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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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progression free survival, RCT = randomized controlled trial, SE = standard error, TCR = T cell receptor, TMB = tumor mutation burden, TPS = tumor proportion score, TRAEs = treatment related adverse events, Tregs = T regulatory cells, X^2 = Chi square test.

Keywords: chemotherapy, immune checkpoint inhibitors, non-small cell lung cancer, programmed cell death-1 (PD1)/ programmed cell death ligand 1 (PD-L1), survival

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, progressionfree 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

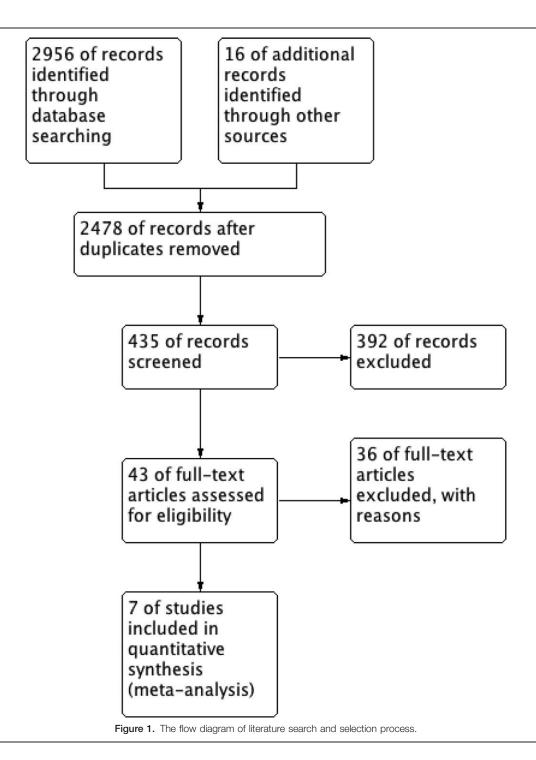
Data extracted from all the seven RCTs included general characteristics of the trial, trial inclusion, and exclusion criteria, baseline characteristics of the participants, main outcomes of the RCT and subgroup analysis. Extracted data were incorporated into the form of tables (Tables 1 and 2).

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



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.

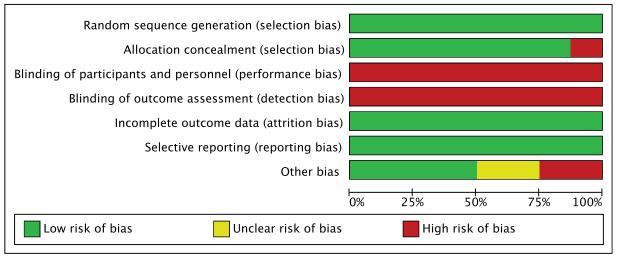


Figure 2. Risk of bias graph. +: low risk of bias; -: high risk of bias; ?: unclear risk of bias.

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 $\geq 1\%$, <5% and $\geq 5\%$, <10% and $\geq 10\%$, and <50% and $\geq 50\%$) 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%, $\geq 1\%$, $\geq 5\%$, $\geq 10\%$, and <50% and $\geq 50\%$ but not with <5% and <10%. A progressively greater improvement was observed with increasing proportion of PD-L1 tumor expression from <1% to $\geq 50\%$ (Fig. 6).

In PFS analysis, $\geq 1\%$, $\geq 10\%$, and $\geq 50\%$ revealed significant improvement in PFS with anti-PD1/PD-L1 agents as compared with PD-L1 expression of <1%, <5%, $\geq 5\%$, <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

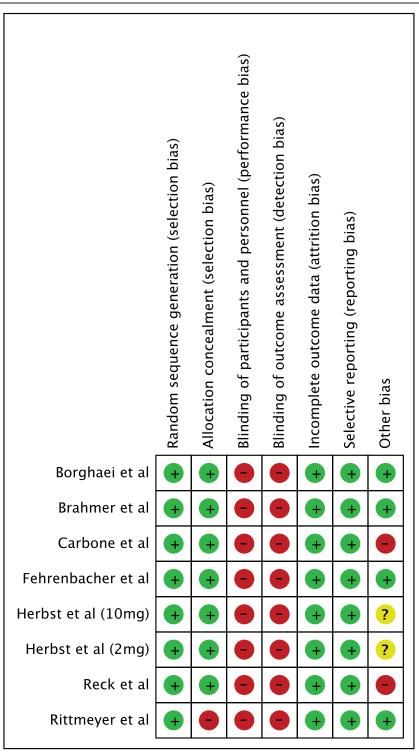


Figure 3. Risk of bias summary.

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 \geq 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

	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	DAK
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	Nivolumab (3 mg/kg every 2	Atezolizumab (1200 mg	Pembrolizumab (2 mg/kg	Pembrolizumab (200 mg	Nivolumab (3 mg/kg every 2 wks)	Atezolizumab (1200 mg
	Wks)	wks)	every 3 wks)	every 2 wks, 10mg/kg every 3 wks)	every 3 wks)		every 3 wks)
Chemotherapy (dosage)	Docetaxel (75 mg/m ² every	Pemetrexed/carboplatin	Pemetrexed/carboplatin	Docetaxel (75mg/m ² every			
	3 wks)	3 wks)	3 wks)	3 wks)	Pemetrexed/cisplatin	Pemetrexed/cisplatin	3 wks)
					Gemcitabine/carboplatin	Gemcitabine/carboplatin	
					Gemcitabine/cisplatin Paclitaxel/carhonlatin	Gemoitabine/cisplatin Paclitavel/carhonlatin	
Inclusion Criteria	≥18 years of age	Stage IV NSCLC	Untreated stage IV or recurrent	≥18 years of age			
	Stage IIIB or IV	Documented stage IIB/IV	Measurable disease as	Advanced NSCLC	≥50% PD-L1 expression	NSCLC	Stage IIIB or IV non-
	squamous-cell NSCLC	non-squamous NSCLC	per RECIST 1.1.	Measurable disease as	At least one measurable	≥1% PD-L1 expression	small-cell lung cancer
	who had disease	Recurrence following	Adequate hematological	per investigator-assessed	lesion as per RECIST	Measurable disease per	Measurable disease per
	recurrence after one	radiation therapy or	and end-organ function	RECIST	1.1.	RECIST 1.1.	RECIST 1.1.
	prior platinum-containing	surgical resection		Progression (as per	No sensitizing EGFR	No previous systemic anti-	One to two previous
	regimen	Disease recurrence or		RECIST 1.1.) after two or	mutations or ALK	cancer therapy for advanced	cytotoxic chemotherapy
	EC0G PS 0-1	progression during or		more cycles of platinum-	translocations	or metastatic disease	regimens (one or more
		after one prior platinum-		doublet chemotherapy as	No previous systemic	Previous palliative	platinum based
		based regimen.		well as an appropriate	therapy for metastatic	radiotherapy, if completed at	combination therapies)
		ECOG PS 0-1		tyrosine kinase inhibitor	disease	least 2 weeks before	
						randomization	
						Previous adjuvant or	
						neoadjuvant chemotherapy, if	
						completed at least o months hefore	
Exclusion Criteria	Autoimmune disease	Autoimmune disease	Active or untreated CNS	Previous treatment with PD-	Receiving systemic	Autoimmune disease or known	History of autoimmune
	symptomatic interstitial	symptomatic interstitial	metastases. history of	1 checkpoint inhibitors or	alucocorticoids	EGFR mutations or ALK	disease
	lung disease, systemic	lung disease, systemic	pneumonitis,	docetaxel, known active	Immunosuppressive	translocations that were	Previous treatments with
	immunosuppression,	immunosuppression,	autoimmune or chronic	brain metastases or	treatment	sensitive to available targeted	docetaxel, CD137
	prior therapy with T-cell	prior treatment with	viral diseases, or	carcinomatous	Untreated brain	therapy	agonists, anti-CTLA4, or
	co-stimulation or	immune-stimulatory	previous treatment with	meningitis, active	metastases		therapies targeting the
	checkpoint-targeted	antitumor agents	docetaxel, CD137	autoimmune disease	Active autoimmune		PD-L1 and PD-1
	agents, or prior docetaxel	including checkpoint-	agonists, anti- CTLA4,	requiring systemic	disease		pathway
	therapy	targeted agents, or	anti-PD-L1, or anti-PD-1	steroids, and interstitial	Active interstitial lung		
		docetaxel.	therapeutic antibodies, or	lung disease or history of	disease		
			PD-L1-PD-1 pathway-	pneumonitis requiring	History of pneumonitis		
Dulman and actuals	c	0	raigering agents				00
Printary end points Secondary end points	us ORR, PFS, Efficacy by PD-	us ORR, PFS, Efficacy by PD-	us ORR, DOR, PFS	US and PFS ORR, DOR, TRAE	PFS OS, ORR, TRAE	PFS per BIRCH (≥3% PD-L1+) PFS per BIRCH (≥1% PD-L1+),	us PFS, ORR, DOR, TRAE
	L1 expression level,	L1 expression level,				OS (≥5% PD-L1+)	
	disease-related symptom	disease-related symptom				0RR (≥5% PD-L1+), TRAE	

Table 1

	Brahmer et al ^[14]	Borghaei et al ^[15]	Fehrenbacher et al ^{t16]}	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)	improvement rate by week 12 MOS: 12.2m (nivo) versus 9.4m (doc) HR = 0.73 (0.59–0.89)	MOS: 12.6m (atez) versus 9.7m (doc) HR=0.73 (0.53-0.99)	MOS: 10.4m (pemb2mg) versus 8.5m (doc) HR = 0.71 (0.58-0.88)	MOS: not reached HR=0.60 (0.41-0.89) <i>P</i> =. <i>005</i>	MOS: 13.7m (nivo) versus 13.8m (doc) HR = 1.07 (0.86–1.33)	MOS: 13.8m (atez) versus 9.6m (doc) HR =0.73 (0.62–0.87)
Pronression-free survival	A COLOR AND AND A COLOR AND A	n –	MDS: 2 7m (afe2) versus	MOS: 12.7m (pemb10 mg) versus 8.5m (doc) HR = 0.61 (0.49–0.75) P < .0001 MMOS: 3.9m (nemp2mo)	MOS- 10 3m (nemb) versus	MDS: 4.2m (nivin) versus 5.8m	MDS: 2 8m (atex) versus
rtogression-rice survva	MUS: .3.011 (IIIV0) VERSUS 2.811 (doc) HR= 0.62 (0.47–0.81) P < .001	MUS: 2.311 (IIIVO) VEISUS 4.2m (doo) HR = 0.92 (0.77–1.1) P = .39	MUS: 2.7/III (attez) versus 3.0/III (doc) HR=0.94 (0.72–1.23) P=/NS	MOS: 5.5111 (Definition) versus 4m (doc) HR = 0.88 (0.74-0-1.05) P = .07 MOS: 4m (pemb10mg) versus 4m (doc) HR = 0.79 (0.66-0.94) P < .004	MOS: 10.5ft (perina) versus 6m (chem) HR=0.50 (0.37-0.68) P<.001	MUO: 4.2111 (TINO) VETSUS 5.3111 (doc) HR = 1.17 (0.95–1.43) P = .13	MUS. Z. diri (att2) Versus 4.0m (doc) HR= 0.95 (0.82–1.10) P=.433
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 Doo: 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 DDR: 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+)(rivo) versus 5.7m (1.4–21.0+) (doc)	Atez: 58 Doc: 57 DDR: 16.3m (10-NE) (atez) versus 6.2m (4.9- 7.6)(doc)
	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=chem non-small cell lung cancer, OR= od treatment-related adverse events.	Atez = atezolizumab, Chem = chemotherapy, CI = confidence interval, Doc = docetaxel, DOR = duration non-small cell lung cancer, OR = odds ratio, ORR = objective response rate, OS = overall survival, PD1 treatment-related adverse events.	oc = docetaxel, DOR = duration of r rate, OS = overall survival, PD1 = p	esponse, EGFR = epidermal growth programmed cell death receptor 1, I	factor receptor, HR = hazard ratio, ^I PD-L1 = programmed cell death lig	<pre> KPAS = Kirsten rat sarcoma oncoge and 1, Pemb = Pembrolizumab, PF</pre>	Atez = atezolizumab, Chem = chemotherapy, CI = confidence interval, Doc = docetaxel, DOR = duration of response, EGFR = epidermal growth factor receptor, HR = hazard ratio, KRAS = Klrsten rat sarcoma oncogene mutation, MOS = median overall survival, Nivo = Nivolemab, NSCLC = non-small cell lung cancer, OR = objective response rate, OS = overall survival, PD1 = programmed cell death receptor 1, PD-L1 = programmed cell death ligand 1, Pemb = Pembrolizumab, PFS = progression-free survival, RCT = randomized controlled trial, TRAE reatment-related adverse events.	ival, Nivo = Nivolumab, NSCLC = Idomized controlled trial, TRAE =

Studies	Brahmer et al ^[14]	t al ^[14]	Borghaei	Borghaei et al ^{t 13} 1	Fehrenbacher et	er et al ^{t 10]}	Herbst et al ^{LI/J}	et al ^{un}	Reck et al ^{tio}	t al ^{troj}	Carbone et al	et al ^{traj}	Rittmeye	Rittmeyer et al ^{izuj}	Cumulat	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	069	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%)		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%)
-	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%)		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	I	I		ı	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	I	'	'		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%)		I	I	ŗ	I	I	I	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%)	ı	ı	271 (100%)	270 (100%)	241 (57%)	222 (52%)	1481 (70%)	1116 (63%)
<5%	75 (56%)	69 (50%)	136 (59%)	138 (62%)	ı	ı	I	ı	ı	ı	1		ı		211 (10%)	207 (12%)
≥5%	42 (31%)	39 (29%)	95 (41%)	86 (38%)	50 (35%)	55 (38%)	ı				208 (77%)	210 (78%)	129 (30%)	136 (32%)	524 (25%)	526 (30%)
<10	81 (60%)	75 (55%)	145 (63%)	145 (65%)	ı	ı	1	ı		,		'	ı		226 (11%)	220 (13%)
≥10%	36 (27%)	33 (24%)	86 (37%)	79 (35%)			ı	ı		·	ı	ı	ı	,	122 (6%)	112 (6%)
≥50%	ı	ı		'	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	ı		44 (15%)	38 (13%)	10 (12%)		(%6) 09	26 (8%)	ı	ı	ı	ı	42 (10%)	43 (10%)	156 (7%)	115 (7%)
Negative	ı		168 (58%)	172 (59%)	72 (87%)	75 (90%)	581 (84%)	294 (86%)	ı		ı		318 (75%)	310 (73%)	1139 (54%)	851 (48%
KRAS status																
Positive	I		28 (10%)	34 (12%)	14 (33%)	13 (43%)	I	ı	I	·	I	1	26 (6%)	33 (8%)	68 (3%)	80 (5%)
Negative		ı	60 (21%)	63 (22%)	28 (67%)	17 (57%)	I	ı			'	I	99 (23%)	104 (24%)	187 (9%)	184 (10%)
EML4-ALK translocation	ttion															
Positive	ı	I	13 (4%)	8 (3%)	0 (0%)	3 (5%)	6 (1%)	2 (1%)	ı	ı	I	ŗ	I	ı	19 (1%)	13 (1%)
Negative		•	113 (39%)	130 (45%)	61 (100%)	55 (95%)	612 (89%)	310 (90%)	·		ı	•		ı	786 (37%)	495 (28%)
CNS metastases																
Yes	0 (1%)	8 (6%)	34 (12%)	34 (12%)	I	ı	I	I	ı	ı	ı	I	I	ı	43 (2%)	42 (2%)
No	126 (93%)	129 (94%)	258 (88%)	256 (88%)		'	,	'			'		18 (11.7%)	10 (6.6%)	402 (19%)	395 (22%)

8

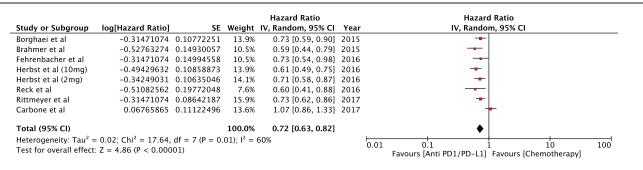


Figure 4. Forest plot of meta-analysis of the overall survival (OS) showing comparison of anti-PD1/ PD-L1 therapy to chemotherapy in advanced NSCLC. NSCLC=non-small cell lung cancer; PD-1=programmed cell death-1; PD-L1=programmed cell death ligand 1.

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 $\geq 50\%$ PD-L1 expression that was the inclusion criteria for Reck et al.^[18] Though greater number of patients with $\geq 50\%$ 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

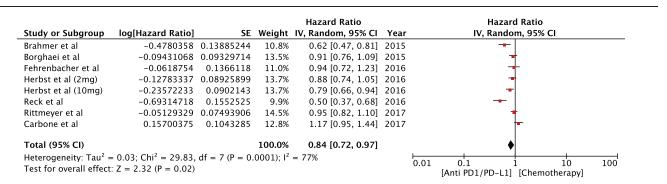


Figure 5. Forest plot of meta-analysis of the progression-free survival (PFS) showing comparison of anti-PD1/PD-L1 therapy to chemotherapy in advanced NSCLC. NSCLC=non-small cell lung cancer; PD-1=programmed cell death-1; PD-L1=programmed cell death ligand 1.

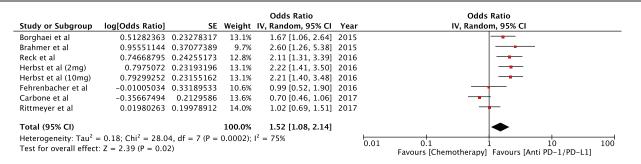
/ 0 / 0	[Hazard Ratio]	SE Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% Cl
6.1.1 <1% PD-L1 Express	ion			
Borghaei et al	-0.13926207 0.16224	4203 3.6%	0.87 [0.63, 1.20]	-+
Brahmer et al	-0.54472718 0.2323	5496 2.5%	0.58 [0.37, 0.91]	
Fehrenbacher et al	0.03922071 0.2647		1.04 [0.62, 1.75]	
Rittmeyer et al	-0.28768207 0.1241		0.75 [0.59, 0.96]	
Subtotal (95% CI)		12.5%	0.78 [0.65, 0.94]	◆
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z =		$= 0.34$; $I^2 = 11$.%	
6.1.2 ≥1% PD-L1 Express				
Borghaei et al	-0.54472718 0.1551	5524 3.7%	0.58 [0.43, 0.79]	
Brahmer et al	-0.37106368 0.2161		0.69 [0.45, 1.05]	
Carbone et al	0.06765865 0.1112		1.07 [0.86, 1.33]	
Fehrenbacher et al	-0.52763274 0.1922		0.59 [0.40, 0.86]	
Herbst et al (10mg)	-0.49429632 0.1085		0.61 [0.49, 0.75]	
Herbst et al (2mg)	-0.34249031 0.1034		0.71 [0.58, 0.87]	
				-
Rittmeyer et al Subtotal (95% CI)	-0.30110509 0.1204	4808 4.3% 27.4%	0.74 [0.58, 0.94]	Å
			0.71 [0.60, 0.84]	•
Heterogeneity: Tau ² = 0.04 Fest for overall effect: Z =		$P = 0.006$; $I^2 =$	67%	
5.1.3 <5% PD-L1 Express	ion			
Borghaei et al	-0.040822 0.1412	5705 3.9%	0.96 [0.73, 1.27]	+
Brahmer et al	-0.35667494 0.1976		0.70 [0.48, 1.03]	
Subtotal (95% CI)		6.9%	0.84 [0.62, 1.14]	
Heterogeneity: $Tau^2 = 0.02$	P = 1.69 df - 1.09			•
Test for overall effect: $Z =$		- 5.15), 1 - 41		
6.1.4 ≥5% PD-L1 Express				
Borghaei et al	-0.84397007 0.1851		0.43 [0.30, 0.62]	
Brahmer et al	-0.63487827 0.2690	4315 2.1%	0.53 [0.31, 0.90]	
Carbone et al	0.01980263 0.1238	5404 4.2%	1.02 [0.80, 1.30]	+
Fehrenbacher et al	-0.61618614 0.2530	9408 2.3%	0.54 [0.33, 0.89]	
Rittmeyer et al	-0.40047757 0.1550	9933 3.7%	0.67 [0.49, 0.91]	
Subtotal (95% CI)		15.5%	0.63 [0.44, 0.89]	◆
Heterogeneity: Tau ² = 0.12 Test for overall effect: Z =		P = 0.001); I ² =	78%	
6.1.5 <10% PD-L1 Expres	sion			
Borghaei et al	-0.040822 0.133	7369 4.1%	0.96 [0.74, 1.25]	+
Brahmer et al	-0.35667494 0.1897		0.70 [0.48, 1.02]	
Subtotal (95% CI)		7.2%	0.84 [0.62, 1.14]	◆
Heterogeneity: Tau ² = 0.02 Test for overall effect: Z =		$= 0.17$; $I^2 = 46$	5%	
6.1.6 ≥10% PD-L1 Expres			0 40 [0 27 0 50]	
Borghaei et al	-0.91629073 0.1950		0.40 [0.27, 0.59]	
Brahmer et al	-0.69314718 0.2950		0.50 [0.28, 0.89]	
Fehrenbacher et al	-0.71334989 0.4058		0.49 [0.22, 1.09]	
Subtotal (95% CI)		6.1%	0.44 [0.32, 0.59]	▼
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z =		= 0.78); l ² = 0%	6	
6.1.7 <50% PD-L1 Expres	sion			
Fehrenbacher et al	-0.61618614 0.2530	9408 2.3%	0.54 [0.33, 0.89]	— —
Herbst et al (2mg)	-0.27443685 0.1198		0.76 [0.60, 0.96]	
Rittmeyer et al	-0.40047757 0.1550		0.67 [0.49, 0.91]	- -
Subtotal (95% CI)		10.3%	0.70 [0.59, 0.83]	♦
Heterogeneity: $Tau^2 = 0.00$ Test for overall effect: Z =		-		
6.1.8 ≥50% PD-L1 Expres				
		2504 2.204	0.00.00.00.1.201	\perp
Carbone et al	-0.10536052 0.1828		0.90 [0.63, 1.29]	
Fehrenbacher et al	-0.71334989 0.4035		0.49 [0.22, 1.08]	
Herbst et al (2mg)	-0.63487827 0.1427		0.53 [0.40, 0.70]	
Reck et al	-0.51082562 0.1977		0.60 [0.41, 0.88]	
Rittmeyer et al	-0.89159812 0.2201		0.41 [0.27, 0.63]	
Subtotal (95% CI)		14.0%	0.58 [0.44, 0.76]	●
Heterogeneity: $Tau^2 = 0.05$	F_{c} ; Chi ² = 8.85, df = 4 (P 3.94 (P < 0.0001)	$= 0.07$; $I^2 = 55$	5%	
Test for overall effect: Z =		100.0%	0.68 [0.62 0.75]	▲ I
Test for overall effect: Z = Total (95% CI)		100.0%	0.68 [0.62, 0.75]	<u> </u>
Test for overall effect: Z =				↓ 0.01 0.1 1 10 10

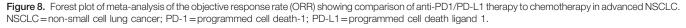
Figure 6. Forest plots of subgroup analysis of association between overall survival (OS) and PD-L1 tumor expression level at cut off values of 1%, 5%, 10%, and 50%. PD-L1 = programmed cell death ligand 1.

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 $\geq 1\%$. 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% Cl
5.2.1 <1% PD-L1 Exp		0 1 F · 0 /		1 10 10 07 7 7 7	
Borghaei et al	0.17395331		4.1%	1.19 [0.88, 1.61]	
Brahmer et al	-0.41551544		3.4%	0.66 [0.43, 1.01]	
^E ehrenbacher et al Subtotal (95% CI)	0.11332868	0.23158268	3.2% 10.8%	1.12 [0.71, 1.76] 0.97 [0.68, 1.40]	•
Heterogeneity: Tau ² = Fest for overall effect:		f = 2 (P = 0.0)	8); $I^2 = 62$	1%	
5.2.2 ≥1% PD-L1 Exp					
Borghaei et al	-0.35667494	0.1461742	4.2%	0.70 [0.53, 0.93]	
Brahmer et al	-0.40047757		3.4%	0.67 [0.44, 1.02]	
Carbone et al	0.15700375	0.1043285	4.7%	1.17 [0.95, 1.44]	
ehrenbacher et al	-0.13926207		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		4.9%	0.88 [0.74, 1.05]	-
Subtotal (95% CI)	-0.12785557	0.06925699	26.2%	0.85 [0.73, 1.05]	•
Heterogeneity: Tau ² = Fest for overall effect:		df = 5 (P = 0.	02); $I^2 = 6$	51%	
5.2.3 <5% PD-L1 Exp					
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)	0.20700207	0.1001909	8.1%	1.01 [0.58, 1.74]	•
Heterogeneity: Tau ² = Fest for overall effect:		f = 1 (P = 0.0)	2); $I^2 = 83$	3%	
5.2.4 ≥5% PD-L1 Exp	ression				
Borghaei et al	-0.61618614	0.17019686	3.9%	0.54 [0.39, 0.75]	
Brahmer et al	-0.61618614		2.9%	0.54 [0.32, 0.91]	
	0.13976194				
Carbone et al			4.6%	1.15 [0.91, 1.45]	
ehrenbacher et al Subtotal (95% CI)	-0.35667494	0.22333386	3.3% 14.7%	0.70 [0.45, 1.08] 0.71 [0.46, 1.10]	
Heterogeneity: Tau ² = Test for overall effect:		df = 3 (P = 0.	0007); I ²		-
5.2.5 <10% PD-L1 Ex	pression				
Borghaei et al	0.21511138	0.13190208	4.4%	1.24 [0.96, 1.61]	
Brahmer et al	-0.35667494		3.8%	0.70 [0.49, 0.99]	
Subtotal (95% CI) Heterogeneity: Tau ² =	$0.14 \cdot Ch^2 = C \cdot C \cdot C$	f_1/P_00	8.2%	0.94 [0.54, 1.65]	\blacksquare
Test for overall effect:		II = I (P = 0.0)	1); 1 = 8:) %	
6.2.6 ≥10% PD-L1 Ex	pression				
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)	0.00. CH2 0.00	6 2 /2 2 -	8.7%	0.55 [0.42, 0.72]	◆
Heterogeneity: Tau ² = Test for overall effect:			1); $I^2 = 0$ %	6	
6.2.7 <50% PD-L1 Ex	pression				
Herbst et al (2mg) Subtotal (95% CI)	0.03922071	0.10243261	4.7% 4.7%	1.04 [0.85, 1.27] 1.04 [0.85, 1.27]	↓
Heterogeneity: Not ap			т. <i>1 /</i> 0	1.07 [0.03, 1.27]	Ť
Test for overall effect:					
5 .2.8 ≥50% PD-L1 Ex Carbone et al		0 16840220	1 00/		
	0.06765865		4.0%	1.07 [0.77, 1.49]	
Fehrenbacher et al	-0.51082562		2.2%	0.60 [0.31, 1.16]	
Herbst et al (2mg)	-0.77652879		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 Subtotal (95% CI)	-0.46203546	0.19123964	3.7% 18.6%	0.63 [0.43, 0.92] 0.62 [0.44, 0.86]	
Heterogeneity: Tau ² = Test for overall effect:					•
	z = 2.07 (1 = 0.004)	,	100		
Total (95% CI)			100.0%	0.79 [0.69, 0.90]	•
Heterogeneity: Tau ² = Fest for overall effect:			0.00001)	$ _{1^{2}} = 78\%$	0.01 0.1 1 10 100

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.





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 \geq 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 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	Events		Events	TOTAL	weight	IV, Random, 95% CI	IV, Random, 95% Cl
4.1.1 Overall Treatm							
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 =				0.22); I ²	= 27%		
Test for overall effect:	Z = 12.34 ((P < 0.000)	01)				
4.1.2 Grade 3,4 or 5	Treatment-	related A	dverse E	vents			
					C 40/	0.10.00.0.101	
Borghaei et al	30	287	144	268	6.4%	0.10 [0.06, 0.16]	
	30 9	287 131	144 71	268 129	6.4% 4.1%	0.10 [0.06, 0.16]	
Brahmer et al							
Brahmer et al Carbone et al	9	131	71	129	4.1%	0.06 [0.03, 0.13]	
Brahmer et al Carbone et al Fehrenbacher et al	9 47	131 267	71 133	129 263	4.1% 6.9%	0.06 [0.03, 0.13] 0.21 [0.14, 0.31]	
Brahmer et al Carbone et al Fehrenbacher et al Herbst et al (10mg)	9 47 17	131 267 142	71 133 55	129 263 135	4.1% 6.9% 5.1%	0.06 [0.03, 0.13] 0.21 [0.14, 0.31] 0.20 [0.11, 0.36]	
Brahmer et al Carbone et al Fehrenbacher et al Herbst et al (10mg) Herbst et al (2mg)	9 47 17 55	131 267 142 343	71 133 55 109	129 263 135 309	4.1% 6.9% 5.1% 7.1%	0.06 [0.03, 0.13] 0.21 [0.14, 0.31] 0.20 [0.11, 0.36] 0.35 [0.24, 0.51]	
Brahmer et al Carbone et al Fehrenbacher et al Herbst et al (10mg) Herbst et al (2mg) Reck et al Rittmeyer et al	9 47 17 55 43	131 267 142 343 339 154 609	71 133 55 109 109	129 263 135 309 309 150 578	4.1% 6.9% 5.1% 7.1% 6.9% 6.2% 7.9%	0.06 [0.03, 0.13] 0.21 [0.14, 0.31] 0.20 [0.11, 0.36] 0.35 [0.24, 0.51] 0.27 [0.18, 0.40] 0.32 [0.20, 0.51] 0.23 [0.18, 0.31]	
Brahmer et al Carbone et al Fehrenbacher et al Herbst et al (10mg) Herbst et al (2mg) Reck et al Rittmeyer et al Subtotal (95% CI)	9 47 17 55 43 41 90	131 267 142 343 339 154	71 133 55 109 109 80 247	129 263 135 309 309 150	4.1% 6.9% 5.1% 7.1% 6.9% 6.2%	0.06 [0.03, 0.13] 0.21 [0.14, 0.31] 0.20 [0.11, 0.36] 0.35 [0.24, 0.51] 0.27 [0.18, 0.40] 0.32 [0.20, 0.51]	
Borghaei et al Brahmer et al Carbone et al Fehrenbacher et al Herbst et al (10mg) Herbst et al (2mg) Reck et al Rittmeyer et al Subtotal (95% CI) Total events	9 47 17 55 43 41 90 332	131 267 142 343 339 154 609 2272	71 133 55 109 109 80 247 948	129 263 135 309 309 150 578 2141	4.1% 6.9% 5.1% 7.1% 6.9% 6.2% 7.9% 50.6%	0.06 [0.03, 0.13] 0.21 [0.14, 0.31] 0.20 [0.11, 0.36] 0.35 [0.24, 0.51] 0.27 [0.18, 0.40] 0.32 [0.20, 0.51] 0.23 [0.18, 0.31] 0.20 [0.14, 0.28]	
Brahmer et al Carbone et al Fehrenbacher et al Herbst et al (10mg) Herbst et al (2mg) Reck et al Rittmeyer et al Subtotal (95% CI)	9 47 17 55 43 41 90 332	131 267 142 343 339 154 609 2272	71 133 55 109 109 80 247 948	129 263 135 309 309 150 578 2141	4.1% 6.9% 5.1% 7.1% 6.9% 6.2% 7.9% 50.6%	0.06 [0.03, 0.13] 0.21 [0.14, 0.31] 0.20 [0.11, 0.36] 0.35 [0.24, 0.51] 0.27 [0.18, 0.40] 0.32 [0.20, 0.51] 0.23 [0.18, 0.31] 0.20 [0.14, 0.28]	
Brahmer et al Carbone et al Fehrenbacher et al Herbst et al (10mg) Herbst et al (2mg) Reck et al Rittmeyer et al Subtotal (95% CI) Total events	9 47 17 55 43 41 90 332 0.17; Chi ²	131 267 142 343 339 154 609 2272 = 32.40, c	71 133 55 109 109 80 247 948 If = 7 (P	129 263 135 309 309 150 578 2141	4.1% 6.9% 5.1% 7.1% 6.9% 6.2% 7.9% 50.6%	0.06 [0.03, 0.13] 0.21 [0.14, 0.31] 0.20 [0.11, 0.36] 0.35 [0.24, 0.51] 0.27 [0.18, 0.40] 0.32 [0.20, 0.51] 0.23 [0.18, 0.31] 0.20 [0.14, 0.28]	
Brahmer et al Carbone et al Fehrenbacher et al Herbst et al (10mg) Herbst et al (2mg) Reck et al Rittmeyer et al Subtotal (95% CI) Total events Heterogeneity: Tau ² =	9 47 17 55 43 41 90 332 0.17; Chi ²	131 267 142 343 339 154 609 2272 = 32.40, c	71 133 55 109 109 80 247 948 If = 7 (P	129 263 135 309 309 150 578 2141 < 0.0001	4.1% 6.9% 5.1% 7.1% 6.9% 6.2% 7.9% 50.6%	0.06 [0.03, 0.13] 0.21 [0.14, 0.31] 0.20 [0.11, 0.36] 0.35 [0.24, 0.51] 0.27 [0.18, 0.40] 0.32 [0.20, 0.51] 0.23 [0.18, 0.31] 0.20 [0.14, 0.28]	
Brahmer et al Carbone et al Fehrenbacher et al Herbst et al (10mg) Herbst et al (2mg) Reck et al Rittmeyer et al Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	9 47 17 55 43 41 90 332 0.17; Chi ²	131 267 142 343 339 154 609 2272 = 32.40, c	71 133 55 109 109 80 247 948 If = 7 (P	129 263 135 309 309 150 578 2141 < 0.0001	4.1% 6.9% 5.1% 7.1% 6.9% 6.2% 7.9% 50.6%); $l^2 = 789$	0.06 [0.03, 0.13] 0.21 [0.14, 0.31] 0.20 [0.11, 0.36] 0.35 [0.24, 0.51] 0.27 [0.18, 0.40] 0.32 [0.20, 0.51] 0.23 [0.18, 0.31] 0.20 [0.14, 0.28] 6	

Figure 9. Forest plot of meta-analysis of the overall and Grade \geq 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.

5.2.1 Fatigue Sorghaei et al	Anti PD1/I Events	PD-L1 (Total	Chemoth Events	erapy Total	Weight	Odds Ratio IV, Random, 95% CI	Odds IV, Randor	Ratio n, 95% Cl
orgnaei et al	46	287	78	268	2.0%	0.46 [0.31, 0.70]		
Brahmer et al	21 56	131 267	42 93	129 263	1.9%	0.40 [0.22, 0.72]		
Carbone et al Herbst et al (10mg)	49	343	93	263	2.0%	0.49 [0.33, 0.72] 0.51 [0.34, 0.76]		
lerbst et al (2mg)	46	339	76	309	2.0%	0.48 [0.32, 0.72]		
eck et al ubtotal (95% CI)	16	154 1521	43	150 1428	1.9% 11.9%	0.29 [0.15, 0.54] 0.46 [0.38, 0.55]		
otal events	234		408			0110 [0150] 0155]	•	
eterogeneity: Tau ² = 1 est for overall effect: 2	0.00; Chi ² Z = 8.48 (P	= 2.76, df < 0.0000	= 5 (P = 1)	0.74); I ²	= 0%			
.2.2 Nauea orghaei et al rahmer et al	34 12	287 131	70 30	268 129	2.0%	0.38 [0.24, 0.60] 0.33 [0.16, 0.68]		
arbone et al	31	267	127	263	2.0%	0.14 [0.09, 0.22]		
erbst et al (10mg) erbst et al (2mg)	31 37	343 339	45 45	309 309	2.0% 2.0%	0.58 [0.36, 0.95] 0.72 [0.45, 1.14]	-	
zck et al	15	154	45	150	1.9%	0.14 [0.08, 0.26]	- 1	
ubtotal (95% CI)		1521		1428	11.7%	0.32 [0.18, 0.57]	+	
otal events eterogeneity: Tau ² = 1 est for overall effect; 2	160 0.44; Chi ² Z = 3.86 (P	= 37.59, d = 0.0001	382 f = 5 (P	< 0.0000	1); l ² = 8	7%		
.2.3 Decreased appet orghaei et al	tite 30	287	42	268	2.0%	0.63 [0.38, 1.04]		
ahmer et al	14	131 267	25 73	129 263	1.9%	0.50 [0.25, 1.01] 0.35 [0.22, 0.56]		
arbone et al erbst et al (10mg)	32 33	267 343	73 49	263 309	2.0%	0.35 [0.22, 0.56]	-	
erhst et al (2mm)	46	339	49	309	2.0%	0.56 [0.35, 0.90] 0.83 [0.54, 1.29]		-
ack et al abtotal (95% CI)	14	154 1521	39	150 1428	1.9% 11.7%	0.28 [0.15, 0.55]		
otal events	169		277			0.51 [0.57, 0.70]	•	
eterogeneity: Tau ² = est for overall effect: 2	0.08; Chi ² :		f = 5 (P :	= 0.05); I	2 = 55%			
2.4 Diarrhea								
orghaei et al ahmer et al	22	287	62	268	2.0%	0.28 [0.16, 0.46]		
arbone et al	10 37	131 267	26 34	129 263	1.8%	0.33 [0.15, 0.71] 1.08 [0.66, 1.79]		-
erbst et al (10mg)	22	343	56	309	2.0%	0.31 [0.18, 0.52]		
erbst et al (2mg) zck et al	24 22	339 154	56 20	309 150	2.0% 1.9%	0.34 [0.21, 0.57] 1.08 [0.56, 2.08]		_
eck et al ubtotal (95% CI)		1521		1428	11.6%	1.08 [0.56, 2.08] 0.47 [0.28, 0.80]	•	
otal events eterogeneity: Tau ² = 1	137 0.34: Chi ² :	= 25 87 4	254 f = 5 (P -	< 0.0001); I ² = 81	×		
est for overall effect: 3	Z = 2.80 (P	= 0.005)	2.01		91			
.2.5 Asthenia orghaei et al	29	287	47	268	2.0%	0.53 [0.32, 0.87]		
rahmer et al	13	131	18	129	1.8%	0.68 [0.32, 1.45]		-
arbone et al ubtotal (95% CI)	8	267 685	28	263 660	1.8% 5.6%	0.68 [0.32, 1.45] 0.26 [0.12, 0.58] 0.47 [0.29, 0.77]		
otal events	50		93				•	
eterogeneity: Tau ² = 1 est for overall effect: 2	0.07; Chi ² Z = 3.01 (P	= 3.20, df = 0.003)	= 2 (P =	0.20); I ²	= 37%			
2.6 Anemia arghaei et al	2	287	28	268	1.3%	0.06 [0.01, 0.26]		
orghaei et al rahmer et al	6	131	53	129	1.7%	0.07 [0.03, 0.17]		
arbone et al erbst et al (10mg)	9 14	267 343	113 40	263 309	1.8% 1.9%	0.05 [0.02, 0.09] 0.29 [0.15, 0.54]		
erbst et al (2mg)	14	339	40	309	1.9%	0.29 [0.15, 0.54]		
eck et al ubtotal (95% CI)	8	154 1521	66	150 1428	1.8% 10.5%	0.07 [0.03, 0.15] 0.10 [0.05, 0.20]		
otal events	49		340				-	
eterogeneity: Tau ² = 1 est for overall effect: 2	0.51; Chi ² - Z = 6.73 (P	= 20.52, d	f = 5 (P - 1)	- 0.0010); l ² = 76	x		
2.7 Neutropenia								
orghaei et al	1	287	83	268	1.0%	0.01 [0.00, 0.06]	·	
ahmer et al	1	131	42	129	1.0%	0.02 [0.00, 0.12]	·	
arbone et al erbst et al (10mg)	0	267 343	48 44	263 309	0.7%	0.01 [0.00, 0.14]		
erbst et al (10mg) erbst et al (2mg)	1	339	44	309	1.0%	0.02 [0.00, 0.13]	·	
eck et al ubtotal (95% CI)	0	154 1521	20	150 1428	0.7% 5.3%	0.02 [0.00, 0.34] 0.01 [0.01, 0.03]		
otal events	4		281			0.01 [0.01, 0.05]	-	
eterogeneity: Tau ² = est for overall effect: 2	0.00; Chi ² : Z = 9.44 (P	= 0.67, df < 0.0000	= 5 (P = 1)	0.98); I ²	= 0%			
.2.8 Alopecia				260	1.05			
orghaei et al rahmer et al	1	287 131 343	67 29 101	268 129 309	1.0% 0.7% 1.4%	0.01 [0.00, 0.08] 0.01 [0.00, 0.21] 0.01 [0.00, 0.05]		
erbst et al (10mq)	2	343	101	309	1.4%	0.01 [0.00, 0.05]	←	
erbst et al (2mg) Jbtotal (95% CI)	3	339 1100	101	309 1015	1.5% 4.5%	0.02 [0.01, 0.06] 0.01 [0.01, 0.03]	-	
ntal events	6		298				-	
eterogeneity: Tau ² = 1 est for overall effect: 2	0.00; Chi ² :	= 0.33, df	= 3 (P =	0.95); l²	= 0%			
	2 = 10.00 (,r < 0.000	01)					
2.9 Myalgia orghaei et al	7	287	30	268	1.8%	0.20 [0.09, 0.46]		
ahmer et al abtotal (95% CI)	2	131	13	129 397	1.3%	0.14 [0.03, 0.63] 0.18 [0.09, 0.38]		
		418		397	3.0%	0.18 [0.09, 0.38]	•	
otal events eterogeneity: Tau ² = I	9 0.00; Chi ²	= 0.17, df	43 = 1 (P =	0.68); I ²	= 0%			
est for overall effect: a	Z = 4.54 (P	< 0.0000	1)					
2.10 Stomatitis								
erbst et al (10mg)	7	343	43	309	1.8%	0.13 [0.06, 0.29]		
erbst et al (10mg) erbst et al (2mg)	7 13 4	339	43 43 18	309	1.9%	0.25 [0.13. 0.47]	=	
erbst et al (10mg) erbst et al (2mg) eck et al ubtotal (95% CI) rtal events	13 4 24	339 154 836	43 18	309 150 768	1.9% 1.6% 5.2%	0.13 [0.06, 0.29] 0.25 [0.13, 0.47] 0.20 [0.06, 0.59] 0.19 [0.12, 0.31]		
erbst et al (10mg) erbst et al (2mg) eck et al a btotal (95% CI) otal events eterogeneity: Tau ² = 1	13 4 24 0.00; Chi ²	339 154 836 = 1.51, df	43 18 104 = 2 (P =	309 150 768	1.9% 1.6% 5.2%	0.25 [0.13. 0.47]		
erbst et al (10mg) erbst et al (2mg) eck et al a btotal (95% CI) otal events eterogeneity: Tau ² = 1	13 4 24 0.00; Chi ²	339 154 836 = 1.51, df	43 18 104 = 2 (P =	309 150 768	1.9% 1.6% 5.2%	0.25 [0.13. 0.47]		
erbst et al (10mg) erbst et al (2mg) eck et al bitotal (95% CI) otal events eterogeneity: Tau ² = ! est for overall effect: 2 2.11 Hyperthyroidis	13 4 0.00; Chi ² Z = 7.03 (P	339 154 836 = 1.51, df < 0.0000	43 18 = 2 (P = 1)	309 150 768 0.47); I ²	1.9% 1.6% 5.2% = 0%	0.25 [0.13, 0.47] 0.20 [0.06, 0.59] 0.19 [0.12, 0.31]		
erbst et al (10mg) erbst et al (2mg) ack et al abtotal (95% CI) otal events eterogeneity: Tau ² = 1 est for overall effect: 2 2.11 Hyperthyroidis erbst et al (10mo)	13 4 0.00; Chi ² Z = 7.03 (P m 20	339 154 836 > < 0.0000 343	43 18 = 2 (P = 1) 3	309 150 768 0.47); I ² 309	1.9% 1.6% 5.2% = 0%	0.25 [0.13, 0.47] 0.20 [0.06, 0.59] 0.19 [0.12, 0.31]	 ►	
erbst et al (10mg) erbst et al (2mg) erbst et al (2mg) erbst et al (2mg) bitotal (95% Cl) tal events eterogeneity: Tau ² = / est for overall effect: 3 2.11 Hyperthyroidis erbst et al (10mg) erbst et al (2mg) sck et al	13 4 0.00; Chi ² Z = 7.03 (P	339 154 836 = 1.51, df < 0.0000 343 339 154	43 18 = 2 (P = 1)	309 150 768 0.47); I ² 309 309 150	1.9% 1.6% 5.2% = 0% 1.5% 1.4%	0.25 [0.13, 0.47] 0.20 [0.06, 0.59] 0.19 [0.12, 0.31] 6.32 [1.86, 21.47] 3.74 [1.05, 13.39]	•	=
erbst et al (10mg) erbst et al (2mg) sck et al biototal (95% CI) stal events eterogeneity: Tau ² = : 2.11 Hyperthyroidis erbst et al (10mg) erbst et al (2mg) sck et al biototal (95% CI)	13 4 0.00; Chi ² - Z = 7.03 (P :m 20 12	339 154 836 = 1.51, df < 0.0000 343 339	43 18 104 = 2 (P = 1) 3 2	309 150 768 0.47); I ² 309 309	1.9% 1.6% 5.2% = 0%	0.25 [0.13, 0.47] 0.20 [0.06, 0.59] 0.19 [0.12, 0.31]	•	<u> </u>
erbst et al (10mg) erbst et al (2mg) sck et al ibtotal (95% CI) tal events tetrogeneity: Tau ² = = esst for overall effect: ; 2.11 Hyperthyroidis erbst et al (10mg) erbst et al (2mg) sck et al ibtotal (95% CI) tal events tetrogeneity: Tau ² = =	$\begin{array}{c} & 13 \\ & 4 \\ & 24 \\ & 0.00; \ Chi^2 \\ & z = 7.03 \ (P \\ & 12 \\ & 12 \\ & 12 \\ & 12 \\ & 44 \\ & 0.00; \ Chi^2 \\ & \end{array}$	339 154 836 = 1.51, df < 0.0000 343 339 154 836 = 0.41, df	43 18 2 (P = 1) 3 3 2 8 = 2 (P =	309 150 768 0.47); I ² 309 309 150 768	1.9% 1.6% 5.2% = 0% 1.5% 1.4% 1.3% 4.2%	0.25 [0.13, 0.47] 0.20 [0.06, 0.59] 0.19 [0.12, 0.31] 6.32 [1.86, 21.47] 3.74 [1.05, 13.39]		
erbst et al (10mg) erbst et al (2mg) erbst et al (2mg) erbtotal (95% CI) otal events eterogeneity: Tau ² = i z.1.1 Hyperthyroidis erbst et al (2mg) erbst et al (2mg) erbst et al (2mg) erbst et al (2mg) tal events eterogeneity: Tau ² = est for overall effect: 2	13 4 24 0.00; Chi ² - Z = 7.03 (P m 20 12 12 12 12 12 44 0.00; Chi ² - Z = 4.25 (P	339 154 836 = 1.51, df < 0.0000 343 339 154 836 = 0.41, df	43 18 2 (P = 1) 3 3 2 8 = 2 (P =	309 150 768 0.47); I ² 309 309 150 768	1.9% 1.6% 5.2% = 0% 1.5% 1.4% 1.3% 4.2%	0.25 [0.13, 0.47] 0.20 [0.06, 0.59] 0.19 [0.12, 0.31] 6.32 [1.86, 21.47] 3.74 [1.05, 13.39]		
erbst et al (10mg) erbst et al (2mg) teck et al 10% (2mg) teck et al 10% (2mg) tecrogeneity: Tau ² = 1 eterogeneity: Tau ² = 1 eterogeneity: Tau ² = 1 (2mg) teck et al (2mg) teck et al (2mg) tecrogeneity: Tau ² = 1 (2mg) tecrogeneity: Tau ² = 1 (2m	13 4 24 0.00; Chi ² + Z = 7.03 (P m 20 12 12 12 12 0.00; Chi ² + Z = 4.25 (P m	339 154 836 = 1.51, df > < 0.0000 343 339 154 836 = 0.41, df > < 0.0001	43 18 104 2 (P = 1) 3 3 2 8 = 2 (P =	309 150 768 0.47); I ² 309 309 150 768 0.81); I ²	1.9% 1.6% 5.2% = 0% 1.5% 1.4% 1.3% 4.2% = 0%	0.25 [0.6, 0.59] 0.20 [0.66, 0.59] 0.19 [0.12, 0.31] 6.32 [1.86, 21.47] 3.74 [1.05, 13.39] 6.25 [1.38, 28.44] 5.22 [2.44, 11.20]	-[-[-] ◆	
erbst et al (10mg) erbst et al (2mg) exk et al biotoal (95% C) bal events eterogenelty: Tau ² = . 2.11 Hyperthyroidis erbst et al (10mg) exk et al biotoal (95% C) biotoal (95% C) biotoal (95% C) biotoal (95% C) cal events eterogenelty: Tau ² = . est for overall effect: 2.12 Hypothyroidism	13 4 24 0.00; Chi ² - Z = 7.03 (P m 20 12 12 12 12 12 44 0.00; Chi ² - Z = 4.25 (P	339 154 836 = 1.51, df < 0.0000 343 339 154 836 = 0.41, df	43 18 104 = 2 (P = 1) 3 3 2 8 = 2 (P =) 1 1	309 150 768 0.47); I ² 309 309 150 768	1.9% 1.6% 5.2% = 0% 1.5% 1.4% 4.2% = 0% 1.0%	0.25 [0.66, 0.59] 0.20 [0.66, 0.59] 0.19 [0.12, 0.31] 6.32 [1.86, 21.47] 3.74 [1.05, 13.39] 6.25 [1.38, 28.44] 5.22 [2.44, 11.20]		∓
erbst et al (10mg) erbst et al (2mg) eck et al botoal (95% CI) tal events eterogeneity: Tau ² = 1 est for overall effect : 2.11 Hyperthyroldis erbst et al (10mg) erbst et al (10mg) erbst et al (2mg) botoal (95% CI) al events eterogeneity: Tau ² = 1 2.12 Hypothyroldis eterogeneity: Tau ² = 1 eth eth al (2mg) erbst et al (10mg) erbst et al (2mg)	13 4 24 0.00; Chi ² - 7.03 (P m 20 12 12 12 12 12 12 12 12 12 12 12 12 12	339 154 836 = 1.51, df < 0.0000 343 339 154 836 = 0.41, df < 0.0001 343 339 154	43 18 104 = 2 (P = 1) 3 3 2 = 2 (P =) 1	309 150 768 0.47); I ² 309 309 150 768 0.81); I ² 309 309 309	$\begin{array}{c} 1.9\% \\ 1.6\% \\ 5.2\% \end{array}$ = 0% $\begin{array}{c} 1.5\% \\ 1.4\% \\ 1.3\% \\ 4.2\% \end{array}$ = 0% $\begin{array}{c} 1.0\% \\ 1.0\% \end{array}$	0.25 (0.13, 0.47) 0.20 (0.06, 0.59) 0.19 (0.12, 0.31) 6.32 (1.86, 21, 47) 3.74 (1.05, 13.39) 6.25 (1.38, 28, 44) 5.22 (2.44, 11.20) 27.38 (3.70, 202, 46) 27.73 (3.75, 205, 08)		
rbst et al (10mg) rbst et al (2mg) ck et al ibotal (95% CI) tal events sterogeneity: Tau ² = 1 st for overall effect: 1 2.11 Hyperthyroidis rbst et al (10mg) rbst et al (10mg) rbst et al (10mg) rbst et al (2mg) thotal (95% CI) thotal (95% CI) rbst et al (2mg) rbst e	$\begin{array}{c} 13\\ 4\\ 24\\ 0.00; Chi^{2}, \\ Z = 7.03 \ (P\\ m\\ 20\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12$	339 154 836 = 1.51, df < 0.0000 343 339 154 836 = 0.41, df < 0.0001 343 339 154 836 \$	43 18 104 = 2 (P = 1) 3 3 2 8 = 2 (P = 1) 1 2 4	309 150 768 0.47): l ² 309 309 150 768 0.81): l ² 309 309 150 768	$\begin{array}{c} 1.9\% \\ 1.6\% \\ 5.2\% \end{array} \\ = 0\% \\ \begin{array}{c} 1.5\% \\ 1.4\% \\ 1.3\% \\ 4.2\% \end{array} \\ = 0\% \\ \begin{array}{c} 1.0\% \\ 1.0\% \\ 1.3\% \\ 3.3\% \end{array}$	0.25 [0.66, 0.59] 0.20 [0.66, 0.59] 0.19 [0.12, 0.31] 6.32 [1.86, 21.47] 3.74 [1.05, 13.39] 6.25 [1.38, 28.44] 5.22 [2.44, 11.20]	 	₩
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what is all (clong) what is all (clong) when all (clong)	$\begin{array}{c} 13\\ 24\\ 0.00; Chi^2\\ Z=7.03 (P\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12\\ 24\\ 25\\ 25\\ 28\\ 14\\ 0.00; Chi^2\\ Z=5.14 (P\\ 15\\ 16\\ 9\\ 40\\ 0.00; Chi^2\\ Z=3.07 (P\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\ 5\\$	$\begin{array}{c} 333\\ 154\\ 836\\ =1.51, df\\ *<0.0000\\ 343\\ 339\\ 154\\ 836\\ =0.41, df\\ 836\\ =1.56, df\\ 836\\ =1.56, df\\ 836\\ =1.47, df\\ =0.0021\\ 131\\ 339\\ 154\\ 836\\ =1.47, df\\ 1267\\ 343\\ 339\\ 339\\ 154\\ 836\\ 836\\ =1.47, df\\ 1267\\ 343\\ 339\\ 339\\ 154\\ 836\\ 836\\ 836\\ 836\\ 836\\ 836\\ 836\\ 836$	43 18 2 (P = 1) 3 3 2 (P = 1) 4 2 (P = 1) 2 (P = 1) 2 (P = 1) 2 (P = 1) 2 (P = 1) 2 (P = 2	309 150 768 309 309 150 768 309 309 150 768 0.46); l ² 150 768 0.46); l ² 150 768 0.48); l ² 150 768 0.48); l ²	$\begin{array}{l} 1.9\%\\ 1.9\%\\ 1.6\%\\ 5.2\%\\ = 0\%\\ \end{array}$	0.12 (0.13, 0.05) 0.12 (0.12, 0.31) 0.12 (0.12, 0.31) 0.12 (0.12, 0.31) 0.12 (0.12, 0.31) 0.12 (0.12, 0.31) 0.12 (0.12, 0.13) 0.12 (0.14, 0.13) 0.12 (0.14, 0.13) 0.12 (0.14, 0.14) 0.12 (0.14,		
what et al (10mg) draw et al ($\begin{array}{c} 13\\ 24\\ 24\\ 0.00; Chi^2 \ P\\ \end{array} \\ \begin{array}{c} 24\\ 24\\ 0.00; Chi^2 \ P\\ \end{array} \\ \begin{array}{c} 24\\ 22\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12\\ 12$	$\begin{array}{c} 339\\ 154\\ 836\\ =1.51, df\\ *<0.0000\\ 343\\ 339\\ 154\\ 836\\ =0.41, df\\ 836\\ =1.6, df\\ 836\\ =1.56, df\\ =1.6, df\\ =1.6, df\\ =1.47, df\\ =1.0, 0021\\ 131\\ 267\\ 343\\ 343\\ \end{array}$	43 104 = 2 (P = 1) 3 3 2 (P = 1) 1 2 (P = 1) 4 = 2 (P = 1) 6 6 6 1 1 1 2 (P = 1) 1 2 (P = 1) 1 1 2 (P = 1) 1 1 1 1 1 1 1 1 1 1 1 1 1	309 150 768 309 309 150 768 0.47); l ² 309 309 309 309 309 309 309 309	$\begin{array}{c} 1.9\%\\ 1.9\%\\ 1.6\%\\ 5.2\%\\ = 0\%\\ \end{array}$	0.21 (0.13, 0.47) 0.19 (0.12, 0.31) 0.19 (0.12, 0.31) 1.74 (10.5, 13.59) 0.22 (2.46, 13.59) 0.22 (2.46, 13.69) 0.22 (2.46, 13.69) 0.23 (13.76, 20.246) 0.27 (13.76, 20.56, 33.51) 1.25 (10.76, 548) 2.27 (11.46, 23.69) 2.31 (10.46, 33.51) 1.25 (10.77, 548) 2.27 (11.46, 23.69) 0.00 (10.16, 13.69) 0.00 (10.16, 13.69) 0.00 (10.16, 14.69) 0.00 (10.16,		
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what et al (2mg) what al (2mg) where a low ensity here a low ensity	113 4 24 2 7 7 7 7 0 10 12 12 12 12 12 12 12 12 12 12 12 12 12	$\begin{array}{c} 339\\ 154\\ 836\\ 836\\ <\\ 343\\ 339\\ 154\\ 836\\ =\\ 0.0000\\ 343\\ 339\\ 154\\ 836\\ =\\ 0.0001\\ 343\\ 339\\ 154\\ 836\\ =\\ 1.56, df\\ =\\ 0.0021\\ 343\\ 339\\ 154\\ 836\\ =\\ 1.47, df\\ 836\\ =\\ 1.47, df\\ 126\\ 339\\ 1080\\ =\\ 6.27, df\\ 200\\ 0.0021\\ 127\\ 343\\ 339\\ 1080\\ =\\ 6.27, df\\ 126\\ 200\\ 0.0021\\ 127\\ 343\\ 339\\ 1080\\ =\\ 6.27, df\\ 126\\ 0.0021\\ 127\\ 343\\ 339\\ 1080\\ =\\ 0.031\\ 15753\\ 1080\\ $	43 18 104 = 2 (P = 1) 3 3 2 8 = 2 (P = 1) 1 2 2 2 2 2 2 2 2 2 2 2 2 2	309 150 768 309 309 309 309 309 309 300 768 309 300 768 309 300 768 309 300 768 309 300 768 309 309 300 768 309 309 309 309 309 309 309 309 309 309	$\begin{array}{c} 1.9\%\\ 1.6\%\\ 5.2\%\\ =0\%\\ 1.5\%\\ 1.4\%\\ 1.4\%\\ 1.4\%\\ 1.4\%\\ 1.4\%\\ 4.2\%\\ =0\%\\ 1.7\%\\ 1.0\%\\ 1.3\%\\ 3.3\%\\ =0\%\\ 1.7\%\\ 1.7\%\\ 1.7\%\\ 1.7\%\\ 1.7\%\\ 1.6\%\\ 1.3\%\\ 2.2\%\\ =0\%\\ 1.7\%\\ 1.7\%\\ 1.2\%\\ 1.5\%\\ 1.9\%\\ 1.0$	0.23 (0.13, 0.47) 0.19 (0.12, 0.31) 0.33 (1.86, 21, 47) 1.33 (1.86, 21, 47) 1.33 (1.86, 21, 47) 1.33 (1.86, 21, 1.39) 1.33 (1.87, 1.39) 2.33 (1.37, 23, 1.33) 2.33 (1.38, 2.43) 2.33 (1.38, 2.43) 2.33 (1.36, 3.34) 2.31 (0.88, 6.01) 2.30 (0.97, 6.48) 0.30 (0.97, 6.48		

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.

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 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-

Table 4

Subgroup analysis; association of baseline factors with overall survival.

dies 5 5 5 5 5 5 5 5 4 4 4 4 4	IV, Random 0.76 [0.65, 0.89] 0.76 [0.61, 0.95] 0.71 [0.56, 0.91] 1.23 [0.61, 2.48] 0.75 [0.66, 0.84] 0.74 [0.63, 0.87] 0.76 [0.62, 0.93] 0.78 [0.68, 0.91] 0.81 [0.64, 1.04]	0.0005 0.01 0.006 0.56 <0.00001 0.0002 0.009 0.001	60% 70% 60% 33% 40% 51% 42%		++++++	IV, Randor	m			
5 5 2 5 5 5 4 4 4	0.76 [0.61, 0.95] 0.71 [0.56, 0.91] 1.23 [0.61, 2.48] 0.75 [0.66, 0.84] 0.74 [0.63, 0.87] 0.76 [0.62, 0.93] 0.78 [0.68, 0.91] 0.81 [0.64, 1.04]	0.01 0.006 0.56 <0.00001 0.0002 0.009	70% 60% 33% 40% 51% 42%		+++++++	-				
5 2 5 5 5 4 4 4	0.71 [0.56, 0.91] 1.23 [0.61, 2.48] 0.75 [0.66, 0.84] 0.74 [0.63, 0.87] 0.76 [0.62, 0.93] 0.78 [0.68, 0.91] 0.81 [0.64, 1.04]	0.006 0.56 <0.00001 0.0002 0.009	60% 33% 40% 51% 42%		+	-			_	
2 5 5 5 4 4 4	1.23 [0.61, 2.48] 0.75 [0.66, 0.84] 0.74 [0.63, 0.87] 0.76 [0.62, 0.93] 0.78 [0.68, 0.91] 0.81 [0.64, 1.04]	0.56 <0.00001 0.0002 0.009	33% 40% 51% 42%		++	•			_	
5 5 4 4	0.75 [0.66, 0.84] 0.74 [0.63, 0.87] 0.76 [0.62, 0.93] 0.78 [0.68, 0.91] 0.81 [0.64, 1.04]	<0.00001 0.0002 0.009	40% 51% 42%		+	•				
5 5 4 4 4	0.74 [0.63, 0.87] 0.76 [0.62, 0.93] 0.78 [0.68, 0.91] 0.81 [0.64, 1.04]	0.0002 0.009	51% 42%		+					
5 4 4 4	0.76 [0.62, 0.93] 0.78 [0.68, 0.91] 0.81 [0.64, 1.04]	0.009	42%		-					
4 4 4	0.78 [0.68, 0.91] 0.81 [0.64, 1.04]					<u></u>				
4	0.81 [0.64, 1.04]	0.001				-				
4			61%			-				
		0.10	58%		-+	-				
4	0.76 [0.62, 0.93]	0.007	68%			-				
	0.78 [0.66, 0.90]	0.001	50%			-				
4	0.76 [0.63, 0.92]	0.005	0%			-				
4	0.78 [0.60, 1.03]	0.08	78%			-				
5	0.78 [0.67, 0.90]	0.0009	47%							
5	0.76 [0.63, 0.92]	0.005	67%			-				
4	0.83 [0.64, 1.08]	0.16	0%		-					
3	0.72 [0.65, 0.81]	< 0.00001	57%		-					
3	1.14 [0.85, 1.53]	0.38	0%			+				
3	0.67 [0.60, 0.76]	< 0.00001	0%		-					
2			5%		-+	-				
2		0.02	0%	-	-	-				
2		0.40	0%			•				
3		< 0.00001	15%		-					
2	0.75 [0.40, 1.43]	0.39	65%	-		_				
3	0.71 [0.63, 0.80]	<0.00001	0%		+					
			0			1	1.5	2	2.5	
N 12 11 12	2	0.60 [0.39, 0.93] 0.89 [0.68, 1.17] 0.71 [0.62, 0.81] 0.75 [0.40, 1.43]	0.60 [0.39, 0.93] 0.02 0.89 [0.68, 1.17] 0.40 0.71 [0.62, 0.81] <0.00001	2: 0.60 [0.39, 0.93] 0.02 0% 2: 0.89 [0.68, 1.17] 0.40 0% 3: 0.71 [0.62, 0.81] <0.00001	2: 0.60 [0.39, 0.93] 0.02 0% 2: 0.89 [0.68, 1.17] 0.40 0% 3: 0.71 [0.62, 0.81] <0.00001	2: 0.60 [0.39, 0.93] 0.02 0% 2: 0.89 [0.68, 1.17] 0.40 0% 3: 0.71 [0.62, 0.81] <0.00001	2: 0.60 [0.39, 0.93] 0.02 0% 2: 0.89 [0.68, 1.17] 0.40 0% 3: 0.71 [0.62, 0.81] <0.00001	2: 0.60 [0.39, 0.93] 0.02 0% 2: 0.89 [0.68, 1.17] 0.40 0% 3: 0.71 [0.62, 0.81] <0.00001	2: 0.60 [0.39, 0.93] 0.02 0% 2: 0.89 [0.68, 1.17] 0.40 0% 3: 0.71 [0.62, 0.81] <0.00001	2: 0.60 [0.39, 0.93] 0.02 0% 2: 0.89 [0.68, 1.17] 0.40 0% 3: 0.71 [0.62, 0.81] <0.00001

apy. Anemia, alopecia, neutropenia, myalgia, and stomatitis were the adverse events attributed to chemotherapy only. On the other hand, immunotherapy was mainly associated with immunemediated 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	Hazard ratio [95% CI]	p value	1 ²		Haza	ard ratio [9	95% CI]			
Sandra Trans. N. Zhen	Studies	IV, Random	1. P. 1990 Aug. 1	10.1		21-0-1	IV, Rando	m			
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%		-				83	
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	1			•				
Wild type	1	1.52 [1.03, 2.25]	0.04	0-6			_			-	
CNS metastases	3 2 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%			-				
					0	0.5	1	1.5	2	2.5	3
				Favors Anti I	PD-1/PD-L	1 therapies		Favors Chemo	therapy		

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.

Author contributions

- Conceptualization: Muhammad Khan, Jie Lin, Guixiang Liao, Yunhong Tian, Yingying Liang, Rong Li, Mengzhong Liu, Yawei Yuan.
- Data curation: Muhammad Khan, Guixiang Liao, Yunhong Tian, Yingying Liang, Rong Li, Mengzhong Liu.
- Formal analysis: Muhammad Khan, Yunhong Tian, Yingying Liang, Rong Li, Mengzhong Liu, Yawei Yuan.
- Funding acquisition: Yingying Liang, Mengzhong Liu, Yawei Yuan.
- Investigation: Muhammad Khan, Rong Li, Yawei Yuan.
- Methodology: Muhammad Khan, Yunhong Tian, Yawei Yuan.
- Project administration: Jie Lin, Yunhong Tian, Yawei Yuan.
- Resources: Muhammad Khan, Guixiang Liao, Rong Li, Yawei Yuan.
- Software: Muhammad Khan, Guixiang Liao, Rong Li.
- Supervision: Muhammad Khan, Jie Lin, Guixiang Liao,
- Yunhong Tian, Yingying Liang, Mengzhong Liu, Yawei Yuan. Validation: Muhammad Khan, Jie Lin, Guixiang Liao, Yunhong
- Tian, Yingying Liang, Mengzhong Liu, Yawei Yuan. Visualization: Jie Lin, Guixiang Liao, Yingying Liang,
- Mengzhong Liu, Yawei Yuan.
- Writing original draft: Muhammad Khan, Yawei Yuan.
- Writing review & editing: Muhammad Khan, Jie Lin, Guixiang Liao, Yawei Yuan.

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