Efficacy and safety of immune checkpoint inhibitors in patients with advanced non–small cell lung cancer (NSCLC): a systematic literature review

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ABSTRACT

Background: Therapeutic strategies with immune checkpoint inhibitors (ICls) counteract the immunosuppressive effects of programmed cell death protein-1 (PD-1) and ligand-1 (PD-L1). ICI treatment has emerged in first- and second-line therapy of non–small cell lung cancer (NSCLC). As immunotherapeutic treatment with ICls is a dynamic field where new drugs and combinations are constantly evaluated, we conducted an up-to-date systematic review on comparative efficacy and safety in patients with advanced NSCLC.

Methods: We searched PubMed up to February 2020 and Embase, CENTRAL, and clinical trial registries up to August 2018. Additionally, we checked reference lists. We dually screened titles, abstracts and, subsequently, full-texts for eligibility. Two reviewers assessed the risk of bias and graded the certainty of evidence following GRADE (Grading of Recommendations Assessment, Development and Evaluation). For second-line therapy, we performed random-effects meta-analyses. Due to considerable clinical heterogeneity, we reported first-line results narratively.

Results: Of 1497 references, we identified 22 relevant publications of 16 studies. For first-line therapy, a combination of an ICI with chemotherapy improved progression-free survival and overall survival compared to chemotherapy but increased the risk of serious adverse events. Single-agent pembrolizumab increased overall and progression-free survival in patients with PD-L1 expression of ≥50% and resulted in less TRAE than chemotherapy. Compared to placebo, maintenance therapy with durvalumab increased overall and progression-free survival at the downside of higher risk of TRAE. For second-line therapy, a random-effects meta-analysis yielded a statistically significantly improved overall survival (OS) and progression-free survival (PFS) for ICls compared to docetaxel (HR 0.69; 95% CI: 0.63–0.75 for OS; HR 0.85; 95% CI: 0.77–0.93 for PFS; 6 studies, 3478 patients; median OS benefit in months: 2.4 to 4.2). In meta-analysis, risk of any treatment-related adverse events of any grade was lower for ICI than docetaxel as second-line therapy (RR 0.76, 95% CI: 0.73–0.79; 6 studies, 3763 patients).

Conclusion: In first-line therapy of patients with advanced NSCLC, ICI is effective when combined with chemotherapy not depending on PD-L1 expression, or as monotherapy in high PD-L1 expressing tumors. For second-line therapy, single-agent ICI improves efficacy and safety compared to docetaxel.

Introduction

Lung cancer is the most frequent type of cancer worldwide, with almost 2.1 million estimated new cases in 2018, according to the World Health Organization (WHO). In 2018, more than 1.7 million people died of lung cancer, comprising 18.4% of all cancer-related deaths. The two main histological types of lung cancer are small cell lung cancer (SCLC), which accounts for approximately 15% of all lung cancers, and non–small cell lung cancer (NSCLC), the remaining 85%. NSCLC can further be subdivided into squamous cell carcinoma, adenocarcinoma, and large cell carcinoma.

Since most patients with lung cancer are not diagnosed until an advanced stage, the prognosis is usually poor. The 5-year survival rate depends on the stage of the tumor, the time of diagnosis, and the histological subtype. Conventional chemotherapy protocols for NSCLC comprise 4 to 6 cycles of platinum-based doublet chemotherapy in first-line treatment and 6 cycles of docetaxel as a second-line regimen. Both regimens employ unspecific cytotoxic agents, which display numerous side effects.

Thus, for decades, cancer research has aimed to find driver mutations of malignant cells, which could be targeted for more selective and effective therapy. Currently, upon NSCLC diagnosis, mutational testing for epidermal growth factor receptor-1 (EGFR), anaplastic lymphoma kinase (ALK), proto-oncogene tyrosine-protein kinase (ROS-1), and serine/threonine-protein kinase B-Raf (BRAF) should be performed in order to start first-line therapy with a targeted agent instead of chemotherapy.

Another breakthrough in recent years has been immunotherapeutic treatment with immune checkpoint inhibitors, which were developed to counteract the immunosuppressive effects of the programmed cell death protein-1 (PD-1)/programmed cell
death-ligand 1 (PD-L1) pathway and to activate the immune system for defense against malignant cells.11 Immune checkpoint inhibitors are monoclonal antibodies, targeting either the programmed cell death receptor PD-1 or its ligand PD-L1. The substances that are already approved for clinical use in NSCLC are: atezolizumab,12 durvalumab,13 nivolumab,14 and pembrolizumab15,16 (see Supplementary Table S1). Recent systematic reviews demonstrated the beneficial effects of immune checkpoint inhibitors on overall survival and progression-free survival for first-16,17 and second-line treatments18,19 compared to chemotherapy in NSCLC patients. International clinical practice guidelines now recommend the use of immune checkpoint inhibitors for first- and second-line therapy of patients with stage IV NSCLC without driver alterations.5,20,21

Immunotherapeutic treatments with checkpoint inhibition, however, is a dynamic field, with new drugs constantly being evaluated in clinical trials. Recent studies have focused on novel compounds such as the abovementioned antibody durvalumab,22 different combination treatments23,24 and assessment of long-term data.23,25–27 Therefore, including these novel aspects we conducted an up-to-date systematic review regarding the comparative efficacy and safety of approved immune checkpoint inhibitors compared with other treatment interventions in patients with advanced NSCLC (stage III or IV).

Methods

We registered our systematic review in the international prospective register of systematic reviews (PROSPERO) under CRD42018104751.28 For this publication, we adhered to the guidance of the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA).29

**Literature searches and information sources**

An experienced information specialist (IK) designed and conducted the database searches. The most recent update search was conducted in February 2020 in PubMed. We initially searched PubMed, Embase.com (Elsevier), CENTRAL (Cochrane Library/Wiley) as well as in clinical trial registries (ClinicalTrials.gov and the World Health Organization’s (WHO) International Clinical Trials Registry Platform) in August 2018. The update search was limited to PubMed, because all of the initially included studies had been retrieved by this search. In addition, we checked the reference lists of relevant review articles and all the included studies to detect relevant articles potentially missed by searches in electronic databases. For bibliographic database searches we used both free-text and controlled vocabulary (e.g., Medical Subject Headings). We restricted our search to randomized controlled trials (RCTs) as well as to the English and German languages. We provide the detailed search strategy in the Supplemental material.

**Eligibility criteria and study selection**

To identify studies that meet our eligibility criteria presented in Table 1, two investigators independently screened titles and abstracts. The included abstracts underwent a subsequent dual full-text screening. For both the abstract and full-text screening, we used pilot-tested review forms. We screened the literature with the web-based systematic review software Covidence.30 Investigators resolved discrepancies of inclusion or exclusion decisions by consensus or by the involvement of a third, senior reviewer.

**Data collection**

For the studies that met our inclusion criteria, we extracted relevant information into pilot-tested data abstraction tables. Items included study and patient characteristics and the description of the intervention and control as well as results for the outcomes of interest for each individual study. A second person checked the extracted data for accuracy and completeness.

**Table 1. Eligibility criteria.**

| Population: Adults with histologically confirmed unresectable NSCLC (stages IIIA, IIIB, and IV) | Inclusion | Exclusion Adults with NSCLC stage I–II or SCLC Other treatments |
| --- | --- | --- |
| Interventions: PD-1 inhibitors (nivolumab, pembrolizumab), PD-L1 inhibitors (atezolizumab, durvalumab) as: | Monotherapy | Other treatment, no treatment |
| combination of two or more | | |
| combination therapy with targeted therapy | | |
| combination therapy with chemotherapy | | |
| Comparators: Chemotherapy | | |
| Targeted therapy | | |
| small molecule inhibitors for EGFR, ROS1, ALK, and MET | | |
| Placebo | | |
| Best Supportive Care | | |
| Outcomes: Progression-free survival | | |
| Overall survival | | |
| Overall adverse events (any cause, treatment related) | | |
| Serious adverse events (any cause, treatment related) | | |
| Study design: Randomized controlled trial | | |
| Publication language: English | | Other languages |
| Search period: 2000–beginning of search | Before 2000 | |

**Abbreviations:** ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; MET = mesenchymal–epithelial transition factor; NSCLC = non–small cell lung cancer; PD-1 = programmed cell death protein-1; PD-L1 = programmed cell death ligand-1; ROS1 = proto-oncogene tyrosine-protein kinase; SCLC = small cell lung cancer
Assessment of risk of bias and certainty of evidence

Two persons independently assessed the included RCTs’ risk of bias with the Cochrane Risk of Bias tool. The risk of bias for each domain was rated as low, high, or unclear. All ratings on risk of bias decisions were documented in tables, and disagreements were solved by consensus. We applied the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to assess the certainty of evidence for each outcome considered relevant for decision-making.

Data synthesis and analysis

If the data were sufficient, we conducted meta-analyses of efficacy and safety outcomes of interest. Otherwise, we described the results narratively. For efficacy, we performed meta-analyses by pooling hazard ratios (HRs) with 95% confidence intervals (CIs) using the random-effects inverse-variance model with the DerSimonian–Laird estimate of tau². We preferred HRs, since they summarize the treatment effect for the entire study duration rather than the median survival solely reflecting one time point on the Kaplan–Meier curve. To achieve comparability, we converted CIs to 95%, if authors reported 97% or 99% CIs. For safety, we conducted random-effects meta-analyses by pooling risk ratios with 95% CIs, calculated from the number of events and the number of patients at risk. We evaluated the studies’ statistical heterogeneity by visually inspecting the forest plots and calculating the I² statistics. For the meta-analyses, we used Stata 14.2 (Stata Corp, College Station, TX, USA).

Results

Study selection

We screened 1497 titles and abstracts of 210 were retrieved as full-texts. Ultimately, 16 RCTs (published in 22 articles) met our inclusion criteria. The PRISMA flowchart (see Figure 1) illustrates the study selection process in detail.

Risk of bias and certainty of evidence

We rated all the domains for each study as a low risk of bias. However, for open-label trials, we rated blinding as a high risk of bias except for overall survival and progression-free survival if assessed by a blinded central review. We present detailed risk of bias assessments and certainty of evidence ratings for each outcome in Supplementary Tables S2 and S3.

Figure 1. PRISMA flow diagram modified from Moher et al.
Study characteristics

Seven open-label24,39,44,45,47,49,50 and three double-blind RCTs22,42,46 evaluated the PD-1/PD-L1 immune checkpoint-inhibitors in patients treated with first-line therapy. The median follow-up of the patients in the included studies ranged from 7.8 to 33.3 months. Six studies compared PD-1/PD-L1 immune checkpoint inhibitors with docetaxel as a second-line therapy in patients with advanced NSCLC and previous treatment.37,38,40,43,48,51 The median follow-up of patients in the included studies ranged from 8.8 to 21 months. All studies were conducted as international multicenter RCTs and were funded or supported by pharmaceutical companies.22,24,37–40,42,51 Table 2 summarizes the characteristics of the included studies for first- and second-line immune checkpoint inhibitor therapy.

Study participants

The number of randomized patients in the first-line therapy studies ranged from 123 to 1739. The study patients’ median age ranged from 62.5 to 66.0 years. The majority were men, except in one study.34 In the studies assessing second-line therapies, the total number of randomized patients ranged from 272 to 1225. The median age ranged from 60 to 64 years. In all the studies, the majority of participants were men. Supplementary Table S4 provides a detailed summary of the participants’ baseline characteristics and the outcomes that were assessed in each included study.

Overall survival and progression-free survival

First-line therapy

We included 10 RCTs that compared immune checkpoint inhibitors alone or in combination with other treatments to various control regimens.22,24,39,42,44–47,49,50 Three trials compared nivolumab,39 or pembrolizumab45,47 to chemotherapy; 6 trials assessed combination treatments of atezolizumab,49,50 nivolumab,33 or pembrolizumab42,44,46 plus chemotherapy relative to chemotherapy alone; one RCT compared a combination of nivolumab plus ipilimumab,23 to chemotherapy; and one trial assessed the efficacy of durvalumab22 compared to placebo in patients with 1 to 42 days after chemoradiotherapy (see Table 2).

Figure 2(a) presents the hazard ratios for overall survival from each trial. Seven studies found a statistically significantly improved overall survival for treatment with immune checkpoint inhibition.23,42,45–47,49,50 Figure 2(b) shows the treatment effects regarding progression-free survival. Except for two studies comparing nivolumab39 or pembrolizumab45 with platinum-based chemotherapy, all the trials showed a statistically significant improvement of progression-free survival in patients treated with immune checkpoint inhibitors.22,23,42,44,46,47,49,50 The absolute time difference in the median overall and progression-free survival is depicted in Supplementary Table S5. In the following sections, we summarize comparisons of immune checkpoint inhibitors with different control regimens in more detail.

Nivolumab or pembrolizumab versus chemotherapy. The multicenter, open-label, phase 3 CheckMate 026 trial39 enrolled 541 patients with recurrent or stage IV NSCLC without prior treatment and a PD-L1 tumor-expression level of ≥1%. Investigators randomized patients to either nivolumab or platinum-based chemotherapy. In patients with a PD-L1 expression level of ≥25% (primary efficacy analysis population, N = 423), overall survival was similar between single-agent nivolumab (n = 211) treatment and platinum-doublet chemotherapy (n = 212) (median 14.4 versus 13.2 months; HR 1.02; 95% CI: 0.80–1.30; see Figure 2(a)). This study also reported no statistically significant difference for progression-free survival in patients with a PD-L1 expression level ≥25% (median 4.2 versus 5.9 months; HR 1.15; 95% CI: 0.91–1.45; see Figure 2(b)).39 Analyses of all randomized patients revealed similar results regarding progression-free survival and overall survival (see Supplementary Table S4).

Two multicenter, open-label, phase 3 RCTs compared pembrolizumab with chemotherapy in patients with previously untreated locally advanced or metastatic NSCLC.45,47 In the KEYNOTE-024 trial,27,47 305 patients with a PD-L1 expression level of ≥50% received either pembrolizumab or chemotherapy. At a median follow-up of 11.2 months, overall survival (median survival not reached in both groups; HR 0.60; 95% CI: 0.41–0.89; see Figure 2(a)) and progression-free survival (median 10.3 versus 6.0 months; HR 0.50; 95% CI: 0.37–0.68; see Figure 2(b)), were statistically significantly longer in the pembrolizumab group than in the chemotherapy group.47 In a later publication with a longer follow-up (median 25.2 months), median overall survival was 30.0 versus 14.2 months (HR 0.63; 95% CI: 0.47–0.86; see Supplementary Figure S1A).27

The second trial, KEYNOTE-42,45 randomized 1274 patients with PD-L1 expression of ≥1% to either pembrolizumab or platinum-based chemotherapy. The median follow-up of this study was 12.8 months. Overall survival was statistically significantly longer with pembrolizumab than with chemotherapy in patients with PD-L1 expression of ≥50% (median 20.0 versus 12.2 months; HR 0.69; 95% CI: 0.56–0.85), ≥20% (median 17.7 versus 13.0 months; HR 0.77; 95% CI: 0.64–0.92) and ≥1% (median 16.7 versus 12.1 months; 0.81; 95% CI: 0.71–0.93; see Figure 2(a)). Progression-free survival, however, was only statistically significantly longer with pembrolizumab than with chemotherapy in patients with a PD-L1 expression of ≥50% (median 7.1 versus 6.4 months; HR 0.81; 95% CI: 0.67–0.99). In study participants with PD-L1 of ≥20% (median 6.2 versus 6.6 months; HR 0.94; 95% CI: 0.80–1.11) and ≥1% (median 5.4 versus 6.5 months; HR 1.07; 95% CI: 0.94–1.21; see Figure 2(b)) this effect could not be observed.45

Atezolizumab, pembrolizumab or nivolumab plus chemotherapy versus chemotherapy. Six multicenter RCTs evaluated the comparative efficacy and safety of a combination of atezolizumab, pembrolizumab or nivolumab plus chemotherapy and platinum-based chemotherapy alone.33,42,44,46,49,50

In the 3-armed, open-label, phase 3 IMpower150 trial,39 1202 patients with metastatic nonsquamous NSCLC were randomized to receive either atezolizumab plus bevacizumab plus carboplatin plus paclitaxel (ABCP), or atezolizumab plus carboplatin plus paclitaxel (ACP), or bevacizumab plus carboplatin plus paclitaxel (BCP). The efficacy was only reported for the ABCP and BCP groups. The median overall survival was...
| Author, year, trial name, NCT | Study design, phase | Funding/Recruiting Period | Countries | Follow-up | N total randomized | Key inclusion criteria | Primary outcome(s) | Intervention N randomized | Comparison N randomized |
|-------------------------------|---------------------|---------------------------|-----------|-----------|-------------------|------------------------|---------------------|------------------------|------------------------|
| **ATEZOLIZUMAB**              |                     |                           |           |           |                   |                        |                     |                        |                        |
| Fehrenbacher et al. 2016      | Randomized, controlled, open-label, phase 2 | August 2013 – March 2014 | 61 academic centers, 13 countries, Europe and North America | Median: Atezolizumab: 14.8 months Docetaxel: 15.7 months | 287 | Atezolizumab 1200 mg every 3 weeks N = 144 | 1200 mg Docetaxel 75 mg/m² BSA every 3 weeks N = 143 |
| POPLAR NCT01903993            | F. Hoffmann-La Roche/Genentech |                          |           |           |                   |                        |                     |                        |                        |
| **RITTMEYER** et al. 2017     | Randomized, controlled, open-label, phase 2 | March 2014 – April 2015 | 194 academic or community oncology centers, 31 countries, Europe, North and South America, New Zealand, and Asia | Median: 21 months | 1225 (secondary efficacy population) 850 (primary efficacy population) | Atezolizumab 1200 mg every 3 weeks N = 425 (primary efficacy population) N = 613 (secondary efficacy population) | Docetaxel 75 mg/m² BSA every 3 weeks N = 425 (primary efficacy population) N = 612 (secondary efficacy population) |
| Fehrenbacher et al. 2018      | F. Hoffmann-La Roche/Genentech |                          |           |           |                   |                        |                     |                        |                        |
| OAK NCT02008227               |                     |                           |           |           |                   |                        |                     |                        |                        |
| **WEST** et al. 2019          | Randomized, controlled, open-label, phase 3 | April 2015 – February 2017 | 131 centers, 8 countries, North America, Europe and Israel | Median: (wild-type population) 18.5 months Chemotherapy: 19.2 months | 724 | Atezolizumab plus chemotherapy: 679 | Atezolizumab 1200 mg every 3 weeks + carboplatin at an AUC of 6 mg/ml per minute every 3 weeks + nab-paclitaxel 100 mg/m² BSA every week for four or six 21-day cycles N = 483 N = 451 (wild-type population) | Carboplatin at an AUC of 6 mg/ml per minute every 3 weeks + nab-paclitaxel 100 mg/m² BSA every week for four or six 21-day cycles N = 240 N = 228 (wild-type population) |
| IMPower 130 NCT02367781       | F. Hoffmann-La Roche/Genentech |                          |           |           |                   |                        |                     |                        |                        |

(Continued)
| Author, year, trial name, NCT Therapy line | Study design, phase | Recruiting Period | Countries | Follow-up | N total randomized | Key inclusion criteria | Intervention N randomized | Comparison N randomized |
|-------------------------------------------|---------------------|-------------------|-----------|-----------|-------------------|------------------------|------------------------|------------------------|
| Socinski et al. 2018^19 IMPower 150 NCT02366143 First-line therapy | Randomized, controlled, open-label, phase 3 | March 2015 – December 2016 | 240 sites, 26 countries, Australia, Asia, Europe, and North and South America | Median: (wild-type population) | 1202 Wild-type population: 1040 | ABCP: Atezolizumab 1200 mg + bevacizumab 15 mg/kg BW + carboplatin at an AUC of 6 mg/m² per minute for four for six 21-day cycles + paclitaxel 200 mg/m² of BSA (175 mg/m² for Asian patients) for four or six 21-day cycles N = 400 N = 356 (wild-type population) ACP: Atezolizumab 1200 mg + carboplatin at an AUC of 6 mg/m² per minute for four or six 21-day cycles + paclitaxel 200 mg/m² of BSA (175 mg/m² for Asian patients) N = 400 N = 336 (wild-type population) |
| Antonia et al. 2017^22 NCT02125461 First-line therapy (consolidation after radiochemotherapy) | Randomized, double-blind, placebo-controlled, phase 3 | May 2014 – April 2016 | Australia, Asia, Europe, North and South America, and South Africa | Median: 14.5 months | 713 | Durvalumab 10 mg/kg BW every 2 weeks for up to 12 months N = 476 (wild-type population) | Placebo every 2 weeks for up to 12 months N = 237 |
| Wu et al. 2019^35 CheckMate 078 NCT02613507 Second-line therapy | Randomized, controlled, open-label, phase 3 | December 2015 – November 2016 | 32 hospitals and cancer centers, China, Russia, Singapore | Median: Nivolumab: 10.4 months Docetaxel: 8.8 months | 504 | Nivolumab 3 mg/kg BW every 2 weeks N = 338 Docetaxel 75 mg/m² of BSA every 3 weeks N = 166 |
| Borghaei et al. 2015^37 CheckMate 057 NCT01673867 Second-line therapy | Randomized, controlled, open-label, phase 3 | November 2012 – December 2013 | Europe and North and South America | Minimum: 13.2 months | 582 | Nivolumab 3 mg/kg BW every 2 weeks N = 292 Docetaxel 75 mg/m² of BSA every 3 weeks N = 290 |

(Continued)
| Author, year, Therapy line | Study design, Funding/ Support | Recruiting Period | Countries | Follow-up | N total randomized | Key inclusion criteria | Intervention N randomised | Comparison N randomised |
|---------------------------|--------------------------------|------------------|-----------|-----------|-------------------|----------------------|------------------------|------------------------|
| Brahmer et al. 2015<sup>18</sup> | Randomized, controlled, open-label, phase 3 Bristol-Myers Squibb | October 2012 – December 2013 | Australia, Europe, and North and South America | Minimum: 11 months | 272 | Patients with stage IIIb or IV squamous cell NSCLC who had disease recurrence after one prior platinum containing regimen; ECOG status of 0 or 1 | Nivolumab 3 mg/kg BW every 2 weeks N = 135 | Docetaxel 75 mg/m² of BSA every 3 weeks N = 137 |
| CheckMate 017 NCT01642004 Second-line therapy | | | | | | | | |
| Carbone et al. 2017<sup>19</sup> | Randomized, controlled, open-label, phase 3 Bristol-Myers Squibb | March 2014 – April 2015 | Australia, Asia, Europe, and North and South America | Median: 13.5 months | 541 | Histologically confirmed squamous cell or non-squamous stage IV or recurrent NSCLC; ECOG status of 0 or 1; No previous systemic anti-cancer therapy as primary therapy for advanced or metastatic disease; PD-L1 expression level ≥1 | Nivolumab 3 mg/kg BW every 2 weeks N = 271 | Platinum-based doublet CT every 3 weeks for 4 to 6 cycles: carboplatin + pemetrexed, cisplatin + pemetrexed, carboplatin + gemcitabine, cisplatin + gemcitabine, or carboplatin + paclitaxel N = 270 |
| CheckMate 026 NCT02041533 First-line therapy | | | | | | | | |
| Hellmann et al. 2018<sup>24</sup> | Randomized, controlled, open-label, phase 3 Bristol-Myers Squibb | August 2015 – November 2016 | Europe, North and South America, Australia, Asia, and Africa | Minimum: 29.3 months | 1739 | Histologically confirmed squamous or non-squamous stage IV or recurrent NSCLC; No previous systemic anticancer therapy as primary therapy for advanced or metastatic disease; ECOG status of 0 or 1 | Nivolumab 3 mg/kg BW every 2 weeks + ipilimumab 1 mg/kg every 6 weeks N = 396 or Nivolumab 240 mg every 2 weeks N = 396 | PD-L1 expression of ≥1% Platinum-doublet CT based on histologic tumor type every 3 weeks for up to 4 cycles N = 397 |
| Hellmann et al. 2019<sup>23</sup> | | | | | | | | |
| CheckMate 227 NCT02477826 First-line therapy | | | | | | | | |
| Pembrolizumab | Randomized, controlled, open-label, phase 2/3 Merck & Co. | August 2013 – February 2015 | 202 academic centers, 24 countries, Africa, Australia, Asia, Europe, and North and South America | Median: 13.1 months | 1084 | Advanced NSCLC; Disease progression after two or more cycles of platinum-doublet chemotherapy; An appropriate tyrosine kinase inhibitor for those with an EGFR-sensitizing mutation or ALK gene rearrangement; ECOG status of 0 or 1; PD-L1 TPS >1 | Pembrolizumab 2 mg/kg BW every 3 weeks N = 345 | Docetaxel 75 mg per m² of BSA every 3 weeks N = 343 |
| Herbst et al. 2016<sup>16</sup> KEYNOTE-010 NCT01905657 Second-line therapy | | | | | | | | |

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| Author, year, trial name, NCT Therapy line | Study design, phase | Funding/ Support | Recruiting Period | Countries | Follow-up | N total randomized | Key inclusion criteria | Intervention | N randomized | Comparison |
|------------------------------------------|---------------------|------------------|------------------|-----------|-----------|------------------|-----------------------|-------------|-------------|-----------|
| Mok et al. 2019\(^{63}\) KEYNOTE-042 NCT02220894 First-line therapy | Randomized, controlled, open-label, phase 3 | Merck Sharp & Dohme | December 2014 – March 2017 | 213 centers, 32 countries, North and South America, Europe, Asia and South Africa | Median: 12.8 months | 1274 | Key inclusion criteria:  
  - Previously untreated locally advanced or metastatic NSCLC  
  - ECOG status of 0 or 1  
  - No EGFR mutation or ALK translocation  
  - PD-L1 TPS ≥1%  
  - Life expectancy 3 months or longer  
  Primary endpoints:  
  - Overall survival in patients with PD-L1 TPS ≥50%, ≥20% or ≥1% | Pembrolizumab 200 mg every 3 weeks for up to 35 cycles  
  N = 637 | Platinum-based CHT of the investigator's choice for 4–6 cycles: carboplatin at an AUC of 5–6 mg/mL/min, + paclitaxel 200 mg/m² of BSA or pemetrexed 500 mg/m²  
  N = 637 |
| Reck et al. 2016\(^{67}\) Reck et al. 2019\(^{37}\) KEYNOTE-024 NCT2142738 First-line therapy | Randomized, controlled, open-label, phase 3 | Merck & Co. | September 2014 – October 2015 | 142 sites, 16 countries, Australia, Europe, and North America | Median: 11.2 months | 305 | Key inclusion criteria:  
  - Stage IV NSCLC  
  - No sensitizing EGFR mutations or ALK translocations  
  - No previous systemic therapy for metastatic disease  
  - ECOG status of 0 or 1  
  - Life expectancy of at least 3 months  
  - PD-L1 tumor proportion score of 50% or more | Pembrolizumab 200 mg every 3 weeks for 35 cycles  
  N = 154 | Platinum-based CHT for 4 to 6 cycles: carboplatin + pemetrexed, cisplatin + pemetrexed, carboplatin + gemcitabine, cisplatin + gemcitabine, or carboplatin + paclitaxel  
  N = 151 |
| Paz-Ares et al. 2018\(^{46}\) KEYNOTE-047 NCT02775435 First-line therapy | Randomized, controlled, double-blind, phase 3 | Merck Sharp & Dohme | August 2016 – December 2017 | 125 sites, 17 countries, Australia, Europe, and North and Central America, Asia | Median: 7.8 months | 559 | Key inclusion criteria:  
  - Stage IV squamous NSCLC  
  - ECOG status of 0 or 1  
  - No previous chemotherapy for metastatic disease | Pembrolizumab 200 mg every 3 weeks for up to 35 cycles  
  + carboplatin at an AUC of 6 mg/mL  
  + paclitaxel 200 mg/m² of BSA or nab-paclitaxel 100 mg/m² of BSA  
  for the first 4 cycles  
  N = 278 | Placebo  
  for up to 35 cycles  
  + carboplatin at an AUC of 6 mg/mL  
  + paclitaxel 200 mg/m² of BSA or nab-paclitaxel 100 mg/m² of BSA  
  for the first 4 cycles  
  N = 281 |
| Langer et al. 2016\(^{44}\) Borghaei et al. 2019\(^{25}\) KEYNOTE-021 NCT02039674 First-line therapy | Randomized, controlled, open-label, phase 2 | Merck & Co. | November 2014 – January 2016 | 26 medical centers, 2 countries, Taiwan and USA | Median: 10.6 months | 123 | Key inclusion criteria:  
  - Nonsquamous stage IIB or IV NSCLC  
  - No previous systemic treatment for stage IIB or IV NSCLC  
  - Absence of targetable EGFR mutations or ALK translocations  
  - ECOG status of 0 or 1 | Pembrolizumab 200 mg + Platinum-based doublet CHT: carboplatin + pemetrexed every 3 weeks for 4 cycles  
  N = 60 | Platinum-based doublet CHT: carboplatin + pemetrexed for 4 cycles  
  N = 63 |

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statistically significantly longer in the ABCP group than in the BCP group (19.2 versus 14.7 months; HR 0.78; 95% CI: 0.64–0.96; Figure 2(a)). Likewise, the progression-free survival (8.3 versus 6.8 months; HR 0.62; 95% CI: 0.52–0.74; see Figure 2(b)) was also statistically significantly longer for the ABCP group.49

The open-label, phase 3 IMpower130 trial20 randomized 724 participants with stage IV nonsquamous NSCLC to atezolizumab plus chemotherapy (carboplatin plus nab-paclitaxel) or chemotherapy alone. In patients with no EGFR and ALK mutations (N = 679) combination of atezolizumab and chemotherapy resulted in statistical significant improvement of overall survival (median 18.6 versus 13.9 months; HR 0.79; 95% CI: 0.64–0.98) progression-free survival (median 7.0 versus 5.5 months; HR 0.64; 95% CI: 0.54–0.77) as compared with chemotherapy alone.50

In the multicenter, open-label, phase 2 KEYNOTE-021 trial,25,44 123 patients were randomized to either pembrolizumab plus platinum-based chemotherapy or to platinum-based chemotherapy alone. After a median follow-up of 10.6 months, primary analysis of overall survival yielded no statistically significant difference between the two groups (median survival not reached in both groups; HR 0.90; 95% CI: 0.42–1.91; see Figure 2(a)).44 The progression-free survival was statistically significantly prolonged for patients treated with pembrolizumab plus chemotherapy (median 13.0 versus 8.9 months; HR 0.53; 95% CI: 0.31–0.91; see Figure 2(b)).44 Improvement in progression-free survival maintained in an updated analysis with a median follow-up of 23.9 months (median 24.0 versus 9.3 months; HR 0.53; 95% CI: 0.33–0.86; see Supplementary Figure S1B).25 Regarding overall survival, this analysis showed a benefit for the pembrolizumab plus chemotherapy group compared with chemotherapy alone (HR 0.56; 95% CI: 0.32–0.95; see Supplementary Figure S1A).23

The open-label, phase 3 CheckMate 227 randomized patients with PD-L1 expression level of <1% (N = 550) to either nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy alone. Overall survival was longer with nivolumab plus chemotherapy than with chemotherapy alone, but the difference did not reach statistical significance (median 15.2 versus 12.2 months; HR 0.78; 97.72% CI: 0.60–1.02, see Figure 2(a)). Compared to chemotherapy alone, progression-free survival was statistically significant longer if chemotherapy was combined with nivolumab (median 5.6 versus 4.7 months; HR 0.73; 97.72% CI: 0.56–0.95; see Figure 2(b)).23

The phase 3, double-blinded RCT KEYNOTE-407 enrolled 559 participants with untreated metastatic squamous NSCLC. This study randomized participants to pembrolizumab or saline placebo both in combination with chemotherapy (carboplatin and either paclitaxel or nanoparticle albumin-bound [nab]-paclitaxel). The median follow-up was 7.8 months. Overall survival (median 15.9 versus 11.3 months; HR 0.64; 95% CI: 0.49–0.85; see Figure 2(a) and progression-free survival (median 6.4 versus 4.8 months; HR 0.56; 95% CI: 0.45–0.70; see Figure 2(b)) were statistically significantly longer in patients treated with pembrolizumab in addition to chemotherapy than placebo and chemotherapy.46

Similar results could be observed in the double-blind, phase 3 KEYNOTE-189 trial,42 where patients with metastatic nonsquamous NSCLC without sensitizing EGFR or ALK mutations were randomized to either pembrolizumab plus platinum-based...
chemotherapy or to placebo plus platinum-based chemotherapy. Overall survival (median survival not reached versus 11.3 months; HR 0.49; 95% CI: 0.38–0.64; see Figure 2(a)) and median progression-free survival were statistically significantly longer in the pembrolizumab group (8.8 versus 4.9 months; HR 0.52; 95% CI: 0.43–0.64; see Figure 2(b)).

**Nivolumab plus ipilimumab versus chemotherapy.** The open-label, phase 3 CheckMate 227 trial enrolled patients with stage IV or recurrent NSCLC without previous chemotherapy. Patients with PD-L1 expression level of ≥1% were randomized to nivolumab plus ipilimumab, nivolumab monotherapy, or chemotherapy. Patients with PD-L1 expression level <1% were randomized to nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy alone. As compared with chemotherapy, in patients with PD-L1 expression level of ≥1% (N = 793) overall survival (median 17.1 versus 14.9 months; HR 0.79; 97.72% CI: 0.65–0.96; see Figure 2(a)) and progression-free survival (HR 0.82; 95% CI: 0.69–0.97; see Figure 2(b)) was significantly improved with nivolumab plus ipilimumab. Results for patients with PD-L1 expression level of <1% and all randomized patients are shown in Supplementary Table S4. Progression-free survival was longer with nivolumab plus ipilimumab as compared with chemotherapy in all randomized patients with a high tumor mutational burden (TMB, defined as ≥10 mutations per megabase; N = 299, median 7.2 versus 5.5 months; HR 0.58; 97.5% CI: 0.41–0.81), irrespective of PD-L1 expression.24

**Durvalumab versus placebo.** The multicenter, double-blind, phase 3 PACIFIC study randomized 713 patients with stage III locally advanced, unresectable NSCLC without disease progression after previous chemoradiotherapy to either durvalumab or placebo as consolidation therapy. For progression-free survival after a median follow-up of 14.5 months, a statistically significant improvement could be seen in patients treated with durvalumab (median 16.8 versus 5.6 months; HR 0.52; 95% CI: 0.42–0.65; see Figure 2(b)).22 Updated analysis after a median follow-up of 25.2 months, showed similar findings for progression-free survival (median 17.2 versus 5.6 months; HR 0.51; 95% CI: 0.41–0.63; see Supplementary Figure S1B).36 Overall survival was statistically significantly prolonged for durvalumab-treated patients as well (HR 0.68; 99.73% CI: 0.47–0.997).36 In addition, a post-hoc, exploratory analysis found consistent benefit after median follow-up of 33.3 months (HR 0.69; 95% CI: 0.55–0.86; see Supplementary Figure S1A).26

**Second-line therapy**

For second-line therapy, a random-effects meta-analysis of 6 RCTs (one with two dosing arms) including 3478 patients yielded a statistically significantly improved

![Figure 2](https://example.com/f2.png)
overall survival for participants treated with immune checkpoint inhibitors as compared to patients treated with single-agent chemotherapy (HR 0.69; 95% CI: 0.63–0.75; I² = 0.0%, see Figure 3(a)). In a meta-analysis based on the results from the same 6 trials and 3478 patients, progression-free survival was statistically significantly improved for patients treated with atezolizumab, nivolumab, or pembrolizumab as compared to patients treated with a taxane-based chemotherapy (HR 0.85; 95% CI: 0.77–0.93; I² = 41.3%, see Figure 3(b)).

Again, the differences in median overall and progression-free survival in months are depicted in Supplemental Table S6. Concerning median progression-free survival, treatment with a single-agent immune checkpoint blockade compared to docetaxel resulted in net differences of −1.9 to +0.7 months. With regard to overall survival, the differences in median overall survival ranged from 2.4 to 4.2 months longer than in patients treated with chemotherapy.

**Safety**

**First-line therapy**

The proportion of patients with adverse events in each study is depicted in Figure 4(a) and Supplementary Table S4. Eight RCTs provided data on treatment-related adverse events (TRAE). 22,23,39,44,45,47,49,50 In four studies that compared either nivolumab or pembrolizumab 39,45,47 or nivolumab plus ipilimumab 22 to chemotherapy, the proportion of patients with TRAE was higher in the chemotherapy control group than in the immune checkpoint inhibitor treatment groups (see Figure 4(a)). One study comparing durvalumab with placebo showed a statistically significantly higher incidence of TRAE in patients treated with immune checkpoint inhibitors (see Figure 4(a)). However, immune checkpoint inhibition was used as consolidation therapy 1 to 42 days after chemoradiotherapy and compared with placebo. 22 In four studies that compared immune checkpoint inhibitors in combination with chemotherapy to chemotherapy alone, the proportion of patients with TRAE were either similar between the groups 44,49,50 or lower in patients receiving only chemotherapy. 23

Regarding serious adverse events, the IMpower150 study published by Socinski et al. 49 found a statistically significant higher incidence in patients treated with atezolizumab plus bevacizumab, carboplatin and paclitaxel (ABCP) compared with patients receiving bevacizumab, carboplatin and paclitaxel (BCP); 42.0% versus 34.0%, risk ratio [RR] 1.23; 95% CI: 1.03–1.48, (see Figure 4(a)). Likewise, the IMpower130 study 50 found significant more serious adverse events in patients receiving atezolizumab in combination with chemotherapy (carboplatin and nab-paclitaxel) than those receiving chemotherapy alone (50.7% versus 37.9%, RR 1.34; 95% CI: 1.11–1.61, see Figure 4(a)) In the PACIFIC trial by Antonia et al. 22 serious adverse

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**Figure 3.** Forest plots for (a) overall survival and (b) progression-free survival in studies assessing immune checkpoint inhibitors as second-line therapy. Wu 2019 CheckMate 078: We converted 97.7% CI (0.52–0.90) for overall survival to 95% CI. Herbst 2016 KEYNOTE-010: intent-to-treat N = 1033 including all three study arms (pembrolizumab 2 mg, N = 344, pembrolizumab 10 mg, N = 346, docetaxel 75 mg, N = 343). Percentage of randomized patients with quantifiable tumor PD-L1 expression: Borghaei 2015 CheckMate 057: 78%; Brahmer 2015 CheckMate 017: 83%; Wu 2019 CheckMate 078: 9%. Abbreviations: CI = confidence interval; D + L = DerSimonian and Laird method; ICI = immune checkpoint inhibitor; kg = kilogram; mg = milligram; N = number of patients; PD-L1 = programmed cell death ligand-1.
events were also more frequent in patients treated with durvalumab than in those treated with placebo, but the difference did not reach statistical significance (28.6% versus 22.6%, RR 1.26; 95% CI: 0.96–1.67).

Compared to chemotherapy, the risk of treatment-related serious adverse events was higher in patients treated with a combination of two immune checkpoint inhibitors,\(^23\) or the combination of an immune checkpoint inhibitor on top of chemotherapy\(^23,44\) (see Figure 4(a)). For single-agent immune checkpoint inhibitor therapy compared to chemotherapy, similar risks of treatment-related serious adverse events were observed\(^39,47\) (see Figure 4(a)). Supplementary Figure S2 shows extended follow-up data on adverse events of three studies that are consistent with prior findings.\(^25,27,36\)

**Second-line therapy**

Based on a random-effects meta-analysis, the risk of overall adverse events was similar between second-line treatment groups with an immune checkpoint inhibitor or docetaxel (3 RCTs, 2019 patients; RR 0.98; 95% CI: 0.97–1.00; \(I^2 = 0.0\%\), see Figure 4(b)). A random-effects meta-analysis of 6 RCTs (one with two dosing arms\(^43\)) including 3763 patients showed statistically significantly fewer TRAE for patients treated with immune checkpoint inhibitors than for those treated with chemotherapy (RR 0.76; 95% CI: 0.73–0.79; \(I^2 = 0.0\%\), see Figure 4(b)). Serious adverse events were similar in patients treated with atezolizumab compared to those receiving docetaxel\(^40,48\) and lower in patients treated with nivolumab compared to docetaxel\(^51\) (see Figure 4(b)). In two RCTs, the risk of treatment-related serious adverse events was lower in the nivolumab than in the docetaxel groups\(^37,38\) (see Figure 4(b)).

**Discussion**

Our systematic review shows for first-line therapy of patients with advanced NSCLC that a combination of an immune checkpoint inhibitor (atezolizumab, nivolumab or pembrolizumab) with platinum-based chemotherapy or nivolumab combined with ipilimumab improved progression-free survival and overall survival compared to chemotherapy. However, combination therapies increased the risk of serious adverse events. For single-agent nivolumab or pembrolizumab compared to chemotherapy alone, we observed different effects depending on the PD-L1 expression level. Pembrolizumab increased overall and progression-free survival in patients
with PD-L1 expression of ≥50% and resulted in less TRAE than chemotherapy. Compared to placebo, maintenance therapy with durvalumab increased overall and progression-free survival at the downside of higher risk of TRAE. Meta-analyses of second-line therapy trials yield statistically significantly improved progression-free survival and overall survival for immune checkpoint inhibitor compared to docetaxel. Immune checkpoint inhibition resulted in lower risk of any and serious TRAE than docetaxel.

As mentioned above PD-L1 expression level is an important factor that decides the choice of therapy in patients with advanced NSCLC without driver mutations. Two first-line therapy trials compared single-agent immunotherapy with pembrolizumab to chemotherapy and resulted in a longer progression-free survival, while nivolumab single-agent treatment displayed no significant benefit for progression-free survival. These two studies differ greatly concerning PD-L1 expression: in the nivolumab study, PD-L1 positivity was defined as ≥5% of tumor cells, while Reck et al. defined the PD-L1 threshold at ≥50%. The progression-free survival findings also translated to overall survival, which was longer in the pembrolizumab study while, for nivolumab, no significant benefit could be displayed in this setting. The third single-agent immunotherapy trial underlined the importance of PD-L1 status; only in the patients with tumor PD-L1 expression of ≥50%, statistically significant progression-free survival benefit could be seen. In patients with PD-L1 expression of ≥20% or ≥1% this effect could not be observed. Consequently, pembrolizumab was initially approved by the Food and Drug Administration (FDA) as a single agent in first and later therapy lines for patients whose tumors express PD-L1 ≥ 50%. This was later expanded in April 2019 to tumors expressing PD-L1 ≥ 1%. However, in tumors with PD-L1 ≥ 1%, pembrolizumab is applied in combination with chemotherapy. Nivolumab, is not approved for first-line treatment of NSCLC patients, but for progression during or after platinum-based chemotherapy (i.e. second-line), regardless of PD-L1 expression. This is due to the fact, that in the second-line CheckMate 017 trial, both patient groups, positive and negative for PD-L1 expression, benefited with regard to overall survival from nivolumab treatment. The results of our meta-analyses underline the rationale for this approval status.

Further patient stratification strategies seem to be important in identifying which patients will benefit from immune checkpoint inhibition in first-line therapy of NSCLC. An interesting biomarker was used in one part of the Checkmate-227 trial: tumor mutational burden (TMB). This is based on the hypothesis that tumors with high TMB have a higher likelihood to display neo-antigens on their surface, which can be subsequently recognized and targeted by T-cells. In CheckMate 227, patients were treated with a combinatorial immune checkpoint

| Study | Comparison | Risk ratio (95% CI) | Treatment | Control | Weight |
|-------|------------|---------------------|-----------|---------|--------|
| Fenlon 2016 POLAR | Altezolab vs. Docetaxel | 0.98 (0.95, 1.02) | 100.0 | 100.0 | 0.002 |
| Reck et al. 2017 OAK | Altezolab vs. Docetaxel | 0.96 (0.93, 0.99) | 100.0 | 100.0 | 0.010 |
| Eder et al. 2015 Checkmate 059 | Nivolumab vs. Docetaxel | 0.87 (0.79, 0.96) | 100.0 | 100.0 | 0.003 |

Figure 4. (Continued).
blockade with nivolumab and ipilimumab. In the TMB-high patient cohort, a double immune checkpoint blockade resulted in significantly longer progression-free survival than chemotherapv. This trial, which had also other study arms, was later analyzed based on the original stratification of PD-L1 negativity (<1%) or positivity (≥1%). Here, an overall survival benefit of double immune checkpoint blockade could be observed in both groups. It was later also demonstrated, that the relative benefit of double immune checkpoint blockade compared to chemotherapy was also seen in patients with low TMB. Thus, TMB has not yet emerged as a biomarker for treatment stratification in NSCLC, in contrast to PD-L1.

Previous systematic reviews have indicated that atezolizumab, nivolumab and pembrolizumab improve outcomes in the second-line treatment of patients with advanced NSCLC as compared to chemotherapy. These results are in line with the findings of our systematic review, which includes data of more recent trials.

With respect to other PD-L1 antibodies, also avelumab was investigated as treatment for NSCLC. Avelumab is currently applied for treatment of metastatic Merkel Cell Carcinoma, Renal Cell Cancer, and Urothelial Carcinoma. With respect to NSCLC, in a large open-label, phase III clinical trial enrolling 792 patients, avelumab treatment did not improve overall survival in patients with platinum-treated PD-L1-positive tumors when compared to docetaxel. Thus, avelumab failed approval status as a therapy for NSCLC.

Our systematic review has several limitations. First, we limited the eligible studies to those in English and German language. Second, we did not include trials investigating antibodies as single agents against other immune checkpoints (e.g., CTLA-4). Third, potential publication bias and selective outcome reporting are other potential limitations of this review. Moreover, the included studies were, especially for first-line therapy, very heterogeneous concerning the interventions and controls and used different cutoff values for PD-L1 expression.

**Conclusion**

In first-line therapy of patients with advanced NSCLC, ICI is effective when combined with chemotherapy not depending on PD-L1 expression, or as monotherapy in high PD-L1 expressing tumors. For second-line therapy, single-agent ICI improves efficacy and safety compared with docetaxel.

**Abbreviations**

| Abbreviation | Definition |
|--------------|------------|
| ABCP         | atezolizumab plus bevacizumab plus carboplatin plus paclitaxel |
| ALK          | anaplastic lymphoma kinase |
| BCP          | bevacizumab plus carboplatin plus paclitaxel |
| CHT          | chemotherapy |
| CI           | confidence interval |
| CTLA-4       | cytotoxic T-lymphocyte–associated protein 4 |
| ECOG         | Eastern Cooperative Oncology Group |
| EGFR         | epidermal growth factor receptor |
| FDA          | US Food and Drug Administration |
| Gy           | grays |
| ICIs         | immune checkpoint inhibitors |
| MET          | mesenchymal–epithelial transition factor |
| NCT          | National Clinical Trial |
| NSCLC        | non–small cell lung cancer |
| N            | number of patients |
| OS           | overall survival |
| PD-1         | programmed cell death protein-1 |
| PD-L1        | programmed cell death ligand-1 |
| PFS          | progression-free survival |
| RCT          | randomized controlled trial |
| ROS1         | proto-oncogene tyrosine-protein kinase |
| RR           | risk ratio |
| SCC          | squamous cell carcinoma |
| SCLC         | small cell lung cancer |
| SD           | standard deviation |
| TMB          | tumor mutational burden |
| TNM          | classification system for malignant tumors (tumor, nodus, metastasis) |
| TRAE         | treatment-related adverse events |
| WHO          | World Health Organization |

**Authors’ contributions**

GW and JS conceptualized this work, conducted literature screening, data extraction, risk of bias assessment and wrote the manuscript. GW performed statistical analysis. HKS conducted literature screening, data extraction, risk of bias assessment, and critically revised the manuscript. IK developed the search strategy, conducted electronic literature searches, and critically revised the manuscript. MP and GG advised this project and critically revised the manuscript. All authors read and approved the final manuscript.

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