.84), p=0.019] and leukopenia (≥3 grade) [RR=0.19 (0.04-0.80), p=0.024] over gefitinib, but upregulate risk of fatigue (all grades) [RR=1.72 (1.18-2.49), p=0.004].

3.5 Sensitive analysis and publication bias

We explored different PD-1/PD-L1 antibodies over gifitinib and discovered that, the all the effects were similar to overall treatments, apart from atezolizumab over gefitinib for objective response rate. And for overall survival, Egger's test suggested that there didn't exist publication bias for PD-1/PD-L1 antibody vs docetaxel (p=0.325) and gefitinib vs docetaxel (p=0.693).

4. Discussion

Our results suggests that PD-1/PD-L1 antibody is more effective than gefitinib for patients with advanced NSCLC indeed. Both sensitivity analysis and publication bias suggest that our results are reliable. Due to the lack of direct comparison of clinical evidence, we first conducted indirect meta-analysis to conclude it.

PD-1/PD-L1, immune checkpoint molecules regulating immune system, will activate abnormally when tumors occur. The interaction between them can cause the recruitment of Src homologous region 2 protein tyrosine phosphatase-1 (SHP-1) and SHP-2, and downstream signaling of TCR PI3K/AK3 and RAS pathway dephosphorylation. Eventually it inhibits T cell proliferation and function, induces apoptosis of antigen-specific T cells, and promotes the differentiation of CD4 + T cells into Foxp3 + regulatory T cells, mediating tumor immune escape. Therefore, antibodies by targeting PD-1/PD-L1 to block the activation of immune checkpoint pathways are developing gradually. Nivolumab, the initial dose-escalation phase I clinical trial of the original PD-1 antibody, was performed in different solid tumors. For expanded advanced NSCLC patients, the median PFS was 74 weeks, 1-year and 2-year survival rates were 42% and 14% (Gettinger *et al.*, 2015). In an independent phase III trial involving 272 patients with NSCLC, nivolumab exhibited better over docetaxel. The results showed that the median OS was 9.2 months for Nivolumab group (n=135) and 6.0 months for docetaxel group (n=137) (P<0.05), and similar results appeared in the median PFS (P<0.05) (Borghaei *et al.*, 2015). Pembrolizumab, a humanized IgG4 antibody targeting PD-1, can also significantly improve OS and ORR in patients with advanced NSCLC compared to docetaxel in KEYNOTE-010 Clinical II/III studies (Herbst *et al.*, 2016). Atezolizumab is a PD-L1 monoclonal antibody, the POPLAR clinical phase III trials revealed atezolizumab significantly could prolong the OS of advanced NSCLC patients over docetaxel (12.6 months [95% CI, 9.7-16.4] vs. 9.7 months [95% CI , 8.6-12.0]; HR, 0.73 [95% CI, 0.53-0.99], P=0.04) (Fehrenbacher *et al.*, 2016).

Gefitinib as an EGFR-TKIs blocks the autophosphorylation and substrate phosphorylation of protein kinases by competitively binding to the magnesium-triphosphate adenosine (Mg-ATP) binding site in the intracellular catalytic region of EGFR-TK, and then blocking the EGFR signal transduction pathway, but also can inhibit the activation of mitogen-activated protein kinase and the formation of tumor cell blood vessels, eventually leading to tumor cell apoptosis. In the second-line drug study, Sun et al reported that gefitinib was better as a second-line treatment for N SCLC than pemetrexed (Sun *et al.*, 2012). A meta-analysis performed by Qi *et al*., suggested PFS and ORR in gefitinib group were higher than those in standard second-line chemotherapy group (Qi *et al.*, 2012). Biaoxue R et al also reported that gefitinib is more effective for NSCLC maintenance therapy, with disease control (DCR) and 1-year survival rates reaching 67.5% and 50.6% (Biaoxue *et al.*, 2012). What's more, the first-line treatment was in the similar way. In a first-line, randomized, open phase III study involving 1,217 advanced NSCLC patients, PFS in the gefitinib group was 1% higher than that in

carboplatin group after 22 months follow-up (24.9% vs. 6.7%, P < 0.001) (Mok *et al.*, 2012).

Therefore, it is obvious that efficacy of PD-1/PD-L1 monoclonal antibody and gefitinib is superior to chemotherapy for the treatment of NSCLC. Even so, the difference of efficacy between these two targeted-drugs is unknown. In addition, the incidence of adverse events of them is also a concern for us. However, so far, there is no decisive conclusion to due to lacking of direct evidence. Given good similarity, homogeneity and validity of indirect evidences, we conduct this indirect meta-analysis by adjusted methods. Our results showed that compared with gefitinib, PD-1/PD-L1 monoclonal antibody could improve OS [HR=0.67 (0.60-0.75), P=0.000] in patients with advanced NSCLC. However, PFS and ORR not. In terms of adverse events, PD-1/PD-L1 monoclonal antibodies compared to gefitinib, could reduce the risk of Nausea(all grades) [HR=0.65(0.44-0.97),P=0.035], neutropenia (≥3 grade) [HR=0.30(0.09-0.93), P=0.038] Diarrhoea (all grades,≥3 grade) [HR=0.26(0.18-0.37）, P=0.016, 0.23(0.08-0.67), P=0.0007], Rash (all grades) [HR=0.35(0.14-0.84, P=0.019] and leukopenia (≥3 grade)[HR=0.19(0.04-0.80), P=0.024]. However, the risk of Fatigue(all grades) increased [HR=1.72(1.18-2.49), P=0.004]. We further conducted a subgroup analysis about OS and found that PD-1/PD-L1 monoclonal antibody was superior to gefitinib in both West country patients and orient patients. Likewise, all the three monoclonal antibodies(Nivolumab, Pembrolizumab and Atezolizumab) could improve OS over gefitinib.

Conclusion

Of course, there are some limitations in our research. For example, in bias risk assessment, we cannot determine the bias risk in some studies and potential bias cannot be avoided. Then, we didn't further explore other factors, such as age, smoking, EGFR status and KARS status and so on, with insufficient data provided. However, our study concluded that, relative to gefitinib, efficacy of PD-1/PD-L1 monoclonal antibody for overall survival is superior to gefitinib for the after-first-line treatment of advanced NSCLC.

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