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Comparative analysis of immune checkpoint inhibitors and chemotherapy in the treatment of advanced non-small cell lung cancer
A meta-analysis of randomized controlled trials

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Abstract

Background: Recently, immune checkpoint inhibitors have shown survival advantage over chemotherapy in the treatment of advanced non-small cell lung cancer (NSCLC). This meta-analysis was conducted to gather and analyze the available evidence (Evidence level I; Randomized Controlled Trials) comparing efficacy and safety of anti-programmed cell death-1 (PD1)/programmed cell death ligand 1 (PD-L1) therapies and chemotherapy in the treatment of advanced NSCLC.

Methods: A search strategy was devised to identify the randomized controlled trials (RCTs) using electronic databases of PubMed, Cochrane Library, and Web of Science. Hazard ratios or odds ratios obtained for overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and treatment related adverse events (TRAEs) were analyzed using fixed effect model or random effects model. Additionally, subgroup analysis was also performed.

Results: A total of seven RCTs (n = 3867) were identified and selected for inclusion in this meta-analysis. Anti-PD1/PD-L1 therapies (nivolumab, pembrolizumab, atezolizumab) resulted in better OS (HR 0.72 [95% confidence interval [CI] 0.63, 0.82; $P < .00001$]), PFS (HR 0.84 [95% CI 0.72, 0.97; $P < .02$]), and ORR (odds ratio [OR] 1.52 [95% CI 1.08, 2.14; $P < .02$]) in comparison to chemotherapy in advanced NSCLC. Improved safety was observed with anti-PD1/PD-L1 therapies (OR 0.31 [95%CI 0.26, 0.38; $P < .00001$]). Subgroups analysis revealed Eastern Cooperative Oncology Group Performance Status (ECOG PS) 1 (HR 0.76 [95%CI 0.62, 0.93; $P = .007$]), squamous cell type (HR 0.76 [95% CI 0.63, 0.92; $P = .005$]), current/former smoker (HR 0.76 [95% CI 0.63, 0.92; $P = .005$]), epidermal growth factor receptor (EGFR) wild type (HR 0.67 [95% CI 0.60, 0.76; $P < .00001$]), Kirsten rat sarcoma oncogene mutation (KRAS) mutant (HR 0.60 [95% CI 0.39, 0.93; $P < .02$]), and absence of central nervous system (CNS) metastases (HR 0.71 [95% CI 0.63, 0.80; $P < .00001$]) were associated with better overall survival.

Conclusions: Anti-PD1/PD-L1 therapies are safe and effective treatment option in advanced non-small cell lung cancer and can be recommended selectively.

Abbreviations: ALK = anaplastic lymphoma kinase, APC = antigen presenting cells, CI = confidence interval, CNS = central nervous system, CTLA-4 = Cytotoxic T Lymphocytic Antigen 4, ECOG PS = Eastern Cooperative Oncology Group Performance Status, EGFR = epidermal growth factor receptor, HR = hazard ratio, HTMB = high tumor mutation burden, ICI = immune checkpoint inhibitors, IFN-γ = interferon gamma, KRAS = Kirsten rat sarcoma oncogene mutation, LTMB = low tumor mutation burden, MHC = major histocompatibility complex, NK = natural killer cells, NSCLC = non-small cell lung cancer, OR = odds ratio, ORR = objective response rate, OS = overall survival, PD1 = programmed cell death, PDL1 = programmed cell death ligand, PFS =

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1. Introduction

Lung cancer is the leading cause of cancer death in both men and women and the second most commonly diagnosed cancer.[1] The 5-year relative survival rate for lung cancer is 18% (15% for men and 21% for women). Only 16% of lung cancers are diagnosed at a localized stage, for which the 5-year survival rate is 56%. While the majority of lung cancers are diagnosed at an advanced stage with 5% 5-year survival rate.[2] Appropriate treatment for lung cancer is based on whether the tumor is small cell or non-small cell as well as the stage and molecular characteristics of the cancer. Non-small cell lung cancer (NSCLC) accounts for >84% of all lung cancers.[1,2]

Platinum based chemotherapy is used as first line treatment in advanced NSCLC with a 15% to 30% response rate.[3] Docetaxel as the second line treatment has shown reasonable results but overall survival benefit is limited.[4,5] Targeted therapies (epidermal growth factor receptor [EGFR] and anaplastic lymphoma kinase [ALK] mutant) as second line treatment have been compared with docetaxel with no survival advantage.[6] Targeted therapies together with docetaxel have also fail to shown any durable results.[7]

Immunotherapy recently has become the most revolutionary treatment in treating solid tumors. Cancer cells evade immune system and induce tumor tolerance by developing coinhibitory signals also called immune checkpoints in the process of T cell activation. Inhibitors to these checkpoints have been developed recently and have already shown tremendous results in prolonging survival of many cancers including NSCLC. Programmed cell death-1 (PD-1) and programmed cell death ligand 1 (PD-L1) is such an coinhibitory signal by blocking of which T cells could continue to function and attack cancer cells.[8] In 2015, antibodies to PD-1 (nivolumab and pembrolizumab) were approved for the treatment of NSCLC as second line therapy. A year later, atezolizumab, a checkpoint inhibitor targeting the PD-L1 was approved as well. Pembrolizumab has also received approval as first-line NSCLC treatment in patients with high PD-L1 tumor expression scores.[9–12] These results have prompted us to assemble data from these randomized controlled trials and undertake a meta-analysis in order to evaluate overall efficacy and safety of these agents in treating advanced NSCLC versus chemotherapy

2. Methods and materials

2.1. Search strategy and study selection

PubMed, Cochrane Library, and Web of Science were searched comprehensively until December 2017 using a wide range of terms including "NSCLC" OR "non small cell lung cancer" AND "ICIs" OR "immune checkpoint inhibitors" OR "Anti PD-1" OR "Anti PD-L1" OR "Immunotherapy" OR "Docetaxel" OR "Chemotherapy." The retrieved studies were scrutinized and examined for title and abstracts by 2 reviewers. Further exploration of full texts articles was conducted in order to check the studies' eligibility for inclusion in accordance with inclusion criteria. A third reviewer resolved the disagreements. This Review

and Meta-analysis was approved by the "Medical Ethics Committee of Guangzhou Medical University Affiliated Cancer Hospital."

2.2. Eligibility criteria

Published randomized controlled trials comparing the anti-PD1/ PD-L1 therapies with chemotherapy in the treatment of advanced non-small cell lung cancer. No language restrictions were applied. Randomized controlled trials (RCTs) that provided complete data of overall survival, progression-free survival, and adverse events in order to analyze the efficacy and safety of immune checkpoint inhibitors. Any RCT with incomplete data was excluded from this meta-analysis.

2.3. Outcomes of interest

Outcomes of primary interest were overall survival, progression-free survival, objective response rate, and treatment-related adverse events. PD-L1 tumor proportion score as predictor of overall survival (OS), progression-free survival (PFS) was assessed as an additional outcome of interest. Subgroup analysis was undertaken for the effects of age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, histology type, smoking history, EGFR/Kirsten rat sarcoma oncogene mutation (KRAS) mutation status, and CNS metastases on overall survival and progression-free survival.

2.4. Data extraction

Data extracted from all the seven RCTs included general characteristics of the trial, trial inclusion, and exclusion criteria, baseline characteristics of the participants, main outcomes of the RCT and subgroup analysis. Extracted data were incorporated into the form of tables (Tables 1 and 2).

2.5. Quality assessment

The Cochrane Collaboration Tool was used to assess the risk of bias in the included studies.[13] CCT assesses each trial for selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective reporting). Risk of bias assessment is illustrated in Figs. 1 and 2. Publication bias was examined by funnel plots (Figure S1C, Figure S2C, Figure S3C, http://links.lww.com/ MD/C407).

2.6. Statistical analysis

Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014 software was used to carry out all the data analysis. Hazard ratios with 95% CI were used for time to event outcomes while dichotomous variables were analyzed using odds ratios (OR) with 95% CI. HRs and ORs were pooled using fixed
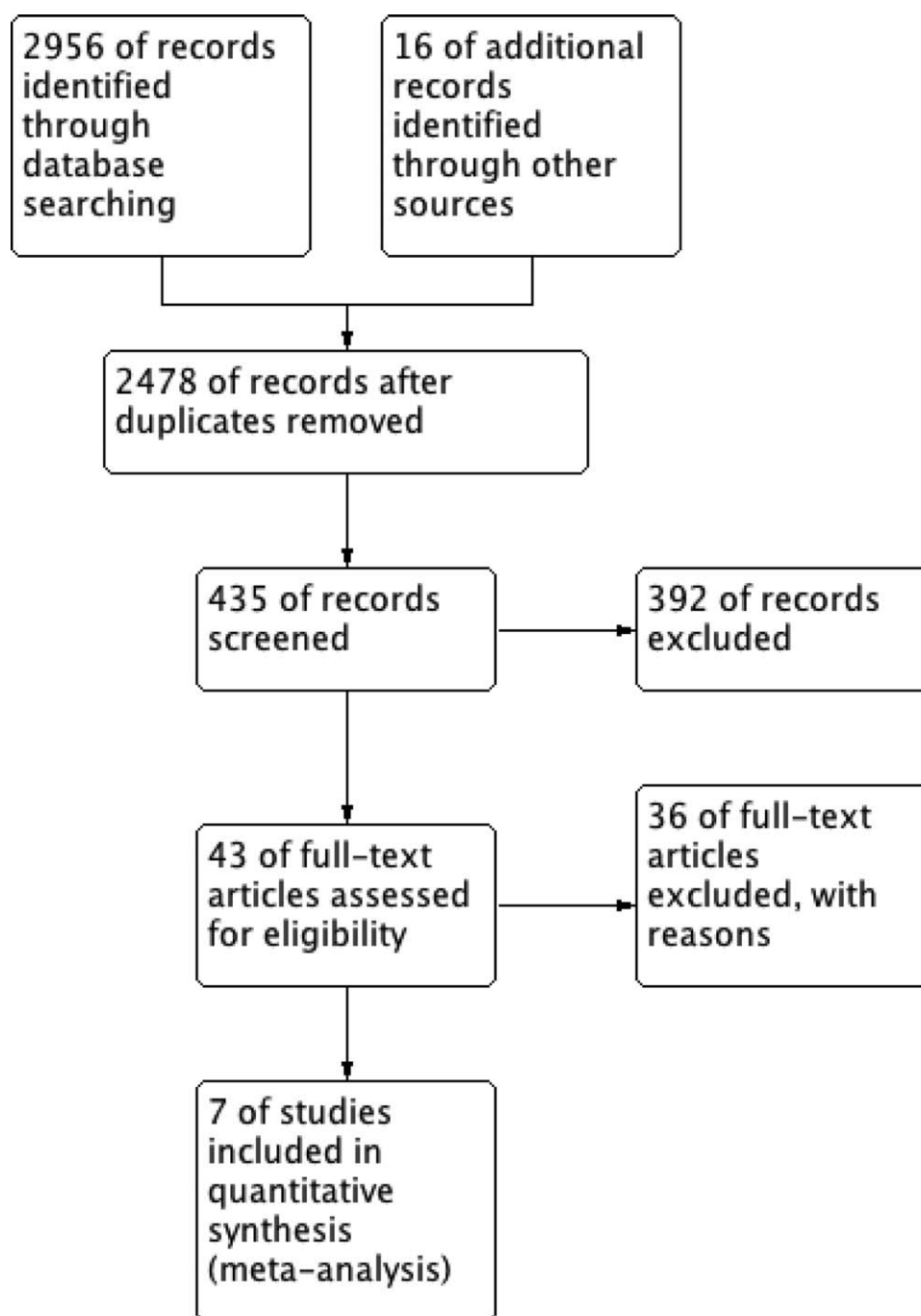
Figure 1. The flow diagram of literature search and selection process.

effects model. Random effects model was applied when high heterogeneity was observed. χ^2 and I^2 statistic were used for heterogeneity evaluation. I^2 statistic >50% and P value <.05 were considered significant heterogeneity.

3. Results

A total of 7 RCTs[14–20] were identified involving 3867 participants with advanced NSCLC. All the RCTs were 2 arm studies where the participants were randomized to either receive anti-PD1/PD-L1 therapies or chemotherapy. Study inclusion flow diagram shows the corresponding results of search strategy and process of selection (Fig. 3). General characteristics of the included studies are outlined in Table 1. There were some small differences in inclusion criteria regarding the PD-L1 expression as 2 of the trials[15,17] included patients with at least 1% or more PD-L1 expression of tumor cells while Reck et al's RCT included patients with at least 50% or more of PD-L1 expression. Two RCTs[18,19] included patient with advanced disease either treated previously or untreated. Baseline characteristics of the participants are outlined in Table 2.
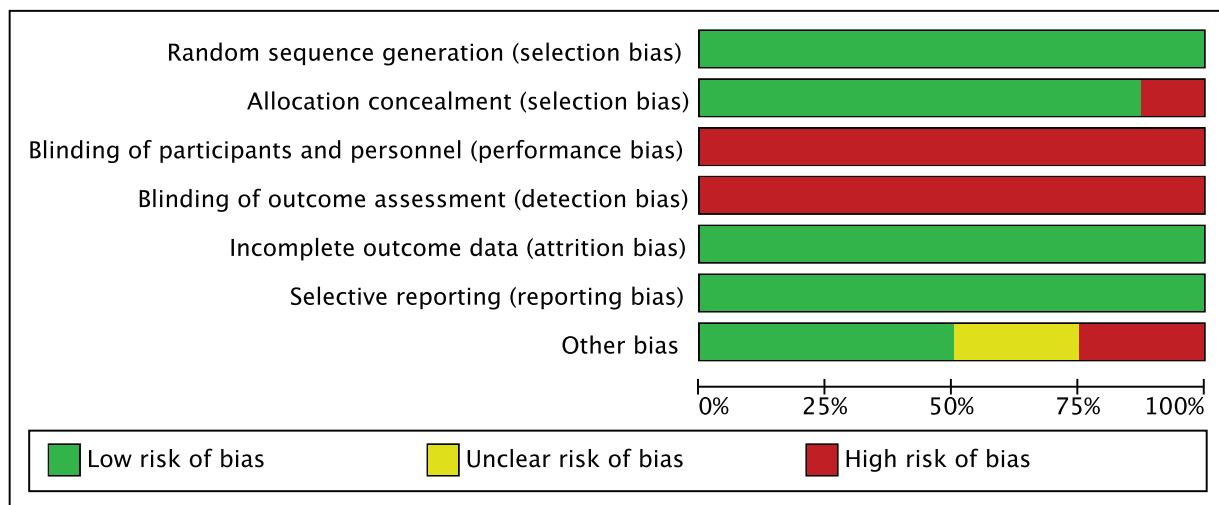
Figure 2. Risk of bias graph. +: low risk of bias; −: high risk of bias; ?: unclear risk of bias.

3.1. Efficacy

Pooled HRs or ORs revealed significant improvement in OS, PFS, objective response rate (ORR), and TRAEs with anti-PD-1/PD-L1 therapies in comparison to chemotherapy.

3.1.1. Overall survival. Anti-PD-1/PD-L1 therapies resulted in better overall survival. Pooled HRs based on 7 studies revealed a significantly lower risk of death with anti PD-1/PD-L1 therapies when compared with chemotherapy (HR: 0.72; 95% CI 0.63, 0.82; $P < .00001$) (Fig. 4). Moderate heterogeneity however significant was reported (heterogeneity: [$P = .01$]; $I^2 = 60\%$).

Subgroup analyses of overall survival were also undertaken based on the sequence of treatment induction (first and second line treatment setting). First line treatment analyses only based on 2 studies revealing no significant difference for treatments (HR: 0.82; 95% CI 0.47, 1.44; $P = .54$) (Figure S1A, http://links.lww.com/MD/C407). Meta-analysis of second line treatment setting revealed significant OS (HR: 0.69; 95% CI 0.63, 0.75; $P < .00001$) without any heterogeneity among the studies. Individual analysis of each therapeutic agent revealed patients treated with nivolumab didn't achieve the OS benefit (HR: 0.78; 95% CI 0.56, 1.09; $P = .14$) associated with ICIs (Figure S1B, http://links.lww.com/MD/C407). Pembrolizumab (HR: 0.65; 95% CI 0.57, 0.75; $P < .00001$) and atezolizumab (HR: 0.73; 95% CI 0.63, 0.85; $P < .0001$) analyses revealed OS advantage.

3.1.2. Progression-free survival. Significant progression free survival was reported with anti PD-1/PD-L1 therapies (pooled HR: 0.84; 95% CI 0.72, 0.97; $P < .02$). High heterogeneity was observed from pooled HRs (heterogeneity: [$P = .0001$]; $I^2 = 77\%$) (Fig. 5). Subgroup analyses of first and second line treatment setting revealed no PFS advantage in first line setting (Figure S2A). However, ICIs as second line treatment revealed significant PFS (HR: 0.86; 95% CI 0.77, 0.95; $P = .004$) without any heterogeneity among the studies. Individual analysis of each therapeutic agent revealed pembrolizumab to be the only agent resulting in significant PFS (HR: 0.72; 95% CI 0.55, 0.95; $P = .02$) (Figure S2B, http://links.lww.com/MD/C407).

3.1.3. PD-L1 expression as biomarker and predictor of survival and PFS. PD-L1 tumor expression scores were categorized into high and low expression categories using different cut off values ($<1\%$ and $\geq1\%$, $<5\%$ and $\geq5\%$, $<10\%$ and $\geq10\%$, and $<50\%$ and $\geq50\%$) to analyze the correlation of PD-L1 expression and anti-PD1/PD-L1 response. OS was significantly improved with anti-PD-1/PD-L1 therapies in patients with PD-L1 expression of $<1\%$, $\geq1\%$, $\geq5\%$, $\geq10\%$, and $<50\%$ and $\geq50\%$ but not with $<5\%$ and $<10\%$. A progressively greater improvement was observed with increasing proportion of PD-L1 tumor expression from $<1\%$ to $\geq50\%$ (Fig. 6).

In PFS analysis, $\geq1\%$, $\geq10\%$, and $\geq50\%$ revealed significant improvement in PFS with anti-PD1/PD-L1 agents as compared with PD-L1 expression of $<1\%$, $<5\%$, $\geq5\%$, $<10\%$, and $<50\%$ (Fig. 7).

3.1.4. Objective response rate. Pooled ORs (OR: 1.52; 95% CI 1.08, 2.14; $P < .02$) for ORR revealed statistically significant objective response as compared with chemotherapy with high heterogeneity (Heterogeneity: [$P = .0002$]; $I^2 = 75\%$) (Fig. 8). A similar response was observed in the meta-analysis of ORR as with PFS. Great response reported in second line treatment setting for immunotherapy (OR: 1.65; 95% CI 1.19, 2.29; $P = .003$) while no first line treatment difference was observed (Figure S3A, http://links.lww.com/MD/C407). Pembrolizumab revealed significant objective response in comparison to chemotherapy (OR: 2.18; 95% CI 1.67, 2.85; $P < .00001$). Meta-analysis of nivolumab and atezolizumab didn't reveal any difference when compared with chemotherapy (Figure S3B, http://links.lww.com/MD/C407).

3.2. Safety

3.2.1. Treatment-related adverse events. Anti-PD/PD-L1 therapies are comparatively safe and reported far less adverse events compared with chemotherapy (OR 0.31 [95% CI 0.26, 0.38; $P < .00001$]). OR 0.20 [95% CI 0.14, 0.28; $P < .00001$]) for ≥3 grade TRAEs was achieved (Fig. 9). Each ICI agent individually reported a similar causation of adverse events (Overall and Grade 3, 4 or 5 TRAEs) in comparison to chemotherapy (Figure S4A and Figure S4B, http://links.lww.com/MD/C407). Respective incidence rates of adverse events were also analyzed mainly based on 5 studies involving nivolumab and pembrolizumab. Fatigue, nausea, decreased appetite, diarrhea, and asthenia were caused by both treatments both more frequent

Figure 3. Risk of bias summary.

with chemotherapy. Anemia, neutropenia, alopecia, myalgia, and stomatitis were mainly reported with chemotherapy. Hypothyroidism, hyperthyroidism, rash, and pneumonitis were mostly occurred in immunotherapy group (Fig. 10). Similar trends of incidence rates of adverse events were reported with nivolumab and pembrolizumab (Figure S4C and Figure S4D, http://links.lww.com/MD/C407).

3.3. Subgroup analysis

Factors associated with OS and PFS are outlined in Table 3. Age (<65 and ≥65, except for >75 years old) and sex (male and female) subgroups equally responded to anti PD-1/PD-L1 therapies achieving significant OS. While ECOG PS 1, squamous cell type, current/former smoker, EGFR wild type, KRAS mutant, and absent CNS metastases subgroups were associated with

Table 1

General characteristics and outcomes data of included randomized controlled studies.

	Brahmer et al[14]	Borghaei et al[15]	Fehrenbacher et al[16]	Herbst et al[17]	Reck et al[18]	Carbone et al[19]	Rittmeyer et al[20]
Designation	Checkmate-017	Checkmate-057	POPLAR	Keynote-010	Keynote-024	Checkmate-026	OAK
NCT	NCT01642004	NCT01673867	NCT01903993	NCT01905657	NCT02142738	NCT02041533	NCT02008227
	2015	2015	2016	2016	2016	2017	2017
Design	Phase III RCT	Phase III RCT	Phase II RCT	Phase II/III RCT	Phase III RCT	Phase III RCT	Phase III RCT
Participants (Imm/Chem)	272 (135/137)	582 (292/290)	287 (144/143)	1033 (690/343)	305 (154/151)	541 (271/270)	850 (425/425)
Immunotherapy (dosage)	Nivolumab (3 mg/kg every 2 wks)	Nivolumab (3 mg/kg every 2 wks)	Atezolizumab (1200mg every 3 wks)	Pembrolizumab (2 mg/kg every 2 wks, 10mg/kg every 3 wks)	Pembrolizumab (200mg every 3 wks)	Nivolumab (3 mg/kg every 2 wks)	Atezolizumab (1200mg every 3 wks)
Chemotherapy (dosage)	Docetaxel (75mg/m² every 3 wks)	Docetaxel (75 mg/m² every 3 wks)	Docetaxel (75 mg/m² every 3 wks)	Docetaxel (75 mg/m² every 3 wks)	Pemetrexed/carboplatin Pemetrexed/cisplatin Gemcitabine/carboplatin Gemcitabine/cisplatin Paclitaxel/carboplatin	Pemetrexed/carboplatin Pemetrexed/cisplatin Gemcitabine/carboplatin Gemcitabine/cisplatin Paclitaxel/carboplatin	Docetaxel (75mg/m² every 3 wks)
Inclusion Criteria	≥18 years of age Stage IIIB or IV squamous-cell NSCLC who had disease recurrence after one prior platinum-containing regimen ECOG PS 0-1	≥18 years of age Documented stage IIIB/IV non-squamous NSCLC Recurrence following radiation therapy or surgical resection Disease recurrence or progression during or after one prior platinum-based regimen. ECOG PS 0-1	≥18 years of age Measurable disease as per RECIST 1.1. Adequate hematological and end-organ function	≥18 years of age Advanced NSCLC Measurable disease as per investigator-assessed RECIST Progression (as per RECIST 1.1.) after two or more cycles of platinum-doublet chemotherapy as well as an appropriate tyrosine kinase inhibitor	Stage IV NSCLC ≥50% PD-L1 expression At least one measurable lesion as per RECIST 1.1. No sensitizing EGFR mutations or ALK translocations No previous systemic therapy for metastatic disease	Untreated stage IV or recurrent NSCLC ≥1% PD-L1 expression Measurable disease per RECIST 1.1. No previous systemic anti-cancer therapy for advanced or metastatic disease Previous palliative radiotherapy, if completed at least 2 weeks before randomization Previous adjuvant or neoadjuvant chemotherapy, if completed at least 6 months before	≥18 years of age Stage IIIB or IV non-small-cell lung cancer Measurable disease per RECIST 1.1. One to two previous cytotoxic chemotherapy regimens (one or more platinum based combination therapies)
Exclusion Criteria	Autoimmune disease, symptomatic interstitial lung disease, systemic immunosuppression, prior therapy with T-cell co-stimulation or checkpoint-targeted agents, or prior docetaxel therapy	Autoimmune disease, symptomatic interstitial lung disease, systemic immunosuppression, prior treatment with immune-stimulatory antitumor agents including checkpoint-targeted agents, or docetaxel.	Active or untreated CNS metastases, history of pneumonitis, autoimmune or chronic viral diseases, or previous treatment with docetaxel, CD137 agonists, anti- CTLA4, anti-PD-L1, or anti-PD-1 therapeutic antibodies, or PD-L1–PD-1 pathway-targeting agents	Previous treatment with PD-1 checkpoint inhibitors or docetaxel, known active brain metastases or carcinomatous meningitis, active autoimmune disease requiring systemic steroids, and interstitial lung disease or history of pneumonitis requiring systemic steroids.	Receiving systemic glucocorticoids Immunosuppressive treatment Untreated brain metastases Active autoimmune disease Active interstitial lung disease History of pneumonitis	Autoimmune disease or known EGFR mutations or ALK translocations that were sensitive to available targeted therapy	History of autoimmune disease Previous treatments with docetaxel, CD137 agonists, anti-CTLA4, or therapies targeting the PD-L1 and PD-1 pathway
Primary end points	OS	OS	OS	OS and PFS	PFS	PFS per BIRCH (≥5% PD-L1+)	OS
Secondary end points	ORR, PFS, Efficacy by PD-L1 expression level, disease-related symptom	ORR, PFS, Efficacy by PD-L1 expression level, disease-related symptom	ORR, DOR, PFS	ORR, DOR, TRAE	OS, ORR, TRAE	PFS per BIRCH (≥1% PD-L1+), OS (≥5% PD-L1+), ORR (≥5% PD-L1+), TRAE	PFS, ORR, DOR, TRAE

	Brahmer et al[14]	Borghaei et al[15]	Fehrenbacher et al[16]	Herbst et al[17]	Reck et al[18]	Carbone et al[19]	Rittmeyer et al[20]
Overall survival	improvement rate by week 12 MOS: 9.2m (nivo) versus 6m (doc) HR=0.59 (0.44–0.79) P<.001	improvement rate by week 12 MOS: 12.2m (nivo) versus 9.4m (doc) HR=0.73 (0.59–0.89) P=.002	MOS: 12.6m (atez) versus 9.7m (doc) HR=0.73 (0.53–0.99) P=.040	MOS: 10.4m (pemb2mg) versus 8.5m (doc) HR=0.71 (0.58–0.88) P=.0008 MOS: 12.7m (pemb10 mg) versus 8.5m (doc) HR=0.61 (0.49–0.75) P<.0001	MOS: not reached HR=0.60 (0.41–0.89) P=.005	MOS: 13.7m (nivo) versus 13.8m (doc) HR=1.07 (0.86–1.33) P=.54	MOS: 13.8m (atez) versus 9.6m (doc) HR=0.73 (0.62–0.87) P=.0003
Progression-free survival	MOS: 3.5m (nivo) versus 2.8m (doc) HR=0.62 (0.47–0.81) P<.001	MOS: 2.3m (nivo) versus 4.2m (doc) HR=0.92 (0.77–1.1) P=.39	MOS: 2.7m (atez) versus 3.0m (doc) HR=0.94 (0.72–1.23) P=NS	MOS: 3.9m (pemb2mg) versus 4m (doc) HR=0.88 (0.74–1.05) P=.07 MOS: 4m (pemb10mg) versus 4m (doc) HR=0.79 (0.66–0.94) P<.004	MOS: 10.3m (pemb) versus 6m (chem) HR=0.50 (0.37–0.68) P<.001	MOS: 4.2m (nivo) versus 5.8m (doc) HR=1.17 (0.95–1.43) P=.13	MOS: 2.8m (atez) versus 4.0m (doc) HR=0.95 (0.82–1.10) P=.493
Objective response rate & Duration of response	Nivo: 27 Doc: 12 OR: 2.6 (1.3–5.5) P=.008 DOR: NR (2.9–20.5+) (nivo) versus 8.4m (1.4+–15.2+)(doc)	Nivo: 56 Doc: 36 OR: 1.7 (1.1–2.6) P=.02 DOR: 17.2 (1.8–22.6+) (nivo) versus 5.6m (1.2+–15.2+)(doc)	Atez: 21 Doc: 21 DOR: 14.3m (11.6–NE) (atez) versus 7.2m (5.6–12.5)(doc)	Pemb2mg: 62 Pemb10mg: 64 Doc: 32 DOR: Pemb2mg=NR (1+–20+) versus 6m (1+–9+)(doc) Pemb10mg=NR (2+–18+) versus 6m (1+–9+) (doc)	Pemb: 69 Chem: 42 DOR: NR (1.9+–14.5+) (pemb) versus 6.3m (2.1+–12.6+)(chem)	Nivo: 55 Doc: 71 OR: 0.70 (0.46–1.06) DOR: 12.1 (1.7–19.4+)(nivo) versus 5.7m (1.4–21.0+) (doc)	Atez: 58 Doc: 57 DOR: 16.3m (10–NE) (atez) versus 6.2m (4.9–7.6)(doc)
Treatment-related adverse events	Nivo: 76 Doc: 111	Nivo: 199 Doc: 236	Atez: 95 Doc: 119	Pemb2mg: 215 Pemb10mg: 226 Doc: 251	Pemb: 113 Chem: 135	Nivo: 190 Doc: 243	Atez: 390 Doc: 496
Grade 3,4 or 5	Nivo: 9 Doc: 71	Nivo: 30 Doc: 144	Atez: 17 Doc: 55	Pemb2mg: 43 Pemb10mg: 55 Doc: 109	Pemb: 41 Chem: 80	Nivo: 47 Doc: 133	Atez: 90 Doc: 247

Atez = atezolizumab, Chem = chemotherapy, CI = confidence interval, Doc = docetaxel, DOR = duration of response, EGFR = epidermal growth factor receptor, HR = hazard ratio, KRAS = Kirsten rat sarcoma oncogene mutation, MOS = median overall survival, Nivo = Nivolumab, NSCLC = non-small cell lung cancer, OR = odds ratio, ORR = objective response rate, PD1 = programmed cell death receptor 1, PD-L1 = programmed cell death ligand 1, Pemb = Pembrolizumab, PFS = progression-free survival, RCT = randomized controlled trial, TRAE = treatment-related adverse events.

Table 2

Baseline characteristics of participants.

| Studies | Brahmer et al[14] | | Borghaei et al[15] | | Fehrenbacher et al[16] | | Herbst et al[17] | | Reck et al[18] | | Carbone et al[19] | | Rittmeyer et al[20] | | Cumulative sum | |
Subgroups	Immuno	Chemo	Immuno	Chemo	Immuno	Chemo	Immuno	Chemo	Immuno	Chemo	Immuno	Chemo	Immuno	Chemo	Immuno	Chemo
Participants	135	137	292	290	144	143	690	343	154	151	271	270	425	425	2111	1759
Median age	62	64	61	64	62	62	63	62	64.5	66	63	65	63	64		
Male sex	111 (82%)	97 (71%)	151 (52%)	168 (58%)	93 (65%)	76 (53%)	425 (62%)	209 (61%)	92 (59.7%)	95 (62.9%)	184 (68%)	148 (55%)	261 (61%)	259 (61%)	1317 (62%)	1052 (60%)
ECOG PS																
0	27 (20%)	37 (27%)	84 (29%)	95 (33%)	46 (32%)	45 (32%)	232 (34%)	116 (34%)	54 (35.1%)	53 (35.1%)	85 (31%)	93 (34%)	155 (36%)	160 (38%)	683 (32%)	599 (34%)
1	106 (79%)	100 (73%)	208 (71%)	193 (67%)	96 (68%)	97 (68%)	454 (66%)	224 (65%)	99 (64.3%)	98 (64.9%)	183 (68%)	174 (64%)	270 (64%)	265 (62%)	1416 (67%)	1151 (65%)
Smoking status																
Current/Former	121 (90%)	129 (94%)	231 (79%)	227 (78%)	117 (81%)	114 (80%)	564 (82%)	269 (78%)	149 (97%)	132 (87%)	238 (88%)	237 (87%)	341 (80%)	139 (33%)	1761 (83%)	1247 (71%)
Never	10 (7%)	7 (5%)	58 (20%)	60 (21%)	27 (19%)	29 (20%)	123 (18%)	67 (20%)	5 (3.2%)	19 (13%)	30 (11%)	29 (11%)	84 (20%)	72 (17%)	337 (16%)	283 (16%)
Histology type																
Squamous	-	-	-	-	49 (34%)	48 (34%)	156 (23%)	66 (19%)	29 (19%)	27 (18%)	66 (24%)	64 (24%)	112 (26%)	110 (26%)	412 (20%)	315 (18%)
Non-squamous	-	-	-	-	95 (66%)	95 (66%)	484 (70%)	240 (70%)	125 (81%)	124 (82%)	205 (67%)	206 (76%)	313 (74%)	315 (74%)	1222 (58%)	980 (56%)
PD-L1 TPS																
<1%	54 (40%)	52 (38%)	108 (47%)	101 (45%)	51 (35%)	41 (29%)	-	-	-	-	-	-	180 (42%)	199 (47%)	393 (19%)	393 (22%)
>1%	63 (47%)	56 (41%)	123 (53%)	123 (55%)	93 (65%)	102 (71%)	690 (100%)	343 (100%)	-	-	271 (100%)	270 (100%)	241 (57%)	222 (52%)	1481 (70%)	1116 (63%)
<5%	75 (56%)	69 (50%)	136 (59%)	138 (62%)	-	-	-	-	-	-	-	-	-	-	211 (10%)	207 (12%)
≥5%	42 (31%)	39 (29%)	95 (41%)	86 (38%)	50 (35%)	55 (38%)	-	-	-	-	208 (77%)	210 (78%)	129 (30%)	136 (32%)	524 (25%)	526 (30%)
<10%	81 (60%)	75 (55%)	145 (63%)	145 (65%)	-	-	-	-	-	-	-	-	-	-	226 (11%)	220 (13%)
≥10%	36 (27%)	33 (24%)	86 (37%)	79 (35%)	-	-	-	-	-	-	-	-	-	-	122 (6%)	112 (6%)
≥50%	-	-	-	-	24 (17%)	23 (16%)	290 (42%)	152 (44%)	154 (100%)	151 (100%)	88 (32%)	126 (47%)	72 (17%)	65 (15%)	628 (30%)	517 (29%)
EGFR status																
Positive	-	-	44 (15%)	38 (13%)	10 (12%)	8 (10%)	60 (9%)	26 (8%)	-	-	-	-	42 (10%)	43 (10%)	156 (7%)	115 (7%)
Negative	-	-	168 (58%)	172 (59%)	72 (87%)	75 (90%)	581 (84%)	294 (86%)	-	-	-	-	318 (75%)	310 (73%)	1139 (54%)	851 (48%)
KRAS status																
Positive	-	-	28 (10%)	34 (12%)	14 (33%)	13 (43%)	-	-	-	-	-	-	26 (6%)	33 (8%)	68 (3%)	80 (5%)
Negative	-	-	60 (21%)	63 (22%)	28 (67%)	17 (57%)	-	-	-	-	-	-	99 (23%)	104 (24%)	187 (9%)	184 (10%)
EML4-ALK translocation																
Positive	-	-	13 (4%)	8 (3%)	0 (0%)	3 (5%)	6 (1%)	2 (1%)	-	-	-	-	-	-	19 (1%)	13 (1%)
Negative	-	-	113 (39%)	130 (45%)	61 (100%)	55 (95%)	612 (89%)	310 (90%)	-	-	-	-	-	-	786 (37%)	495 (28%)
CNS metastases																
Yes	9 (7%)	8 (6%)	34 (12%)	34 (12%)	-	-	-	-	-	-	-	-	18 (11.7%)	10 (6.6%)	43 (2%)	42 (2%)
No	126 (93%)	129 (94%)	258 (88%)	256 (88%)	-	-	-	-	-	-	-	-	-	-	402 (19%)	395 (22%)

CNS = central nervous system, ECOG PS = Eastern Cooperative Oncology Group Performance Status, EGFR = epidermal growth factor receptor, EML4-ALK = echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase, KRAS = Kirsten rat sarcoma oncogene mutation, NSCLC = non-small cell lung cancer, PD-L1 TPS = programmed cell death ligand 1 tumor proportion score.
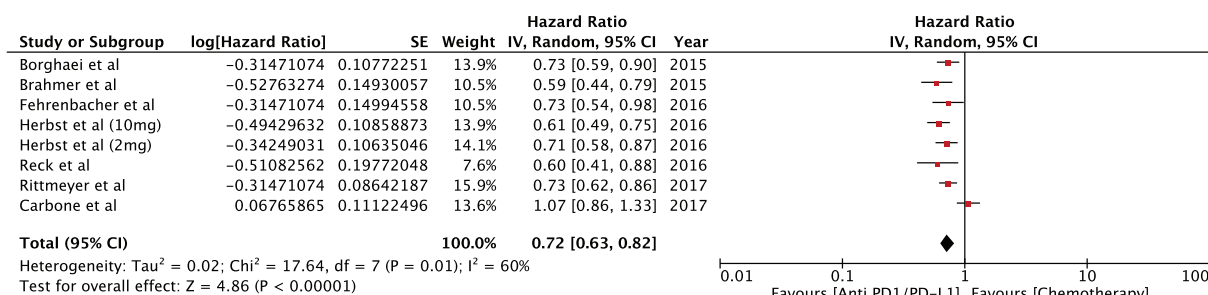
Figure 4. Forest plot of meta-analysis of the overall survival (OS) showing comparison of anti-PD1/ PD-L1 therapy to chemotherapy in advanced NSCLC. NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed cell death ligand 1.

better overall survival. OS subgroup analysis is summarized in Table 4. Age had no impact on PFS with <65 years. old subgroup responded comparatively better to anti-PD1/PD-L1 therapies (P = .07). Male sex, ECOG PS 1, never smoker, KRAS wild type and absent CNS metastases subgroups were associated with better PFS. Histology types showed no association to PFS while EGFR mutant as well as wild type was associated with significant PFS. PFS subgroup analysis is summarized in Table 5.

4. Discussion

Apart from TCR binding to MHC-bound antigen on APCs, binding of B7-CD28 costimulatory molecules is needed for T cell activation; one providing specificity and the other amplification. Overstimulation is kept in check by the binding of coinhibitory molecules like CTLA-4, PD-1, and its ligands (PD-L1 and PD-L2) providing self-antigen immune tolerance.[21] These immune check points are exploited by tumors in order to limit anti tumor response and tumor destruction by creating a balance between tumor and immune system leading to immune escape.[22] The binding of PD-1 expressed on the surface of activated T cells, B cells, NK cells to its ligand PD-L1 expressed on tumor cells including NSCLC and tumor infiltrated lymphocytes leads to apoptosis of tumor-specific T cells promoting CD4+ T cells differentiation into Tregs and tumor cell resistance thereby inhibiting T cell response. Two antibodies targeting PD-1 (nivolumab and pembrolizumab) and one antibody targeting PD-L1 (atezolizumab) have been approved for treatment of advanced NSCLC.[23]

We meta-analyzed randomized controlled trials to assess efficacy of these agents in advanced NSCLC. Our results showed significant advantage in terms of OS, PFS, and ORR with these agents when compared with chemotherapy in patients with advanced disease. Risk of death was significantly lower with anti-PD-1/PD-L1 therapies. Meta-analysis of progression-free survival (P = .02) and ORR (P = .02) were also significant for anti-PD-1/PD-L1 therapies. However, higher heterogeneity was observed among the studies for PFS and ORR so random effects model was adapted. Duration of response was evidently longer in all the studies[14–20] in immunotherapy arm. Carbone et al's RCT[19] stands alone as in this particular clinical trial no survival, PFS or ORR benefit was achieved. Here, it needs to be mention that 60% of the patients originally allocated to receive chemotherapy had also received nivolumab as subsequent therapy might have affected the overall survival. In five of the included RCTs the chemotherapy regimen was single agent docetaxel as second line treatment while 2 of the RCTs had used different chemotherapy regimens and some patients included in these 2 trials were untreated previously. These might be some of the factors contributing to heterogeneity existed among the studies. Nonetheless, Reck et al reported positive results in line with previous studies cancelling the notion of difference in inclusion criteria as basis for heterogeneity. Carbone et al reported no survival benefit in subgroup of patients with ≥50% PD-L1 expression that was the inclusion criteria for Reck et al.[18] Though greater number of patients with ≥50% PD-L1 expression was allocated in chemotherapy arm as compared with nivolumab arm. Different agents were used in these 2 studies however both had the same target pathway (PD-1). The only
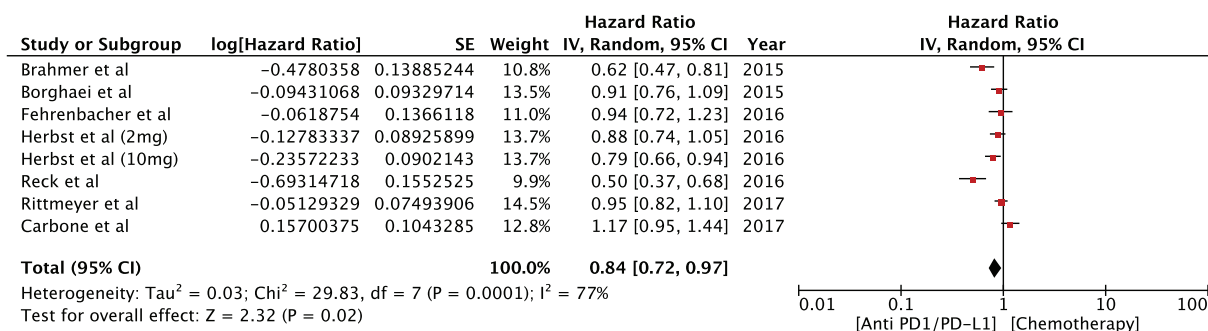

Figure 5. Forest plot of meta-analysis of the progression-free survival (PFS) showing comparison of anti-PD1/ PD-L1 therapy to chemotherapy in advanced NSCLC. NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed cell death ligand 1.

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
6.1.1 <1% PD–L1 Expression					
Borghaei et al	−0.13926207	0.16224203	3.6%	0.87 [0.63, 1.20]	
Brahmer et al	−0.54472718	0.23236496	2.5%	0.58 [0.37, 0.91]	
Fehrenbacher et al	0.03922071	0.26470704	2.2%	1.04 [0.62, 1.75]	
Rittmeyer et al	−0.28768207	0.12418642	4.2%	0.75 [0.59, 0.96]	
Subtotal (95% CI)			12.5%	**0.78 [0.65, 0.94]**	
Heterogeneity: Tau² = 0.00; Chi² = 3.36, df = 3 (P = 0.34); I² = 11%					
Test for overall effect: Z = 2.63 (P = 0.008)					
6.1.2 ≥1% PD–L1 Expression					
Borghaei et al	−0.54472718	0.15516524	3.7%	0.58 [0.43, 0.79]	
Brahmer et al	−0.37106368	0.21614741	2.7%	0.69 [0.45, 1.05]	
Carbone et al	0.06765865	0.11122496	4.5%	1.07 [0.86, 1.33]	
Fehrenbacher et al	−0.52763274	0.19228872	3.1%	0.59 [0.40, 0.86]	
Herbst et al (10mg)	−0.49429632	0.10858873	4.5%	0.61 [0.49, 0.75]	
Herbst et al (2mg)	−0.34249031	0.10343498	4.6%	0.71 [0.58, 0.87]	
Rittmeyer et al	−0.30110509	0.12044808	4.3%	0.74 [0.58, 0.94]	
Subtotal (95% CI)			27.4%	**0.71 [0.60, 0.84]**	
Heterogeneity: Tau² = 0.04; Chi² = 18.12, df = 6 (P = 0.006); I² = 67%					
Test for overall effect: Z = 3.88 (P = 0.0001)					
6.1.3 <5% PD–L1 Expression					
Borghaei et al	−0.040822	0.14125705	3.9%	0.96 [0.73, 1.27]	
Brahmer et al	−0.35667494	0.19765949	3.0%	0.70 [0.48, 1.03]	
Subtotal (95% CI)			6.9%	**0.84 [0.62, 1.14]**	
Heterogeneity: Tau² = 0.02; Chi² = 1.69, df = 1 (P = 0.19); I² = 41%					
Test for overall effect: Z = 1.09 (P = 0.28)					
6.1.4 ≥5% PD–L1 Expression					
Borghaei et al	−0.84397007	0.18518801	3.2%	0.43 [0.30, 0.62]	
Brahmer et al	−0.63487827	0.26904315	2.1%	0.53 [0.31, 0.90]	
Carbone et al	0.01980263	0.12385404	4.2%	1.02 [0.80, 1.30]	
Fehrenbacher et al	−0.61618614	0.25309408	2.3%	0.54 [0.33, 0.89]	
Rittmeyer et al	−0.40047757	0.15509933	3.7%	0.67 [0.49, 0.91]	
Subtotal (95% CI)			15.5%	**0.63 [0.44, 0.89]**	
Heterogeneity: Tau² = 0.12; Chi² = 18.36, df = 4 (P = 0.001); I² = 78%					
Test for overall effect: Z = 2.64 (P = 0.008)					
6.1.5 <10% PD–L1 Expression					
Borghaei et al	−0.040822	0.1337369	4.1%	0.96 [0.74, 1.25]	
Brahmer et al	−0.35667494	0.18977538	3.1%	0.70 [0.48, 1.02]	
Subtotal (95% CI)			7.2%	**0.84 [0.62, 1.14]**	
Heterogeneity: Tau² = 0.02; Chi² = 1.85, df = 1 (P = 0.17); I² = 46%					
Test for overall effect: Z = 1.09 (P = 0.27)					
6.1.6 ≥10% PD–L1 Expression					
Borghaei et al	−0.91629073	0.19505259	3.0%	0.40 [0.27, 0.59]	
Brahmer et al	−0.69314718	0.29500813	1.9%	0.50 [0.28, 0.89]	
Fehrenbacher et al	−0.71334989	0.40588999	1.2%	0.49 [0.22, 1.09]	
Subtotal (95% CI)			6.1%	**0.44 [0.32, 0.59]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.49, df = 2 (P = 0.78); I² = 0%					
Test for overall effect: Z = 5.49 (P < 0.00001)					
6.1.7 <50% PD–L1 Expression					
Fehrenbacher et al	−0.61618614	0.25309408	2.3%	0.54 [0.33, 0.89]	
Herbst et al (2mg)	−0.27443685	0.11989888	4.3%	0.76 [0.60, 0.96]	
Rittmeyer et al	−0.40047757	0.15509933	3.7%	0.67 [0.49, 0.91]	
Subtotal (95% CI)			10.3%	**0.70 [0.59, 0.83]**	
Heterogeneity: Tau² = 0.00; Chi² = 1.60, df = 2 (P = 0.45); I² = 0%					
Test for overall effect: Z = 4.03 (P < 0.0001)					
6.1.8 ≥50% PD–L1 Expression					
Carbone et al	−0.10536052	0.18282594	3.2%	0.90 [0.63, 1.29]	
Fehrenbacher et al	−0.71334989	0.40351693	1.2%	0.49 [0.22, 1.08]	
Herbst et al (2mg)	−0.63487827	0.14275913	3.9%	0.53 [0.40, 0.70]	
Reck et al	−0.51082562	0.19772048	3.0%	0.60 [0.41, 0.88]	
Rittmeyer et al	−0.89159812	0.22016485	2.7%	0.41 [0.27, 0.63]	
Subtotal (95% CI)			14.0%	**0.58 [0.44, 0.76]**	
Heterogeneity: Tau² = 0.05; Chi² = 8.85, df = 4 (P = 0.07); I² = 55%					
Test for overall effect: Z = 3.94 (P < 0.0001)					
Total (95% CI)			100.0%	**0.68 [0.62, 0.75]**	
Heterogeneity: Tau² = 0.04; Chi² = 77.15, df = 30 (P < 0.00001); I² = 61%					
Test for overall effect: Z = 7.80 (P < 0.00001)				0.01 0.1 1 10 100	
Test for subgroup differences: Chi² = 16.39, df = 7 (P = 0.02), I² = 57.3%				[Anti PD1/PD–L1] [Chemotherapy]	

Figure 6. Forest plots of subgroup analysis of association between overall survival (OS) and PD-L1 tumor expression level at cut off values of 1%, 5%, 10%, and 50%. PD-L1 = programmed cell death ligand 1.

difference in Carbone et al's RCT and other studies seems to be the high cross over affecting the overall survival analysis. Patient selection particularly previous radiotherapy and PD-L1 testing methods could also have influenced negative results. This comparison also suggest that anti-PD1/PD-L1 agents efficacy might not be limited to its use as second line treatment and could have positive results in advanced disease as first line choice of treatment warranting further evaluation.[24,25] A recently concluded trial (KEYNOTE-042 Trial) compared pembrolizumab with chemotherapy in the first line setting with PD-L1 expression of ≥1%. This trial reported better survival with pembrolizumab regardless of the PD-L1 expression level (PD-L1

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
6.2.1 <1% PD–L1 Expression					
Borghaei et al	0.17395331	0.15409886	4.1%	1.19 [0.88, 1.61]	
Brahmer et al	−0.41551544	0.21783684	3.4%	0.66 [0.43, 1.01]	
Fehrenbacher et al	0.11332868	0.23158268	3.2%	1.12 [0.71, 1.76]	
Subtotal (95% CI)			**10.8%**	**0.97 [0.68, 1.40]**	
Heterogeneity: Tau² = 0.06; Chi² = 5.15, df = 2 (P = 0.08); I² = 61%					
Test for overall effect: Z = 0.15 (P = 0.88)					
6.2.2 ≥1% PD–L1 Expression					
Borghaei et al	−0.35667494	0.1461742	4.2%	0.70 [0.53, 0.93]	
Brahmer et al	−0.40047757	0.21197216	3.4%	0.67 [0.44, 1.02]	
Carbone et al	0.15700375	0.1043285	4.7%	1.17 [0.95, 1.44]	
Fehrenbacher et al	−0.13926207	0.16437679	4.0%	0.87 [0.63, 1.20]	
Herbst et al (10mg)	−0.23572233	0.0902143	4.9%	0.79 [0.66, 0.94]	
Herbst et al (2mg)	−0.12783337	0.08925899	4.9%	0.88 [0.74, 1.05]	
Subtotal (95% CI)			**26.2%**	**0.85 [0.73, 1.00]**	
Heterogeneity: Tau² = 0.02; Chi² = 12.95, df = 5 (P = 0.02); I² = 61%					
Test for overall effect: Z = 1.94 (P = 0.05)					
6.2.3 <5% PD–L1 Expression					
Borghaei et al	0.27002714	0.1343222	4.4%	1.31 [1.01, 1.70]	
Brahmer et al	−0.28768207	0.1864509	3.8%	0.75 [0.52, 1.08]	
Subtotal (95% CI)			**8.1%**	**1.01 [0.58, 1.74]**	
Heterogeneity: Tau² = 0.13; Chi² = 5.89, df = 1 (P = 0.02); I² = 83%					
Test for overall effect: Z = 0.02 (P = 0.98)					
6.2.4 ≥5% PD–L1 Expression					
Borghaei et al	−0.61618614	0.17019686	3.9%	0.54 [0.39, 0.75]	
Brahmer et al	−0.61618614	0.26379433	2.9%	0.54 [0.32, 0.91]	
Carbone et al	0.13976194	0.11884547	4.6%	1.15 [0.91, 1.45]	
Fehrenbacher et al	−0.35667494	0.22333386	3.3%	0.70 [0.45, 1.08]	
Subtotal (95% CI)			**14.7%**	**0.71 [0.46, 1.10]**	
Heterogeneity: Tau² = 0.16; Chi² = 17.13, df = 3 (P = 0.0007); I² = 82%					
Test for overall effect: Z = 1.54 (P = 0.12)					
6.2.5 <10% PD–L1 Expression					
Borghaei et al	0.21511138	0.13190208	4.4%	1.24 [0.96, 1.61]	
Brahmer et al	−0.35667494	0.17941315	3.8%	0.70 [0.49, 0.99]	
Subtotal (95% CI)			**8.2%**	**0.94 [0.54, 1.65]**	
Heterogeneity: Tau² = 0.14; Chi² = 6.59, df = 1 (P = 0.01); I² = 85%					
Test for overall effect: Z = 0.20 (P = 0.84)					
6.2.6 ≥10% PD–L1 Expression					
Borghaei et al	−0.65392647	0.1802475	3.8%	0.52 [0.37, 0.74]	
Brahmer et al	−0.54472718	0.28787379	2.7%	0.58 [0.33, 1.02]	
Fehrenbacher et al	−0.51082562	0.33663342	2.2%	0.60 [0.31, 1.16]	
Subtotal (95% CI)			**8.7%**	**0.55 [0.42, 0.72]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 2 (P = 0.91); I² = 0%					
Test for overall effect: Z = 4.34 (P < 0.0001)					
6.2.7 <50% PD–L1 Expression					
Herbst et al (2mg)	0.03922071	0.10243261	4.7%	1.04 [0.85, 1.27]	
Subtotal (95% CI)			**4.7%**	**1.04 [0.85, 1.27]**	
Heterogeneity: Not applicable					
Test for overall effect: Z = 0.38 (P = 0.70)					
6.2.8 ≥50% PD–L1 Expression					
Carbone et al	0.06765865	0.16840329	4.0%	1.07 [0.77, 1.49]	
Fehrenbacher et al	−0.51082562	0.33663342	2.2%	0.60 [0.31, 1.16]	
Herbst et al (2mg)	−0.77652879	0.12128156	4.5%	0.46 [0.36, 0.58]	
Reck et al	−0.69314718	0.1552525	4.1%	0.50 [0.37, 0.68]	
Rittmeyer et al	−0.46203546	0.19123964	3.7%	0.63 [0.43, 0.92]	
Subtotal (95% CI)			**18.6%**	**0.62 [0.44, 0.86]**	
Heterogeneity: Tau² = 0.10; Chi² = 17.96, df = 4 (P = 0.001); I² = 78%					
Test for overall effect: Z = 2.87 (P = 0.004)					
Total (95% CI)			**100.0%**	**0.79 [0.69, 0.90]**	
Heterogeneity: Tau² = 0.08; Chi² = 114.93, df = 25 (P < 0.00001); I² = 78%					
Test for overall effect: Z = 3.59 (P = 0.0003)					
Test for subgroup differences: Chi² = 18.99, df = 7 (P = 0.008), I² = 63.1%					

0.01   0.1   1   10   100
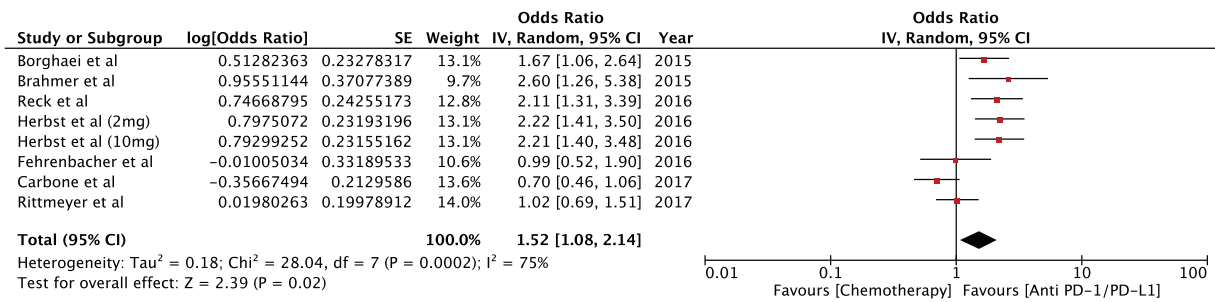[Anti PD1/PD-L1]   [Chemotherapy]

Figure 7. Forest plots of subgroup analysis of association between progression-free survival (PFS) and PD-L1 tumor expression level at cut off values of 1%, 5%, 10%, and 50%. PD-L1 = programmed cell death ligand 1.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Borghaei et al	0.51282363	0.23278317	13.1%	1.67 [1.06, 2.64]	2015
Brahmer et al	0.95551144	0.37077389	9.7%	2.60 [1.26, 5.38]	2015
Reck et al	0.74668795	0.24255173	12.8%	2.11 [1.31, 3.39]	2016
Herbst et al (2mg)	0.7975072	0.23193196	13.1%	2.22 [1.41, 3.50]	2016
Herbst et al (10mg)	0.79299252	0.23155162	13.1%	2.21 [1.40, 3.48]	2016
Fehrenbacher et al	−0.01005034	0.33189533	10.6%	0.99 [0.52, 1.90]	2016
Carbone et al	−0.35667494	0.2129586	13.6%	0.70 [0.46, 1.06]	2017
Rittmeyer et al	0.01980263	0.19978912	14.0%	1.02 [0.69, 1.51]	2017
Total (95% CI)			**100.0%**	**1.52 [1.08, 2.14]**	

Heterogeneity: Tau^2 = 0.18; Chi^2 = 28.04, df = 7 (P = 0.0002); I^2 = 75%
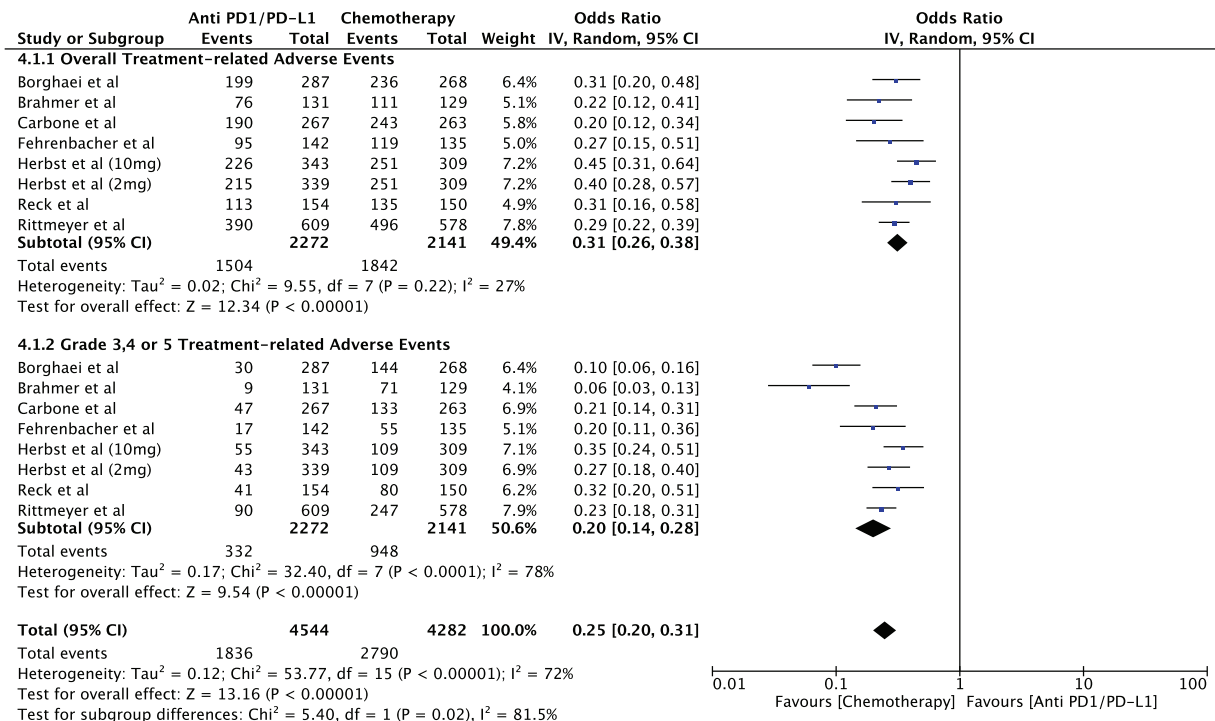Test for overall effect: Z = 2.39 (P = 0.02)

Figure 8. Forest plot of meta-analysis of the objective response rate (ORR) showing comparison of anti-PD1/PD-L1 therapy to chemotherapy in advanced NSCLC. NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed cell death ligand 1.

50% or more: 20 months vs 12.2 months; PD-L1 20% or more: 17.7 months vs 13 months; PD-L1 1% or more: 16.7 months vs 12.1 months).[26] This study establishes the fact that survival advantage in the first line setting is not limited to PD-L1 expression of ≥50%.
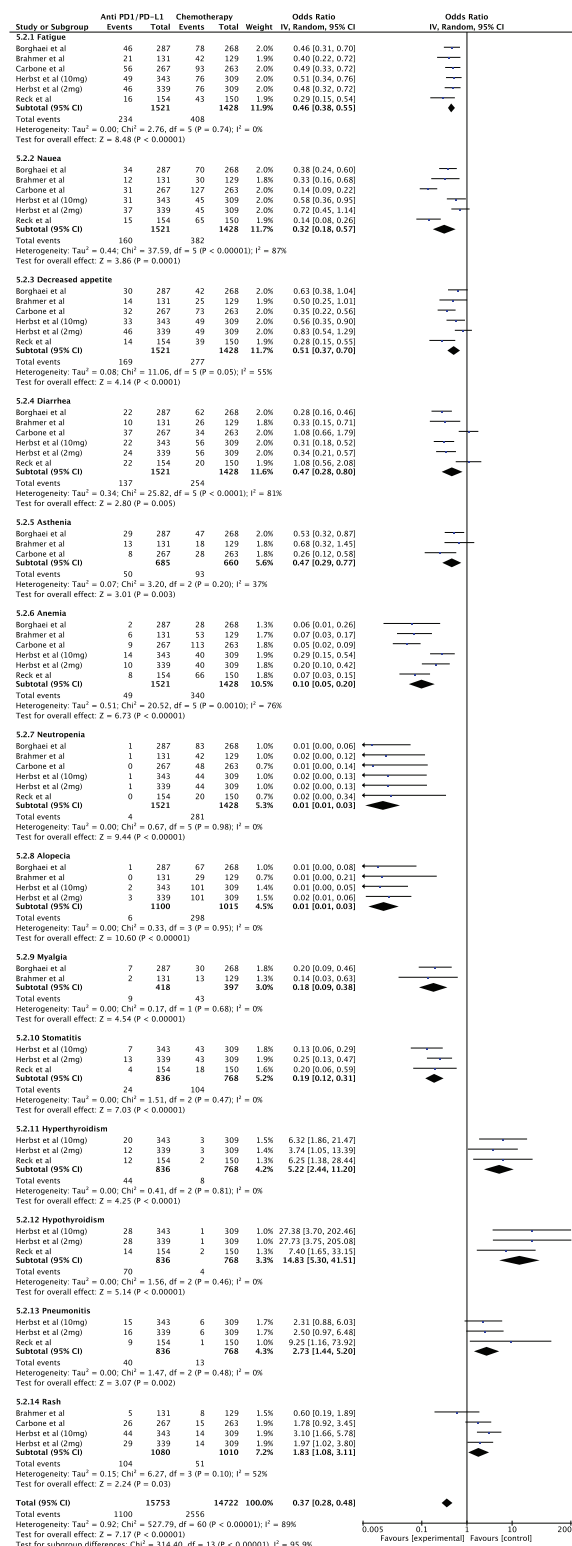
PD-L1 expression of tumor cells has been identified as biomarker and predictor of efficacy of anti-PD1/PD-L1 therapies in advanced NSCLC.[14–20] PD-L1 expression had been associated with poor prognosis in NSCLC endorsing the idea of its use for assessing anti-PD1/PD-L1 responses.[27] We meta-analyzed the PD-L1 tumor proportion score against overall survival with different cut-off values. We found significant association between PD-L1 expression and overall survival for cut-off values of 5% and 10%. However, meta-analysis revealed significant responses from both cut-off values 1% and 50%. With more studies examining the cut-off values at 5% and 10% might change the significant difference. Significant response from <1% PD-L1 expression subgroup contradicts previous studies[28] and

endorses the argument that PD-L1 tumor expression might not be enough to explain responses with anti-PD1/PD-L1 therapies.[14] Meta-analysis of PD-L1 expression versus progression free survival yielded different set of results. Significant differences existed for cut-off values 1%, 10%, and 50% but not 5%. In PFS analysis <50% group was only based on 1 RCT.[17] These inconsistent results weaken PD-L1 tumor expression correlation and association with anti-PD1/PD-L1 response.

Tumor mutation burden is another predictor identified in some studies reporting a positive association between tumor mutation burden (TMB) and efficacy of PD1 checkpoint inhibition.[29,30] However, in our meta-analysis only Carbone et al[19] estimated progression free survival among patients with high and low tumor mutation burden reporting a highly significant PFS for patients with high mutation load (HR 0.62; 0.34, 1.00). Median progression free survival by tumor mutation burden was progressively increased from low (n = 62; 4.2 mo [1.5, 5.6]) to high tumor mutation burden (n = 47; 9.7 mo [5.1, NR]). A

Study or Subgroup	Anti PD1/PD-L1 Events	Total	Chemotherapy Events	Total	Weight	Odds Ratio IV, Random, 95% CI
4.1.1 Overall Treatment-related Adverse Events						
Borghaei et al	199	287	236	268	6.4%	0.31 [0.20, 0.48]
Brahmer et al	76	131	111	129	5.1%	0.22 [0.12, 0.41]
Carbone et al	190	267	243	263	5.8%	0.20 [0.12, 0.34]
Fehrenbacher et al	95	142	119	135	5.0%	0.27 [0.15, 0.51]
Herbst et al (10mg)	226	343	251	309	7.2%	0.45 [0.31, 0.64]
Herbst et al (2mg)	215	339	251	309	7.2%	0.40 [0.28, 0.57]
Reck et al	113	154	135	150	4.9%	0.31 [0.16, 0.58]
Rittmeyer et al	390	609	496	578	7.8%	0.29 [0.22, 0.39]
Subtotal (95% CI)		**2272**		**2141**	**49.4%**	**0.31 [0.26, 0.38]**
Total events	1504		1842			

Heterogeneity: Tau^2 = 0.02; Chi^2 = 9.55, df = 7 (P = 0.22); I^2 = 27%
Test for overall effect: Z = 12.34 (P < 0.00001)

4.1.2 Grade 3,4 or 5 Treatment-related Adverse Events						
Borghaei et al	30	287	144	268	6.4%	0.10 [0.06, 0.16]
Brahmer et al	9	131	71	129	4.1%	0.06 [0.03, 0.13]
Carbone et al	47	267	133	263	6.9%	0.21 [0.14, 0.31]
Fehrenbacher et al	17	142	55	135	5.1%	0.20 [0.11, 0.36]
Herbst et al (10mg)	55	343	109	309	7.1%	0.35 [0.24, 0.51]
Herbst et al (2mg)	43	339	109	309	6.9%	0.27 [0.18, 0.40]
Reck et al	41	154	80	150	6.2%	0.32 [0.20, 0.51]
Rittmeyer et al	90	609	247	578	7.9%	0.23 [0.18, 0.31]
Subtotal (95% CI)		**2272**		**2141**	**50.6%**	**0.20 [0.14, 0.28]**
Total events	332		948			

Heterogeneity: Tau^2 = 0.17; Chi^2 = 32.40, df = 7 (P < 0.0001); I^2 = 78%
Test for overall effect: Z = 9.54 (P < 0.00001)

Total (95% CI)		**4544**		**4282**	**100.0%**	**0.25 [0.20, 0.31]**
Total events	1836		2790			

Heterogeneity: Tau^2 = 0.12; Chi^2 = 53.77, df = 15 (P < 0.00001); I^2 = 72%
Test for overall effect: Z = 13.16 (P < 0.00001)
Test for subgroup differences: Chi^2 = 5.40, df = 1 (P = 0.02), I^2 = 81.5%

Figure 9. Forest plot of meta-analysis of the overall and Grade ≥ 3, 4, or 5 treatment-related adverse events (TRAEs) showing comparison of anti-PD1/ PD-L1 therapy to chemotherapy in advanced NSCLC. NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed cell death ligand 1.

Figure 10. Forest plot of meta-analysis of the overall incidence rates of treatment-related adverse events (TRAEs) showing comparison of anti-PD1/PD-L1 therapy to chemotherapy in advanced NSCLC. NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed cell death ligand 1.

Table 3

Subgroups association with OS and PFS.

Subgroups	Overall survival	Progression-free survival
Age	<65 and ≥65	<65
Gender	M and F	Only M
ECOG PS	1	1
Histology	Squamous	None
Smoking	Current/former	Never
EGFR	Wild type	Both
KRAS	Mutant	Wild type
CNS metastases	Absent	Absent

CNS = central nervous system, ECOG PS = Eastern Cooperative Oncology Group Performance Status, EGFR = epidermal growth factor receptor, KRAS = Kirsten rat sarcoma oncogene mutation, LTMB = low tumor mutation burden; OS = overall survival, PFS = progression free survival.

LTMB). However, overall survival was not associated with TMB load (HR 0.99; 0.71, 1.40).

PD-L1 tumor expression in NSCLC as predictor of immune response has become less reliable recently. Luterstein et al[31] pointed out that previous radiotherapy was better predictor to that of PD-L1 expression status. IFN-γ has also been reported as biomarker and predictor of immune response in NSCLC. Fehrenbacher et al[16] reported positive association between IFN-γ and overall survival (HR 0.43 [0.24–0.77]). Furthermore, IFN-γ was correlated with PD-L1 expression of tumor-infiltrating immune cells. Similarly, PD-L1+ immune cells in the stromal compartment (S-PD-L1) and PD-1+ intraepithelial tumor infiltrating lymphocytes (T-PD-1) were identified as independent prognostic factors for NSCLC.[32]

EGFR mutation is suggested to induce PD-L1 expression in NSCLC and thereby better response to anti-PD/PD-L1 therapies. This correlation is controversial with some studies reported no such association between PD-L1 expression and EGFR/KRAS/ALK expression in NSCLC.[33,34] Meta-analysis of the EGFR status and Overall survival revealed EGFR+ NSCLC to be non-respondent to anti-PD1/PD-L1 therapies. EGFR wild type derived the survival benefit associated with these therapies. On the other hand, KRAS+ NSCLC responded to anti-PD1/PD-L1 agents with significant survival while the wild type was non-respondent.
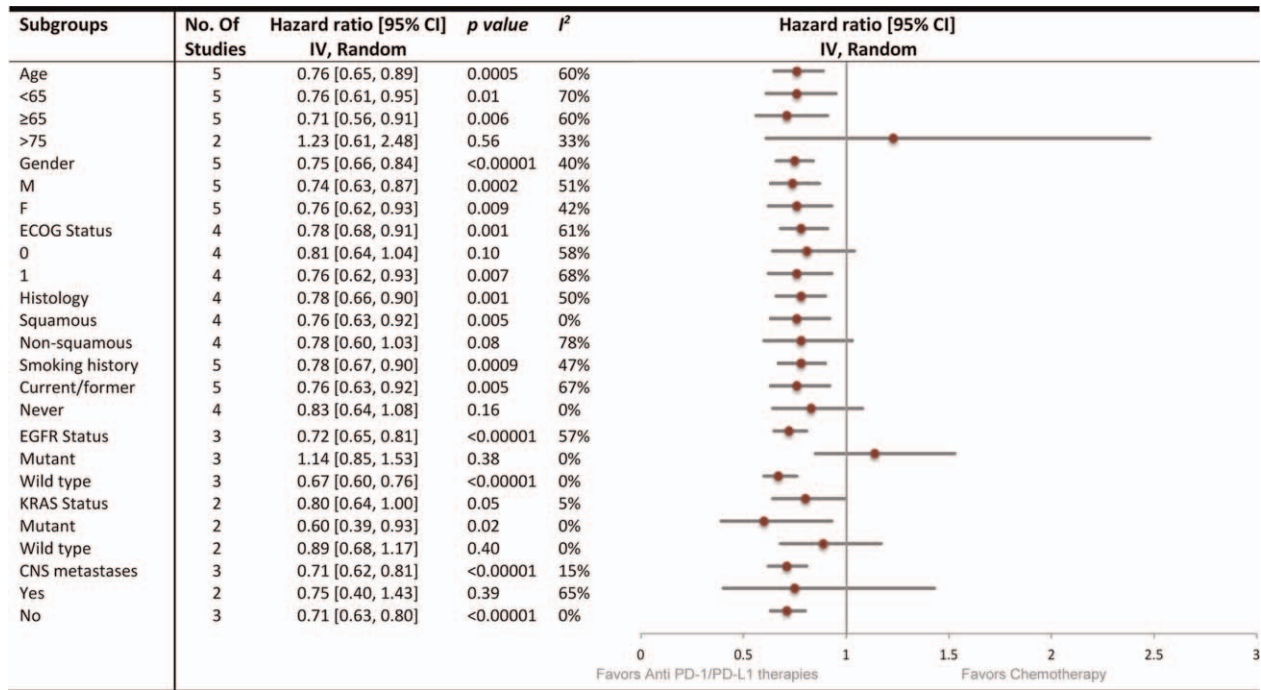
Other subgroup analysis included age, sex, smoking history, histology, ECOG status, and CNS metastases correlation with OS and PFS. Age subgroups (<65 and ≥65 years old except for ≥75 years old) derived OS advantage equally. Age had no significant effect on PFS with <65 years old achieving better PFS however not significant. Men and women achieved significantly better OS but only male sex was associated with better PFS. Current/former smoker category responded better with OS while never smoker category was associated with better PFS. Squamous cell type was associated with better survival however histology had no influence on PFS. NSCLC with no CNS metastases and ECOG performance score 1 were associated with better OS and PFS.

Chemotherapy has long been associated with severe adverse events. Immunotherapy reported far less adverse events compared with chemotherapy. Overall treatment-related adverse events were reported in all included studies and favored chemotherapy. Grade 3, 4, or 5 adverse events were also associated with chemotherapy. Unlike the efficacy outcomes, the safety outcome was reported with similar incidence rates across all 7 RCTs favoring chemotherapy arm. Fatigue, nausea, diarrhea, decreased appetite, and asthenia were related to both treatment arms but significantly more frequent with chemother-

contrast analysis was observed in chemotherapy arm (6.9 mo vs 5.8 mo). Overall response revealed the same trend a better response was shown by nivolumab (HTMB 47/47 vs 23/111 LTMB) compared with chemotherapy (HTMB 28/60 vs 33/94

Table 4

Subgroup analysis; association of baseline factors with overall survival.

Subgroups	No. Of Studies	Hazard ratio [95% CI] IV, Random	p value	I²	Hazard ratio [95% CI] IV, Random
Age	5	0.76 [0.65, 0.89]	0.0005	60%	
<65	5	0.76 [0.61, 0.95]	0.01	70%	
≥65	5	0.71 [0.56, 0.91]	0.006	60%	
>75	2	1.23 [0.61, 2.48]	0.56	33%	
Gender	5	0.75 [0.66, 0.84]	<0.00001	40%	
M	5	0.74 [0.63, 0.87]	0.0002	51%	
F	5	0.76 [0.62, 0.93]	0.009	42%	
ECOG Status	4	0.78 [0.68, 0.91]	0.001	61%	
0	4	0.81 [0.64, 1.04]	0.10	58%	
1	4	0.76 [0.62, 0.93]	0.007	68%	
Histology	4	0.78 [0.66, 0.90]	0.001	50%	
Squamous	4	0.76 [0.63, 0.92]	0.005	0%	
Non-squamous	4	0.78 [0.60, 1.03]	0.08	78%	
Smoking history	5	0.78 [0.67, 0.90]	0.0009	47%	
Current/former	5	0.76 [0.63, 0.92]	0.005	67%	
Never	4	0.83 [0.64, 1.08]	0.16	0%	
EGFR Status	3	0.72 [0.65, 0.81]	<0.00001	57%	
Mutant	3	1.14 [0.85, 1.53]	0.38	0%	
Wild type	3	0.67 [0.60, 0.76]	<0.00001	0%	
KRAS Status	2	0.80 [0.64, 1.00]	0.05	5%	
Mutant	2	0.60 [0.39, 0.93]	0.02	0%	
Wild type	2	0.89 [0.68, 1.17]	0.40	0%	
CNS metastases	3	0.71 [0.62, 0.81]	<0.00001	15%	
Yes	2	0.75 [0.40, 1.43]	0.39	65%	
No	3	0.71 [0.63, 0.80]	<0.00001	0%	

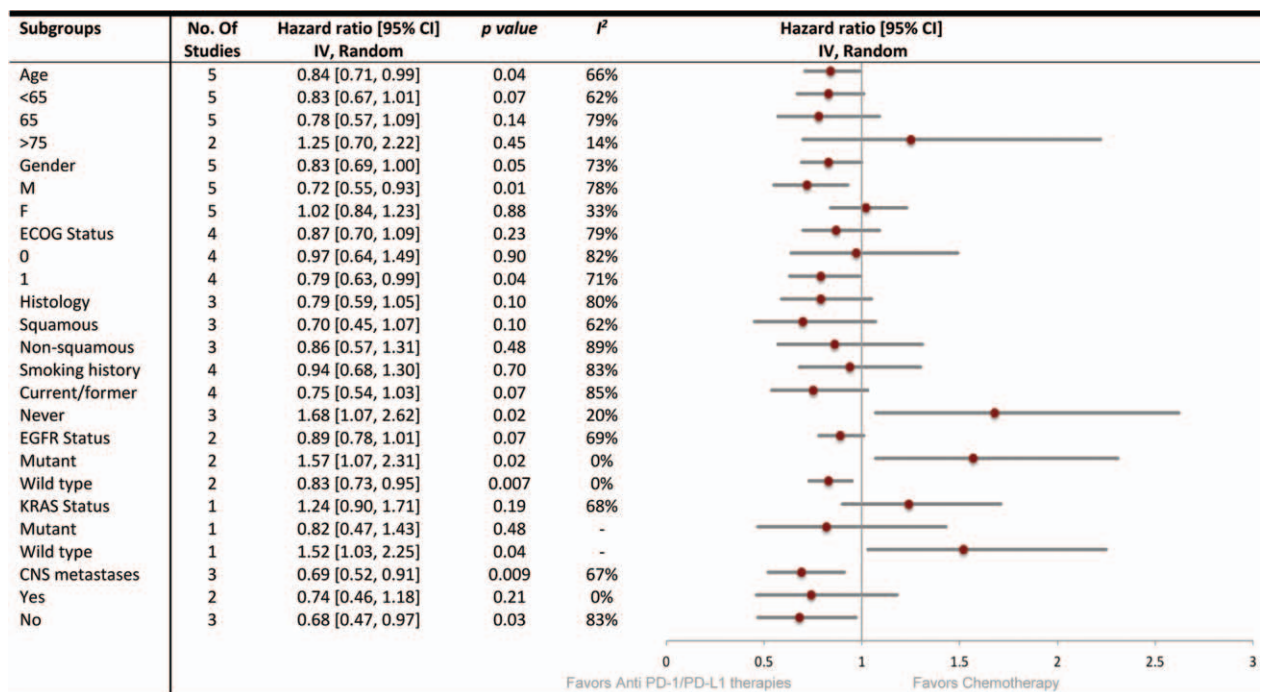Favors Anti PD-1/PD-L1 therapies — Favors Chemotherapy

apy. Anemia, alopecia, neutropenia, myalgia, and stomatitis were the adverse events attributed to chemotherapy only. On the other hand, immunotherapy was mainly associated with immune-mediated adverse events namely hypothyroidism, hyperthyroidism, pneumonitis and rash.

This meta-analysis has some limitations. None of the studies were double or single blinded. OAK study[20] lacked allocation concealment. Two RCTs[18,19] included some patients that were previously untreated and chemotherapy regimen applied was different compared with rest of the 5 RCTs that used docetaxel as

Table 5

Subgroup analysis; association of baseline factors with progression-free survival.

Subgroups	No. Of Studies	Hazard ratio [95% CI] IV, Random	p value	I²	Hazard ratio [95% CI] IV, Random
Age	5	0.84 [0.71, 0.99]	0.04	66%	
<65	5	0.83 [0.67, 1.01]	0.07	62%	
65	5	0.78 [0.57, 1.09]	0.14	79%	
>75	2	1.25 [0.70, 2.22]	0.45	14%	
Gender	5	0.83 [0.69, 1.00]	0.05	73%	
M	5	0.72 [0.55, 0.93]	0.01	78%	
F	5	1.02 [0.84, 1.23]	0.88	33%	
ECOG Status	4	0.87 [0.70, 1.09]	0.23	79%	
0	4	0.97 [0.64, 1.49]	0.90	82%	
1	4	0.79 [0.63, 0.99]	0.04	71%	
Histology	3	0.79 [0.59, 1.05]	0.10	80%	
Squamous	3	0.70 [0.45, 1.07]	0.10	62%	
Non-squamous	3	0.86 [0.57, 1.31]	0.48	89%	
Smoking history	4	0.94 [0.68, 1.30]	0.70	83%	
Current/former	4	0.75 [0.54, 1.03]	0.07	85%	
Never	3	1.68 [1.07, 2.62]	0.02	20%	
EGFR Status	2	0.89 [0.78, 1.01]	0.07	69%	
Mutant	2	1.57 [1.07, 2.31]	0.02	0%	
Wild type	2	0.83 [0.73, 0.95]	0.007	0%	
KRAS Status	1	1.24 [0.90, 1.71]	0.19	68%	
Mutant	1	0.82 [0.47, 1.43]	0.48	-	
Wild type	1	1.52 [1.03, 2.25]	0.04	-	
CNS metastases	3	0.69 [0.52, 0.91]	0.009	67%	
Yes	2	0.74 [0.46, 1.18]	0.21	0%	
No	3	0.68 [0.47, 0.97]	0.03	83%	

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chemotherapy regimen. Carbone et al's RCT reported huge crossover with 60% of the patients in chemotherapy arm needed nivolumab for subsequent therapy confounding intent to treat survival analysis. Two RCTs included patients with at least 1% PD-L1 tumor expression while Reck et al study included patients with 50% or more PD-L1 expression. These factors most probably be contributing to heterogeneity existed between the studies.

Immunotherapy as a treatment modality is getting its deserving space with recent developments. Immunotherapeutics has shown tremendous improvements in patients' survival outcomes in several cancers like melanoma and lung cancer. Its adjuvant role with radiotherapy is worth mentioning as huge amount of research being going on in this direction with promising results.[35] A recent study explored yet another dimension of cancer immunotherapy, "the role of microbiome in cancer immunotherapy." Antibiotics diminishing the efficacy of immunotherapy with anti-PD1/PD-L1 therapies unraveled the role of gut microbiome in cancer immunotherapy. Gut microbiome as therapeutic supplement with immunotherapy and efficacy marker is evolving.[36] These advancements are suggesting a promising role of immunotherapy in near future.

5. Conclusions

Anti-PD1/PD-L1 therapies represent better choice over chemotherapy in advance NSCLC. Immune response associated with PD1 pathway inhibition in NSCLC is more complex and could not be fully explained only by PD-L1 tumor expression and hence further investigations are warranted to identify more biomarkers. Proper selection of patients is recommended in order to derive full advantage of these agents. Further studies are needed to prove efficacy of these agents in first line treatment.

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