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, PD-L1 = programmed cell death ligand, PFS =
1. Introduction

Lung cancer is the leading cause of cancer death in both men and women and the second most commonly diagnosed cancer. 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 36%. While the majority of lung cancers are diagnosed at an advanced stage with 5% 5-year survival rate. 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 lung cancer (NSCLC) accounts for >84% of all lung cancers. Platinum based chemotherapy is used as first line treatment in advanced NSCLC with a 15% to 30% response rate. Docetaxel as the second line treatment has shown reasonable results but overall survival benefit is limited. 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. Targeted therapies together with docetaxel have also fail to shown any durable results.

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. 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. 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. 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. \( \chi^2 \) 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.
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: \( I^2 = 60\% \)).

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

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

|               | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|---------------|---------------------------------------------|----------------------------------------|----------------------------------------------------------|-------------------------------------------------|----------------------------------------|-------------------------------------|-----------|
| 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      | -                                           | -                                      | -                                                        | +                                               | +                                      | +                                   |           |

Figure 3. Risk of bias summary.

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.**

| Designation          | Inclusion Criteria                                                                 | Exclusion Criteria                                                                 |
|----------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Checkmate-017        | ≥18 years of age. Documented stage IB/IV non-squamous NSCLC with measurable disease as per RECIST 1.1. Adequate hematologic and end-organ function. | Autoimmune disease, symptomatic interstitial lung disease, systemic immunosuppression, prior therapy with T-cell co-stimulation or checkpoint-targeted agents, or prior docetaxel therapy. |
| Checkmate-057        | ≥18 years of age. Documented stage IB/IV non-squamous NSCLC with measurable disease as per RECIST 1.1. Adequate hematologic and end-organ function. | Autoimmune disease, symptomatic interstitial lung disease, systemic immunosuppression, prior therapy with T-cell co-stimulation or checkpoint-targeted agents, or prior docetaxel therapy. |
| POPULAR              | ≥18 years of age. Documented stage IB/IV non-squamous NSCLC with measurable disease as per RECIST 1.1. Adequate hematologic and end-organ function. | Autoimmune disease, systemic interstitial lung disease, systemic immunosuppression, prior therapy with T-cell co-stimulation or checkpoint-targeted agents, or prior docetaxel therapy. |
| Keynote-010          | ≥18 years of age. Documented stage IB/IV non-squamous NSCLC with measurable disease as per RECIST 1.1. Adequate hematologic and end-organ function. | Active or untreated QNS metastases, history of pneumonitis, autoimmune or chronic viral disease, or previous treatment with docetaxel, CD137, anti-CTLA4, anti-PD-L1, or anti-PD-1 therapeutic antibodies, or PD-L1/PD-1-pathway-targeting agents. |
| Keynote-024          | ≥18 years of age. Documented stage IB/IV non-squamous NSCLC with measurable disease as per RECIST 1.1. Adequate hematologic and end-organ function. | Receiving systemic glucocorticoids. |
| Checkmate-026        | ≥18 years of age. Documented stage IB/IV non-squamous NSCLC with measurable disease as per RECIST 1.1. Adequate hematologic and end-organ function. | Autoimmune disease or known EGFR mutations or ALK translocations that were sensitive to available targeted therapy. |
| NCT02142738          | ≥18 years of age. Documented stage IB/IV non-squamous NSCLC with measurable disease as per RECIST 1.1. Adequate hematologic and end-organ function. | Previous treatments with docetaxel, CD137, and anti-CTLA4 agents, or therapies targeting the PD-L1 or PD-1 pathway. |
| OAK                  | ≥18 years of age. Documented stage IB/IV non-squamous NSCLC with measurable disease as per RECIST 1.1. Adequate hematologic and end-organ function. | History of autoimmune disease. |

**Primary end points**
- OS
- ORR, PFS, Efficacy by PD-L1 expression level, disease-related symptom

**Secondary end points**
- OS
- ORR, DOR, TRAE
- OS and PFS
- OS, ORR, TRAE
- PFS
- OS, ORR, TRAE
- PFS per BIRCH (≥5% PD-L1+)
- PFS per BIRCH (≥1% PD-L1+)
- OS (≥5% PD-L1+)
- ORR (≥5% PD-L1+), TRAE
| Brahm et al. | Bonghi et al. | Fehrenbacher et al. | Herbst et al. | Reck et al. | Carbone et al. | Rittmeyer et al. |
|------------|--------------|---------------------|--------------|------------|---------------|---------------|
| Overall survival | MOS: 9.2m (nivo) versus 6m (doc) HR = 0.59 (0.44–0.79) P < .001 | 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 (0.50–0.98) P = .008 | MOS: not reached | MOS: 13.7m (nivo) versus 13.8m (doc) HR = 0.60 (0.41–0.89) P = .005 |
| | | | | | | MOS: 16.8m (atez) versus 8.5m (doc) HR = 0.61 (0.49–0.79) P = .001 |
| Progression-free survival | MOS: 3.5m (nivo) versus 2.6m (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 = .77 | MOS: 3.9m (pemb2mg) versus 4.1m (doc) HR = 0.93 (0.74–1.15) P < .001 | MOS: 4m (pemb2mg) versus 4m (doc) HR = 0.90 (0.70–1.14) P = .70 | MOS: 2.8m (atez) versus 4.0m (doc) HR = 0.95 (0.82–1.10) P = .87 |
| Objective response rate | Nivo: 27 Doc: 12 OR: 2.6 (1.3–5.5) P = .009 | Nivo: 56 Doc: 36 OR: 1.7 (1.1–2.6) P = .02 | Atez: 21 Doc: 21 DOR: 14.3m (11.6–NE) (atez) versus 7.2m (5.6–12.5) (doc) | Pemb2mg: 62 Doc: 64 OR: 1.4 (1.1–1.8) (pemb2mg) versus 6.2m (5.0–7.5) (doc) | Pemb69 Doc: 69 OR: 1.7 (1.4–2.1) (pemb69) versus 6.2m (4.9–7.6) (doc) | Pemb: 58 Doc: 71 OR: 1.7 (1.4–2.1) (pemb) versus 6.2m (4.9–7.6) (doc) |
| & Duration of response | Nivo: 27 Doc: 12 DOR: 14.3m (11.6–NE) (atez) versus 7.2m (5.6–12.5) (doc) | Nivo: 56 Doc: 36 DOR: 12.1m (9.6–14.5) (nivo) versus 6.2m (4.9–7.6) (doc) | Atez: 21 Doc: 21 DOR: 14.3m (11.6–NE) (atez) versus 7.2m (5.6–12.5) (doc) | Pemb2mg: 62 Doc: 64 OR: 1.4 (1.1–1.8) (pemb2mg) versus 6.2m (5.0–7.5) (doc) | Pemb69 Doc: 69 OR: 1.7 (1.4–2.1) (pemb69) versus 6.2m (4.9–7.6) (doc) | Pemb: 58 Doc: 71 OR: 1.7 (1.4–2.1) (pemb) 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 Doc: 226 | Pemb: 113 Doc: 135 | Pemb: 58 Doc: 71 |
| Grade 3,4 or 5 | Nivo: 9 Doc: 71 | Nivo: 30 Doc: 144 | Atez: 17 Doc: 55 | Pemb2mg: 43 Doc: 55 | Pemb: 41 Doc: 80 | Pemb: 58 Doc: 71 |

Ate = 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, 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 = treatment-related adverse events.
| Subgroups | Participants | Median age | Male sex | ECOG PS | Smoking status | Histology type | PD-L1 TPS | EGFR status | KRAS status | EML4-ALK translocation | CNS metastases |
|-----------|--------------|------------|----------|---------|----------------|----------------|-----------|-------------|-------------|-----------------------|---------------|
|           |              | 62         | 111 (82%)| 0       | Current/Former | Squamous       | <1%       | Positive    | Positive    | Positive               | Yes       |
| Brahmer et al [14] | 135 | 62 | 137 | 64 | 135 | 62 | 144 | 60 | 90 | 99 | 135 | 62 |
| Borghaei et al [15] | 137 | 64 | 202 | 61 | 143 | 64 | 144 | 62 | 90 | 99 | 202 | 61 |
| Fehrenbacher et al [16] | 292 | 61 | 200 | 64 | 43 | 62 | 63 | 64 | 92 | 95 | 292 | 61 |
| Herbst et al [17] | 290 | 64 | 205 | 62 | 42 | 62 | 63 | 64 | 92 | 92 | 290 | 62 |
| Reck et al [18] | 144 | 62 | 201 | 64 | 43 | 62 | 63 | 64 | 92 | 92 | 144 | 62 |
| Carbone et al [19] | 143 | 64 | 200 | 64 | 43 | 62 | 63 | 64 | 92 | 92 | 143 | 64 |
| Rittmeyer et al [20] | 690 | 64 | 208 | 64 | 43 | 62 | 63 | 64 | 92 | 92 | 690 | 64 |
| Cumulative sum | 425 | 64 | 211 | 64 | 43 | 62 | 63 | 64 | 92 | 92 | 211 | 64 |

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**Notes:**
- 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.
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 \((P = 0.07)\). 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 checkpoints 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 \((P = 0.02)\) and ORR \((P = 0.02)\) 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

**Table 4.** OS subgroup analysis

| Study or Subgroup       | Log[Hazard Ratio] | SE     | Weight | Hazard Ratio | Year | Hazard Ratio |
|-------------------------|------------------|--------|--------|--------------|------|--------------|
|                          |                  |        |        | IV, Random, 95% CI |     | IV, Random, 95% CI |
| Brahmer et al           | -0.51470274      | 0.10772251 | 13.9%  | 0.79 [0.59, 0.99] | 2015 |             |
| Borghaei et al          | -0.52738274      | 0.14930657 | 10.5%  | 0.59 [0.44, 0.77] | 2015 |             |
| Fehrenbacher et al      | -0.51347974      | 0.10494955 | 10.5%  | 0.73 [0.54, 0.98] | 2015 |             |
| Herbst et al (10mg)     | -0.49429652      | 0.10858879 | 13.9%  | 0.61 [0.49, 0.75] | 2016 |             |
| Herbst et al (2mg)      | -0.4429031       | 0.10650346 | 14.3%  | 0.71 [0.58, 0.87] | 2016 |             |
| Reck et al              | -0.51082562      | 0.19727048 | 7.6%   | 0.60 [0.43, 0.88] | 2016 |             |
| Rittmeyer et al         | -0.31470274      | 0.08642187 | 15.9%  | 0.73 [0.62, 0.86] | 2017 |             |
| Carbone et al           | 0.06786858       | 0.11622496 | 13.6%  | 1.07 [0.86, 1.33] | 2017 |             |
| Total (95% CI)          | 100.0%           | 0.72 [0.63, 0.82] |     |             |     |             |

Heterogeneity: \(\tau^2 = 0.02; \chi^2 = 29.83; df = 7 (P = 0.0001); I^2 = 77\%

Test for overall effect: \(Z = 2.32 (P = 0.02)\)

**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.

**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.
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 suggests 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 | 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 | -0.4151544 | 0.21783684 | 3.4% | 0.66 [0.43, 1.01] |
| Fehrenbacher et al | 0.11382668 | 0.26153626 | 3.2% | 1.12 [0.72, 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 | -0.1926207 | 0.16437697 | 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)** | **8.3%** | **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 | 0.2233386 | 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 | -0.54437738 | 0.28787579 | 2.7% | 0.58 [0.33, 1.02] |
| Fehrenbacher et al | -0.51082562 | 0.3366342 | 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 | 0.3366342 | 2.2% | 0.60 [0.31, 1.16] |
| Herbst et al (2mg) | -0.77652879 | 0.12218156 | 4.5% | 0.46 [0.36, 0.58] |
| Reck et al | -0.69347178 | 0.1952925 | 4.1% | 0.50 [0.37, 0.68] |
| Rittmeier et al | -0.46203546 | 0.19213964 | 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) |

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. 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 a biomarker and predictor of efficacy of anti-PD1/PD-L1 therapies in advanced NSCLC. PD-L1 expression had been associated with poor prognosis in NSCLC endorsing the idea of its use for assessing anti-PD1/PD-L1 responses. 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 and endorses the argument that PD-L1 tumor expression might not be enough to explain responses with anti-PD1/PD-L1 therapies. 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. 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. However, in our meta-analysis only Carbone et al. 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 significant difference was found only for high mutation load (HR 0.62; 0.34, 1.00).

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.

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.

| Study or Subgroup | log(Odds Ratio) | SE | Weight | Odds Ratio | IV, Random, 95% CI |
|-------------------|----------------|----|--------|------------|-------------------|
| Berghel et al     | 0.5128263      | 0.2372837 | 13.1K | 1.67 [1.06, 2.64] | 2015 |
| Brahmer et al     | 0.6351146      | 0.1707785 | 9.7K  | 2.60 [1.26, 5.38] | 2015 |
| Reck et al        | 0.2946538      | 0.2425173 | 12.8K | 2.11 [1.31, 3.39] | 2016 |
| Herbst et al (2mg) | 0.7975072      | 0.2319196 | 13.1K | 2.22 [1.41, 3.50] | 2016 |
| Herbst et al (10mg) | 0.79299252   | 0.2315162 | 13.1K | 2.21 [1.40, 3.48] | 2016 |
| Fehrtenbacher et al | -0.01005034  | 0.1318553 | 10.6K | 0.99 [0.52, 1.90] | 2016 |
| Carbone et al     | -0.3566494     | 0.2125956 | 13.6K | 0.70 [0.46, 1.06] | 2017 |
| Rittmeier et al   | 0.01980265     | 0.1995912 | 14.0K | 1.02 [0.69, 1.51] | 2017 |

Total (95% CI) 100.0% 1.32 [1.08, 2.14] Heterogeneity: Tau² = 0.18; Chi² = 28.04, df = 7 (P = 0.0002); I² = 75%
Test for overall effect: Z = 2.39 (P = 0.02)

| Study or Subgroup | Anti PD1/PD-L1 | Chemotherapy | Total | Weight | Odds Ratio | IV, Random, 95% CI |
|-------------------|----------------|--------------|-------|--------|------------|-------------------|
| 4.1.1 Overall Treatement-related Adverse Events | 199 | 287 | 236 | 268 | 6.4% | 0.31 [0.20, 0.48] |
| Berghel et al     | 76 | 131 | 111 | 129 | 5.1% | 0.22 [0.12, 0.41] |
| Brahmer et al     | 190 | 267 | 243 | 263 | 5.8% | 0.20 [0.12, 0.34] |
| Fehrtenbacher et al | 95 | 142 | 119 | 135 | 3.0% | 0.27 [0.15, 0.51] |
| Herbst et al (10mg) | 226 | 343 | 251 | 369 | 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        | 313 | 450 | 155 | 498 | 4.9% | 0.32 [0.16, 0.58] |
| Rittmeier et al   | 390 | 609 | 496 | 578 | 7.8% | 0.29 [0.22, 0.39] |
| Subtotal (95% CI) | 2272 | 2141 | 494 | 0.51 [0.26, 0.83] |

Total events 1504 1842
Heterogeneity: Tau² = 0.02; Chi² = 9.55, df = 7 (P = 0.22); I² = 27%
Test for overall effect: Z = 12.34 (P < 0.00001)

| Study or Subgroup | Anti PD1/PD-L1 | Chemotherapy | Total | Weight | Odds Ratio | IV, Random, 95% CI |
|-------------------|----------------|--------------|-------|--------|------------|-------------------|
| 4.1.2 Grade 3, 4 or 5 Treatment-related Adverse Events | 36 | 287 | 144 | 268 | 6.4% | 0.10 [0.06, 0.16] |
| Berghel et al     | 9 | 131 | 71 | 129 | 4.1% | 0.06 [0.03, 0.33] |
| Carbone et al     | 47 | 267 | 133 | 263 | 6.9% | 0.23 [0.14, 0.31] |
| Fehrtenbacher 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) | 349 | 399 | 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] |
| Rittmeier et al   | 96 | 609 | 247 | 578 | 7.0% | 0.23 [0.18, 0.31] |
| Subtotal (95% CI) | 2272 | 2141 | 50.6% | 0.20 [0.14, 0.28] |

Total events 332 948
Heterogeneity: Tau² = 0.17; Chi² = 32.40, df = 7 (P < 0.0001); I² = 78%
Test for overall effect: Z = 9.54 (P < 0.00001)

| Study or Subgroup | Anti PD1/PD-L1 | Chemotherapy | Total | Weight | Odds Ratio | IV, Random, 95% CI |
|-------------------|----------------|--------------|-------|--------|------------|-------------------|
| 4.2 Total | 4544 | 4282 | 100.0% | 0.25 [0.20, 0.31] |

Total events 1383 2790
Heterogeneity: Tau² = 0.13; Chi² = 53.37, df = 15 (P < 0.00001); I² = 72%
Test for overall effect: Z = 13.16 (P < 0.00001)
Test for subgroup differences: Chi² = 5.40, df = 1 (P = 0.02); I² = 81.5%
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 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-\(\gamma\) has also been reported as biomarker and predictor of immune response in NSCLC. Fehrenbacher et al[16] reported positive association between IFN-\(\gamma\) and overall survival (HR 0.43 [0.24–0.77]). Furthermore, IFN-\(\gamma\) 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 3

| Subgroups association with OS and PFS. | Overall survival | Progression-free survival |
|---------------------------------------|-----------------|---------------------------|
| Overall survival                      |                 |                           |
| Age (<65 and ≥65)                     |                 |                           |
| Gender (M and F)                      |                 |                           |
| ECOG PS (1)                           |                 |                           |
| Histology (Squamous)                  |                 |                           |
| Smoking (Current/former)              |                 |                           |
| EGFR (Wild type)                      |                 |                           |
| KRAS (Mutant)                         |                 |                           |
| CNS metastases (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.

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**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.
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

| Subgroup analysis; association of baseline factors with overall survival. |
|-----------------------------|----------------|----------------|--------------|
| Subgroups                  | No. Of Studies | Hazard ratio [95% CI] | p value | I² |
| 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 [0.65, 0.93]     | 0.005   | 0%  |
| Non-squamous               | 4              | 0.78 [0.60, 1.08]     | 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 [0.64, 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                        | 3              | 0.75 [0.59, 1.04]     | 0.39    | 65% |
| No                         | 3              | 0.71 [0.63, 0.80]     | <0.00001| 0%  |

| Subgroup analysis; association of baseline factors with progression-free survival. |
|-----------------------------|----------------|----------------|--------------|
| Subgroups                  | No. Of Studies | Hazard ratio [95% CI] | p value | I² |
| Age                        | 5              | 0.84 [0.71, 0.99]     | 0.04    | 66% |
| <65                        | 5              | 0.83 [0.76, 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]     | 0.04    | 81% |
| ECOG Status                | 4              | 0.87 [0.70, 1.09]     | 0.88    | 33% |
| 0                          | 4              | 0.97 [0.64, 1.49]     | 0.02    | 82% |
| Histology                  | 3              | 0.79 [0.59, 1.05]     | 0.10    | 80% |
| Squamous                   | 3              | 0.70 [0.54, 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, 2.63]     | 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% |
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. 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. 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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