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# Efficacy and safety of immune checkpoint inhibitors for advanced non-small cell lung cancer with or without PD-L1 selection: A systematic review and network meta-analysis

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## Abstract

**Background:** Immune checkpoint inhibitors (ICIs) are standard treatments for advanced non-small cell lung cancer (NSCLC); however, evidence regarding their relative efficacy and safety is lacking. This study compared the efficacy and safety of all currently available ICI treatments in patients with advanced NSCLC to identify optimal treatment regimens.

**Methods:** PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase databases were systematically searched for randomized controlled trials (RCTs) published up to August 8, 2022. The primary outcomes were overall survival (OS) and progression-free survival (PFS). Secondary outcomes included objective response rate (ORR) and adverse events (AEs).

**Results:** Forty RCTs involving 22,526 patients were selected, and a total of 26 treatment regimens were identified. Treatment with anti-programmed cell death protein-1 (anti-PD-1) provided superior OS compared with anti-programmed death ligand 1 (anti-PD-L1) treatment. ICIs plus platinum-based chemotherapy (PBC) were superior to ICIs treatment alone, although the addition of PBC increased treatment toxicity. Cemiplimab ranked first for OS and lowest for any-grade AEs in advanced NSCLC patients without PD-L1 selection. Regarding grade ≥3 AEs, the toxicity of ICI monotherapy or ICI–ICI combination was consistently lower than that of the other treatments. For patients without PD-L1 selection, cemiplimab showed the best OS, pembrolizumab plus docetaxel (Pem-DXT) showed the best PFS, and atezolizumab plus bevacizumab and PBC (Atezo-Beva-PBC) showed the best ORR. Pembrolizumab plus PBC and Atezo-Beva-PBC were the most likely optimal treatments for OS and PFS in patients with PD-L1 expression <1%, respectively. In patients with PD-L1 expression ≥1%, treatment regimens containing anti-PD-1 provided superior OS benefits compared with those of anti-PD-L1 treatment, and sintilimab plus PBC (Sint-PBC) provided the best OS benefit; as for PFS, ICI plus PBC consistently showed greater PFS benefits than ICI or PBC alone. For patients with anti-PD-L1 expression of 1–49%, camrelizumab plus PBC provided the best benefit for OS and PFS among included treatment. Durvalumab-tremelimumab-PBC and Atezo-Beva-PBC respectively presented the highest OS and PFS for patients with PD-L1 expression ≥50%. Moreover, cemiplimab and Atezo-Beva-PBC yielded the best OS and PFS benefits as first-line treatments for patients with advanced NSCLC, respectively.

**Conclusions:** Although ICI plus PBC likely resulted in superior survival outcomes compared to ICI treatment alone, it did increase toxicity. Cemiplimab presented a well-balanced efficacy and safety profile in advanced NSCLC treatment. Our findings with the current ICIs comparisons will aid future trials for cancer immunotherapy.

**Registration:** PROSPERO, https://www.crd.york.ac.uk/PROSPERO/, CRD42022323879.

**Keywords:** Non-small cell lung cancer; Immune checkpoint inhibitor; Programmed death ligand 1; Cemiplimab; Bayesian network meta-analysis

## Introduction

The incidence of lung cancer, the most common cause of cancer-related deaths, is increasing worldwide.[1] Non-small cell lung cancer (NSCLC) comprises approximately 85% of all lung cancer cases.[2] Patients with NSCLC are mostly diagnosed at an advanced disease stage, showing poor prognosis.[3] Platinum-based chemotherapy (PBC) is the standard first-line therapy in patients with advanced NSCLC without targetable genetic alterations.[4] However, these interventions have limited survival benefits, with a median overall survival (OS)

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of <1 year.[5] Considering the high prevalence and poor prognosis of advanced NSCLC, new interventions and therapeutic combinations are urgently required to increase survival.

Immune checkpoint inhibitors (ICIs) have shown promising benefits and a favorable safety profile in cancer treatments, especially advanced NSCLC. ICI targets include cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein-1 (PD-1), and programmed death ligand 1 (PD-L1).[6] Compared with standard chemotherapy, pembrolizumab (Pem), an anti-PD-1 monoclonal antibody, improves OS in advanced NSCLC with PD-L1 expression ≥1%, and it improves OS when combined with PBC as a first-line treatment, regardless of the PD-L1 tumor proportion score.[7–9] Results from randomized controlled trials (RCTs) with atezolizumab (Atezo), an anti-PD-L1 antibody, showed that Atezo monotherapy improved OS to a greater extent than docetaxel (DXT), regardless of PD-L1 expression.[10,11] Based on these data, Atezo has been approved for the treatment of advanced NSCLC previously treated with chemotherapy.[12] Similarly, nivolumab (Nivo) combined with ipilimumab (Ipi) improved OS compared to PBC for NSCLC with PD-L1 expression ≥1%.[13] Furthermore, Nivo-Ipi plus PBC (Nivo-Ipi-PBC) for two cycles followed by Nivo-Ipi improved OS compared to chemotherapy alone for NSCLC without PD-L1 selection.[14] Although ICIs have shown beneficial effects in advanced NSCLC, the relative efficacy and safety of different ICI strategies independently or combined with chemotherapy, remain controversial.

Therefore, we performed a Bayesian network meta-analysis (NMA) of RCTs to determine the efficacy and safety of all currently available ICIs for advanced NSCLC, whether independently or combined with chemotherapy, to ultimately identify optimal treatment regimens. We also conducted subgroup analyses based on PD-L1 expression and first-line treatment with ICIs. This meta-analysis may be helpful for future clinical studies on ICIs treatment in advanced NSCLC.

## Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines with an extension for NMA.[15] The study protocol was registered with PROSPERO (https://www.crd.york.ac.uk/PROSPERO/, No. CRD42022323879).

### Data sources and search strategies

We systematically searched PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase databases for articles published up to August 8, 2022. The detailed search strategies are listed in Supplementary Table 1, http://links.lww.com/CM9/B712. Language restrictions were not imposed in our search for eligible studies. The reference lists of identified trials, reviews, and meta-analyses were also reviewed to identify additional resources.

### Inclusion criteria and study selection

The inclusion criteria of the selected RCTs were as follows: (1) population: patients with advanced NSCLC (stage III or IV); (2) intervention and comparison: RCTs that investigated at least one type of ICI monotherapy or combination therapy in patients with NSCLC; (3) outcomes: primary outcomes included OS and progression-free survival (PFS), and secondary outcomes were objective response rate (ORR) and adverse events (AEs) of any grade or grade ≥3; and (4) study design: RCT.

RCTs published only in conference abstracts, posters, or presentations were excluded. If several studies were based on the same trial, those with the most comprehensive data were the ones included.

### Data extraction and quality evaluation

The following data were extracted from each RCT: publication details, such as first author and publication year, trial design details, national clinical trial number, number of patients, phase of RCT, and treatment regimens of the intervention and control groups; patient characteristics, such as age, sex, and disease status; and clinical outcomes, including median and hazard ratios (HRs) and 95% confidence intervals (CIs) for PFS and OS, and the incidence of ORR and AEs.

The methodological quality of the included RCTs was evaluated using the Cochrane Risk of Bias 2 tool, grading each included trial in terms of bias risk as follows: low bias, high bias, or some concerns about bias.[16] Egger regression with a funnel plot was performed to further detect publication bias of the included studies, and significant asymmetry and publication bias were defined at $P$ <0.10.

### Statistical analysis

We conducted traditional pairwise meta-analyses to simultaneously compare multiple trials with different ICI monotherapies or combination therapies. Outcomes were pooled using a random-effects model. OS and PFS outcomes were expressed as HRs with 95% CIs. ORR and AEs were expressed as odds ratios (ORs) and 95% CIs.

Bayesian NMA was performed using the WinBUGS 1.4.3 software (MRC Biostatistics Unit, Cambridge, UK). For each treatment comparison, random effects models were employed, and each model was run for 100,000 iterations, the first 10,000 of which were discarded. The surface under the cumulative ranking probabilities was used to estimate the rank probabilities and evaluate the likelihood of each treatment regimen in the best to worst order. Network plots were constructed based on the connections between the included studies.

A pairwise meta-analysis was performed to compare with the corresponding pooled results from the Bayesian framework. Inconsistency and heterogeneity were assessed using the $Q$ test and statistical inconsistency index ($I^2$).

Heterogeneity was identified when the $I^2$ value was >50%. Transitivity and similarity were assessed by meta-regression analysis using the gemtc package in R version 4.0.5, 2021 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Systematic review and study characteristics

The literature search yielded 6106 articles, of which 195 full-text articles were assessed for eligibility. Ultimately, 40 RCTs involving 22,526 participants were included in the NMA [Figure 1].[9,10,12–14,17–51] The included studies were published between 2012 and 2022, and the sample sizes ranged from 78 to 1274 participants. A total of 26 treatment regimens were identified, including the following: cemiplimab (Cemip), Pem, Nivo, Atezo, durvalumab (Durva), avelumab (Ave), Nivo-Ipi, Pem plus Ipi (Pem-Ipi), Durva plus tremelimumab (Durva-Treme), daratumumab plus Atezo (Darat-Atezo), sintilimab plus PBC (Sint-PBC), Pem plus PBC (Pem-PBC), sugemalimab plus PBC (Sugema-PBC), camrelizumab plus PBC (Camre-PBC), Atezo plus PBC (Atezo-PBC), Nivo plus PBC (Nivo-PBC), Ipi plus PBC (Ipi-PBC), Durva plus PBC (Durva-PBC), tislelizumab plus PBC (Tisle-PBC), Atezo plus bevacizumab (Beva) plus PBC (Atezo-Beva-PBC), Nivo-Ipi-PBC, Durva-Treme plus PBC (Durva-Treme-PBC), Pem plus docetaxel (Pem-DXT), Beva plus PBC (Beva-PBC), PBC, and DXT. The Beva-PBC, PBC, and DXT treatments were used as reference for network comparisons among the identified treatment regimens [Supplementary Table 2, http://links.lww.com/CM9/B712].

The trial quality was evaluated using the Cochrane Risk of Bias 2 tool [Supplementary Figure 1, http://links.lww.com/CM9/B712], and a funnel plot confirmed the absence of publication bias among the included studies [Supplementary Figure 2, http://links.lww.com/CM9/B712].

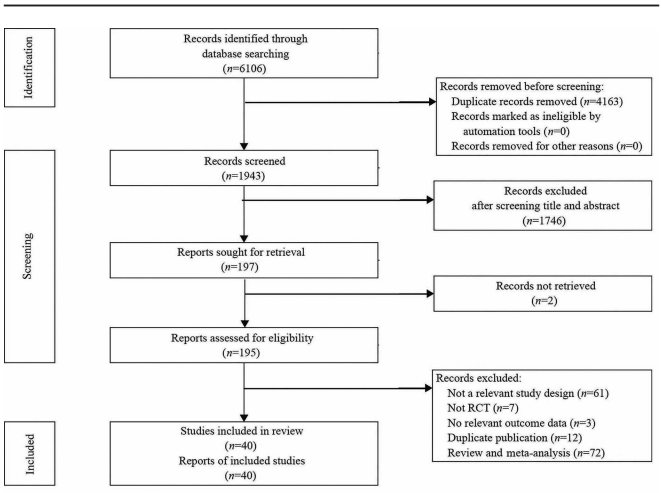


**Figure 1:** Flowchart of search and selection of literature. RCT: Randomized clinical trial.

### Overall survival

A total of 23 ICI-based treatments were assessed for OS, PFS, and ORR in advanced NSCLC patients without PD-L1 selection [Figure 2A]. Treatment regimens containing anti-PD-1 likely provided a superior OS benefit compared to those with anti-PD-L1. Cemip yielded the best OS benefit, followed by Sint-PBC and Pem-PBC. ICI-PBC likely provided a greater OS benefit than ICIs alone (except Nivo versus Nivo-PBC [HR, 0.98; 95% CI, 0.80–1.19]), including Pem-PBC, which offered a marked benefit versus Pem alone (HR, 0.75; 95% CI, 0.61–0.94) and Pem-DXT (HR, 0.44; 95% CI, 0.22–0.88). Among the ICI-PBC treatments, Sint-PBC yielded the greatest OS benefit [Figure 3]. Based on Bayesian ranking profiles, Cemip was ranked first for OS (probability, 90%), followed by Sint-PBC (probability, 88%) and Pem-PBC (probability, 88%) [Figure 4].

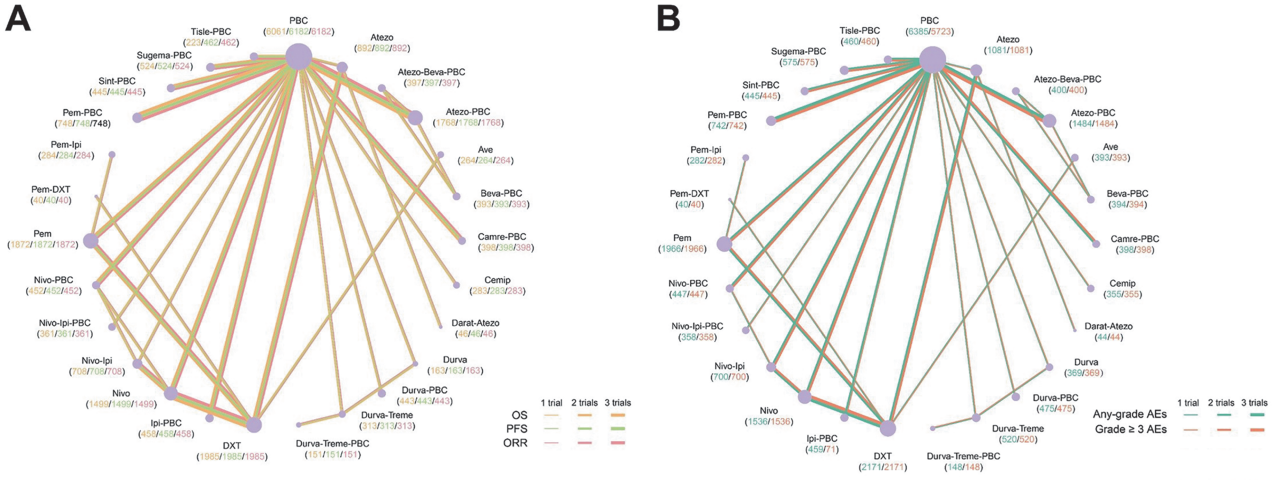


**Figure 2:** Network plots of efficacy and toxicity of ICIs. (A) Comparisons were performed on OS, PFS, and ORR for patients without PD-L1 selection. (B) Comparisons were performed on any-grade AEs, and grade ≥3 AEs for patients without PD-L1 selection. AEs: Adverse events; Atezo: Atezolizumab; Ave: Avelumab; Beva: Bevacizumab; Camre: Camrelizumab; Cemip: Cemiplimab; Darat: Daratumumab; Durva: Durvalumab; DXT: Docetaxel; ICIs: Immune checkpoint inhibitors; Ipi: Ipilimumab; Nivo: Nivolumab; ORR: Objective response rate; OS: Overall survival; PBC: Platinum-based chemotherapy; PD-L1: Programmed death ligand 1; Pem: Pembrolizumab; PFS: Progression-free survival; Sint: Sintilimab; Sugema: Sugemalimab; Tisle: Tislelizumab; Treme: Tremelimumab.

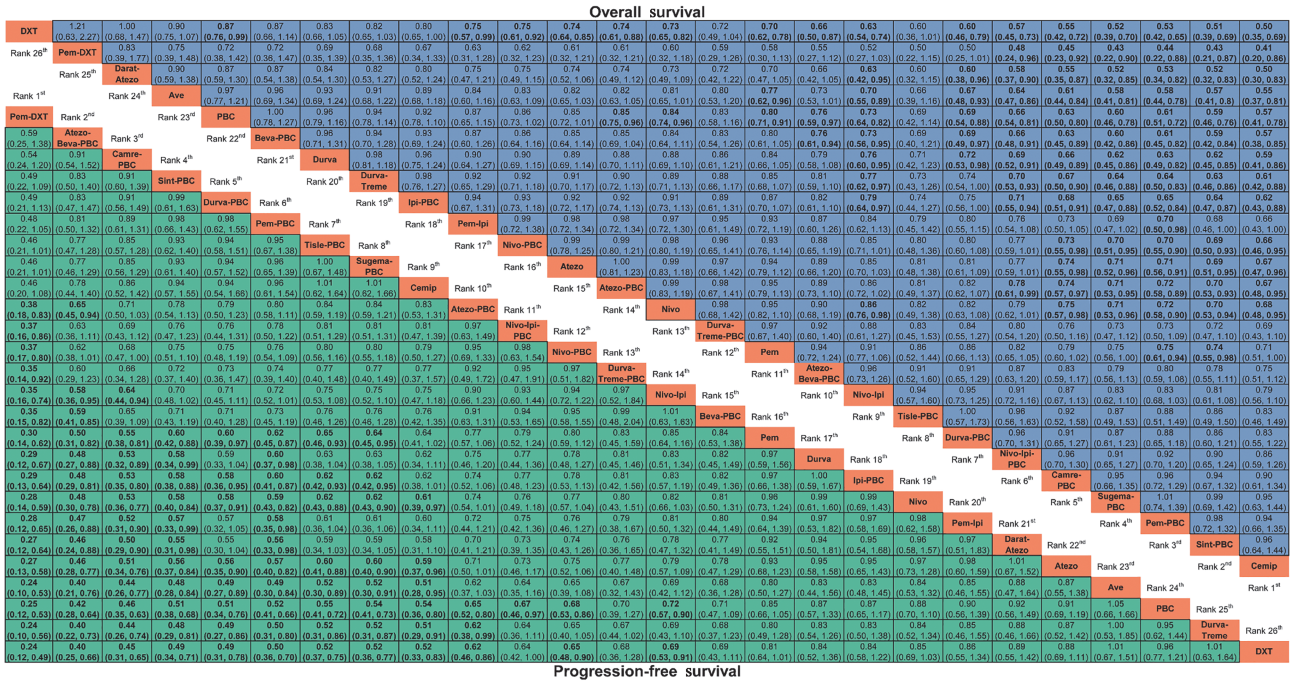


**Figure 3:** Efficacy of ICIs for patients with advanced NSCLC without PD-L1 selection. HR and 95% CIs for OS (upper triangle in blue) and PFS (lower triangle in green), and an HR <1.00 provides better survival benefits. The results are presented as column-defined treatment versus row-defined treatment. Atezo: Atezolizumab; Ave: Avelumab; Beva: Bevacizumab; Camre: Camrelizumab; Cemip: Cemiplimab; CI: Confidence interval; Darat: Daratumumab; Durva: Durvalumab; DXT: Docetaxel; HR: Hazard ratio; ICIs: Immune checkpoint inhibitors; Ipi: Ipilimumab; Nivo: Nivolumab; NSCLC: Non-small cell lung cancer; OS: Overall survival; PBC: Platinum-based chemotherapy; PD-L1: Programmed death ligand 1; PFS: Progression-free survival; Pem: Pembrolizumab; Sint: Sintilimab; Sugema: Sugemalimab; Tisle: Tislelizumab; Treme: Tremelimumab.

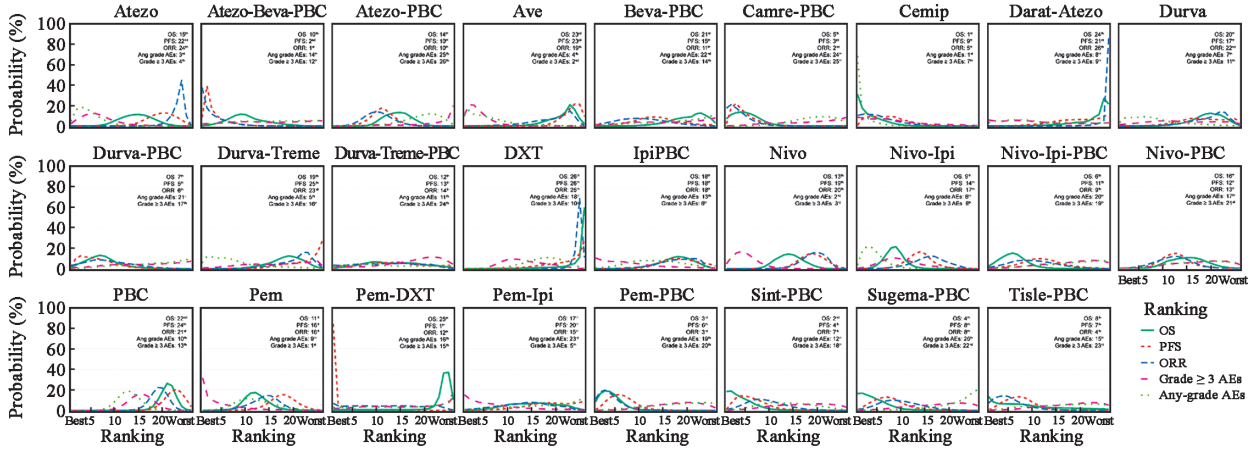


**Figure 4:** Bayesian ranking profiles for ICIs on efficacy and safety for patients with advanced NSCLC without PD-L1 selection. Ranking plots indicate the probability of each treatment being ranked from first to last on OS, PFS, ORR, any-grade AEs, and grade ≥3 AEs. AEs: Adverse events; Atezo: Atezolizumab; Ave: Avelumab; Beva: Bevacizumab; Camre: Camrelizumab; Cemip: Cemiplimab; Darat: Daratumumab; Durva: Durvalumab; DXT: Docetaxel; ICIs: Immune checkpoint inhibitors; Ipi: Ipilimumab; Nivo: Nivolumab; NSCLC: Non-small cell lung cancer; ORR: Objective response rate; OS: Overall survival; PBC: Platinum-based chemotherapy; Pem: Pembrolizumab; PFS: Progression-free survival; Sint: Sintilimab; Sugema: Sugemalimab; Tisle: Tislelizumab; Treme: Tremelimumab.

### *Progression-free survival*

Patients who received ICI-PBC showed better PFS than those who received ICIs without PBC therapy, including Pem-PBC, which showed a marked benefit compared with Pem alone (HR, 0.62; 95%CI, 0.45–0.87). Among the ICI-PBC treatments, Atezo-Beva-PBC provided better PFS benefit compared to Atezo-PBC (HR, 0.65; 95% CI, 0.45–0.94) and Ipi-PBC (HR, 0.48; 95% CI, 0.29–0.81) [Figure 3]. Ranking profiles suggested that Pem-DXT was ranked first for PFS (probability, 98%), followed by Atezo-Beva-PBC (probability, 90%) and Camre-PBC (probability, 86%) [Figure 4].

### *Objective response rate*

Patients who received ICI plus PBC had a higher ORR than those who received ICI without PBC therapy.

Atezo-Beva-PBC, Camre-PBC, and Pem-PBC had significantly higher ORRs than Pem, Nivo-Ipi, Ipi-PBC, Ave, and Nivo, respectively. The ORR in Atezo-Beva-PBC was notably higher than that in Beva-PBC (OR, 1.93; 95% CI, 1.02–3.63) [Supplementary Figure 3, http://links.lww.com/CM9/B712]. Atezo-Beva-PBC ranked first for ORR (probability, 91%), followed by Camre-PBC (probability, 89%) and Pem-PBC (probability, 88%) [Figure 4].

### *AEs*

AEs of any-grade and grade ≥3 were determined to evaluate safety and toxicity. Network plots are shown in Figure 2B. Regarding grade ≥3 AEs, the toxicity of ICI monotherapy or ICI–ICI combination was consistently lower than that of the other treatments. Although no significant difference was found between ICI monotherapy and ICI–ICI combinations, Pem had the lowest risk of grade ≥3 AEs (probability, 88%), followed by Ave, Nivo, and Atezo [Figure 4]. Overall, the addition of PBC to ICIs increased treatment toxicity; however, Ipi-PBC and Atezo-Beva-PBC showed lower risks of grade ≥3 AEs than PBC alone. In this analysis, Atezo-PBC had the highest risk of grade ≥3 AEs [Supplementary Figure 3, http://links. lww. com/CM9/B712]. For any-grade AEs, Cemip (probability, 86%) showed the lowest risk of any-grade AEs followed by Nivo, Atezo, and Ave [Figure 4]. The addition of PBC to ICIs treatment increased toxicity, and Sugema-PBC had the highest risk of any-grade AEs [Supplementary Figure 4, http://links. lww. com/CM9/B712].

### *Subgroup analyses based on PD-L1 expression*

Following four subgroups were defined according to PD-L1 expression levels: <1%, ≥1%, 1–49%, and ≥50%. OS and PFS were estimated for each group, and optimal treatments differed across the four subpopulations.

#### Subgroup of patients with PD-L1 expression <1%

Fourteen ICI-based treatments were evaluated in the subgroup analysis for OS [Supplementary Figure 5A, http://links.lww.com/CM9/B712] and PFS [Supplementary Figure 6A,http://links.lww.com/CM9/B712]. Regarding OS, treatment regimens containing anti-PD-1 likely provided superior OS benefits compared to those with anti-PD-L1, similarly to OS without PD-L1 selection. Specifically, Pem-PBC yielded a significantly superior OS benefit compared with Durva-PBC (HR, 0.49; 95% CI, 0.26–0.92) and Durva (HR, 0.47; 95% CI, 0.28–0.81). Atezo-Beva-PBC provided the best PFS benefit, followed by Sugema-PBC and Camre-PBC. Furthermore, Atezo-Beva-PBC significantly increased PFS compared with Atezo-PBC, Nivo, and Atezo. Additionally, although no significant differences were observed, DXT monotherapy and PBC were more likely to provide superior PFS benefits than Atezo, and Atezo yielded the worst PFS benefit among all included treatments [Supplementary Figure 7, http://links.lww.com/CM9/B712]. Based on Bayesian ranking profiles, Pem-PBC (probability, 83%) and Atezo-Beva-PBC (probability, 91%) were the most likely optimal treatments for OS [Supplementary Figure 8, http://links.lww.com/CM9/B712] and PFS [Supplementary Figure 9, http://links.lww.com/CM9/B712] in patients with PD-L1 expression <1%, respectively.

#### Subgroup of patients with PD-L1 ≥1%

Fourteen ICI-based treatments were evaluated in subgroup analysis for OS [Supplementary Figure 5B, http://links.lww.com/CM9/B712] and PFS [Supplementary Figure 6B, http://links.lww.com/CM9/B712]. Treatment regimens containing anti-PD-1 consistently provided superior OS benefits compared with those of anti-PD-L1 treatment, and Sint-PBC provided the best OS benefit, followed by Camre-PBC. Patients who received ICI-PBC consistently showed better OS than ICI alone, such as those treated with Pem-PBC, yielding a significantly superior OS benefit compared to Pem (HR, 0.75; 95% CI, 0.56–0.99). As for PFS, Pem-DXT yielded the best PFS benefit. ICI plus PBC consistently showed greater PFS benefits than ICI or PBC alone. Camre-PBC, Pem-PBC, Tisle-PBC, Durva-PBC, Sugema-PBC, and Sint-PBC significantly prolonged PFS compared with Nivo-Ipi, Atezo, Nivo, Pem, Pem-Ipi, and Ave [Supplementary Figure 10, http://links.lww.com/CM9/B712]. Based on Bayesian ranking profiles, Sint-PBC (probability, 92%) and Pem-DXT (probability, 96%) were the most likely optimal treatments for OS [Supplementary Figure 8, http://links.lww.com/CM9/B712] and PFS [Supplementary Figure 9,http://links.lww.com/CM9/B712] in patients with PD-L1 expression ≥1%, respectively.

#### Subgroup of patients with PD-L1 expression of 1–49%

Ten ICI-based treatments were evaluated in subgroup analysis for OS [Supplementary Figure 5C, http://links.lww.com/CM9/B712] and PFS [Supplementary Figure 6C, http://links.lww.com/CM9/B712]. Anti-PD-1 plus PBC was superior to other treatments; Camre-PBC yielded the best OS benefit, followed by Pem-PBC. Pem-PBC yielded a significantly better OS than Atezo-PBC (HR, 0.53; 95% CI, 0.30–0.93). Camre-PBC yielded the best PFS benefit, followed by Atezo-Beva-PBC. Camre-PBC was significantly superior to Atezo (HR, 0.48; 95% CI, 0.23–0.95) and Pem (HR, 0.35; 95% CI, 0.17–0.68) [Supplementary Figure 11, http://links.lww.com/CM9/B712]. Camre-PBC provided the best benefit for OS (probability, 88%) and PFS (probability, 85%), making it the most likely optimal treatment for this subgroup [Supplementary Figures 8 and 9, http://links.lww.com/CM9/B712].

#### Subgroup of patients with PD-L1 expression ≥50%

In this subgroup analysis, 15 and 16 ICI-based treatments were evaluated for OS [Supplementary Figure 5D, http://links.lww.com/CM9/B712] and PFS [Supplementary Figure 6D,http://links.lww.com/CM9/B712], respectively. Significant differences in OS were not observed between ICI treatments, although Durva-Treme-PBC yielded the best OS benefit, followed by Atezo. Atezo-Beva-PBC was the optimal treatment for improving PFS,

followed by Camre-PBC and Pem-PBC [Supplementary Figure 12, http://links.lww.com/CM9/B712]. Durva-Treme-PBC (probability, 81%) and Atezo-Beva-PBC (probability, 96%) were the optimal treatments for OS and PFS in patients with PD-L1 expression ≥50%, respectively [Supplementary Figures 8 and 9, http://links.lww.com/CM9/B712].

### Comparison of ICIs as the first-line treatment for advanced NSCLC

Nineteen ICI-based treatments were evaluated in this subgroup analysis for OS [Supplementary Figure 5E, http://links.lww.com/CM9/B712] and PFS [Supplementary Figure 6E, http://links.lww.com/CM9/B712] in advanced NSCLC patients without PD-L1 selection. Treatment regimens containing anti-PD-1 yielded a superior OS benefit compared to anti-PD-L1 treatments. Cemip promoted the best OS benefit, followed by Sint-PBC and Pem-PBC. ICI-PBC promoted greater OS benefits than ICIs without PBC (except for Atezo versus Atezo-PBC; HR, 0.98; 95% CI, 0.71–1.36). Among the ICI-PBC treatments, Sint-PBC yielded the greatest OS benefit. Sint-PBC, Pem-PBC, and Camre-PBC significantly increased the OS compared with Atezo-PBC, Nivo, Ipi-PBC, Durva-Treme, and Durva [Supplementary Figure 13, http://links.lww.com/CM9/B712]. Cemip ranked first for OS (probability, 88%), followed by Sint-PBC (probability, 87%) and Pem-PBC (probability, 85%). These results were similar to the primary results of OS without PD-L1 selection [Figure 4 and Supplementary Figure 8, http://links. lww.com/CM9/B712]. Atezo-Beva-PBC yielded the best PFS benefit (probability, 90%), followed by Camre-PBC and Sugema-PBC [Supplementary Figures 9, http://links.lww.com/CM9/B712]. Patients who received ICI-PBC had a consistently better PFS than those who received ICIs alone [Supplementary Figures 13, http://links.lww.com/CM9/B712].

### Heterogeneity, inconsistency, and transitivity assessment

Pairwise meta-analysis results were almost consistent with the pooled NMA results from the Bayesian framework [Supplementary Figure 14, http://links.lww.com/CM9/B712]. This result revealed that the included trials had favorable transitivity and consistency between direct and indirect comparisons. Heterogeneity among pairwise meta-analysis was also evaluated. The results illustrated that most of the comparisons across the included trials had minimal or median heterogeneity [Supplementary Figures 15 and 16, http://links.lww.com/CM9/B712]. The results of pairwise meta-analysis on the basis of the frequentist approach were almost consistent with the corresponding pooled results from the Bayesian framework [Supplementary Figures 15 and 16, http://links.lww.com/CM9/B712]. Additionally, based on the meta-regression results, similar clinical characteristics were observed across all the included studies, indicating acceptable interstudy transitivity [Supplementary Figure 17, http://links.lww.com/CM9/B712].

## Discussion

To our knowledge, this is a relatively comprehensive study to evaluate the efficacy and safety profiles of the currently available ICI treatments, administered independently or combined with chemotherapy (PBC or DXT), in patients with advanced NSCLC. Treatment regimens with anti-PD-1 activity show a superior OS benefit compared with anti-PD-L1 treatments. ICI-PBC was correlated with higher survival probability than ICIs alone (except for Nivo-PBC). Cemip, Pem-DXT, and Atezo-Beva-PBC provided the best benefits for patients with advanced NSCLC without PD-L1 selection in terms of OS, PFS, and ORR, respectively. For patients with PD-L1 expression <1%, Pem-PBC and Atezo-Beva-PBC were demonstrated to be the optimal treatment options in terms of OS and PFS, respectively. For patients with PD-L1 expression ≥1%, Sint-PBC and Pem-DXT were the optimal treatments in terms of OS and PFS, respectively. Camre-PBC exhibited the best OS and PFS in patients with PD-L1 levels of 1–49%. For patients with PD-L1 expression ≥50%, Durva-Treme-PBC and Atezo-Beva-PBC conferred the best OS and PFS, respectively. Cemip and Atezo-Beva-PBC yielded the best OS and PFS benefits as first-line treatments for patients with advanced NSCLC, respectively. Additionally, the toxicity of ICI monotherapy or ICI–ICI combination was lower than that of the other treatments but was elevated by the addition of PBC. Cemip showed the lowest risk of any-grade AEs, whereas Pem had the lowest risk of grade ≥3 AEs. Cemip had well-balanced efficacy and safety profile, across all available ICI treatments, ranking first for OS, ninth for PFS, fifth for ORR, first for the lowest risk of any-grade AEs, and seventh for the lowest risk of grade ≥3 AEs in advanced NSCLC without PD-L1 expression selection.

Overall, regimens containing anti-PD-1 provided greater treatment benefits than anti-PD-L1 treatments. This result is consistent with previous studies in which anti-PD-1 therapy reduced the risk of mortality and prolonged survival when compared with anti-PD-L1 therapy.[52,53] One possible explanation for this is that PD-1 antibodies can block, simultaneously, PD-1 binding to PD-L1 and PD-L2, thereby inhibiting additional immune escape pathways.[54]

This study revealed that ICI-PBC was more likely to increase survival than ICIs alone. This finding is particularly relevant in patients with PD-L1 expression <1% , as most patients with advanced NSCLC have undetectable, low, or negative PD-L1 expressions.[55] This finding also raises a clinically important question on whether ICI-PBC increases survival relative to ICIs (whether alone or in combination) in patients with advanced NSCLC. Direct comparisons in randomized trials are needed to further answer this question. These results suggested that ICI-PBC combination enhanced antitumor activity. Although the definite mechanism that drives higher tumor response is not yet well understood, available evidence suggests a specific coordination effect of combination immunotherapy, thereby increasing tumor sensitivity to combination therapy.[56]

In this study, Atezo-Beva-PBC provided the best ORR for patients with advanced NSCLC without PD-L1 selection. In addition to the known antiangiogenic effects of

Beva, vascular endothelial growth factor (VEGF) inhibition has immunomodulatory effects.[57] Hence, the addition of Beva may enhance the efficacy of Atezo by reversing VEGF-mediated immunosuppression.[58] Beva may increase T-lymphocyte infiltration by neutralizing the VEGF-stimulated tumor angiogenesis.[59] Moreover, ICIs combined with antiangiogenic agentia could shift the hostile immune-suppressive tumor microenvironment toward an immune-active tumor microenvironment.[60] This immunotherapeutic effect may be enhanced by further tissue perfusion and immune cell infiltration.[61] Therefore, the angiogenesis inhibitors, Beva, may act synergistically with ICIs.

Interestingly, Nivo-Ipi-PBC significantly prolonged OS compared with Ipi-PBC. This might derive from Nivo-Ipi-PBC synergistical effect, simultaneously targeting PD-1 and CTLA-4. The most likely explanation is that Ipi promotes T-cell activation and proliferation, whereas Nivo supports existing T cells in targeting tumor cells. In addition, some T cells activated by Ipi can differentiate into memory T cells, which are likely to produce a long-term immune response.[62] Based on this knowledge, one might suggest that Nivo-Ipi-PBC could potentially help patients achieve early disease control. But, further research is necessary for direct comparisons between Nivo-Ipi-PBC and Ipi-PBC.

Regarding safety profiles, the toxicity of ICIs monotherapy or ICI-ICI combination treatment was lower than that of other treatments but was increased by the addition of PBC. Available data suggest that combination therapies provide survival benefits regardless of PD-L1 expression.[12,63,64] Although the specific mechanism is not well understood, preclinical data suggest that anti-DNA-repair agents combined with ICIs may be a promising strategy.[65] However, the increased risk of toxicity due to chemotherapy requires careful consideration.[66]

Cemip presented a well-balanced efficacy and safety profile. The EMPOWER-Lung 1 trial[21] provided strong evidence that Cemip is a new first-line monotherapy option for advanced NSCLC with PD-L1 expression ≥50%. In this trial, compared with chemotherapy, Cemip significantly prolonged OS and PFS, reducing the risk of death by 43.4% and 32.4% in the population with PD-L1 expression ≥50% and intention-to-treat population, respectively.[21] Cemip monotherapy could be ideal in patients with high PD-L1 expression, especially ≥90%, providing a favorable risk-benefit ratio compared with an ICI-chemotherapy combination.[21] Considering these evidence and the fact that the EMPOWER-Lung 1 study showed effective results in NSCLC patients with high PD-L1 expression, especially those with at least 50%, we consider PD-L1 expression as a determinant feature to assess the potential responsiveness to PD-1 pathway blockade.

PD-1/PD-L1 inhibitors and PD-L1 expression status were previously evaluated in different types of cancer, including lung and renal cancers; however, the PD-L1 expression status was found to be insufficient in determining the patients who should be administered PD-1 or PD-L1 blockade therapy.[67] This study revealed that advanced NSCLC patients with high PD-L1 proportions could be ideal candidates for ICIs therapeutics, providing superior benefit when compared to other approaches. A recently published study evaluated immunotherapy combinations for advanced NSCLC and suggested that anti-PD-1 combinations exhibited better survival outcomes than anti-PD-L1 combinations, with comparable safety profiles.[68] In this study, we also evaluated ICI monotherapy for advanced NSCLC, and the results showed that Cemip had well-balanced efficacy and safety in advanced NSCLC. Pairwise traditional meta-analyses evaluated PD-1/PD-L1 inhibitors as the first- or second-line therapy for NSCLC.[69,70] The use of these inhibitors as the first-line therapy for NSCLC was found to be overall better tolerated than chemotherapy.[69] The benefits of PD-1 inhibitors (versus docetaxel) as the second-line treatment option for NSCLC were limited to the PD-L1 >1% subpopulation.[70] In this study, we evaluated ICIs as the first-line therapy for NSCLC using a NMA. Standard pairwise meta-analysis can only compare two drug classes, which are evaluated in head-to-head trials. In a complex condition with several treatment options, some of which have not been directly compared, the NMA can integrate direct evidence from studies to compare particular treatments, indirect evidence from one or several intermediate comparators within a single framework, and even rank treatments per efficacy and safety.[71]

Although encouraging findings have been presented here, some limitations must be considered. First, the data were extracted from published articles lacking individual patient data, which might have resulted in bias in data analysis. Therefore, the results of the subgroup analysis are suggestive and inconclusive. Second, heterogeneity was present among the different ICI monotherapies or combination therapies, with different types of chemotherapy and ICI. Moreover, for different types of PBC, we should consider their distinct synergies with immunotherapy. Besides, not all included chemotherapies have the same effect, which might cause differences in efficacy and risk factors among the various combination treatment strategies. Future investigations are necessary to identify the most efficacious ICI regimen to maximize its benefits. Third, eligible patients in each of the included RCTs exhibited distinct characteristics that might have impacted our results, namely regarding geographic region, tumor histology, and RCT cutoff points. Finally, real-world studies were not included; real-world data are needed to evaluate real-world safety and extend our findings to larger patient populations in the real clinical practice.

In conclusion, this analysis confirmed that therapeutic combinations with anti-PD-1 provided potentially better survival outcomes than anti-PD-L1 combinations. Although ICI-PBC was more likely to improve survival than ICIs alone, the addition of PBC to ICIs increased off-tumor toxicity. Regarding treatment recommendations for advanced NSCLC without PD-L1 selection, Cemip featured a well-balanced efficacy and safety; it ranked first for OS and lowest for any-grade AEs across all

available ICIs. Furthermore, for patients with PD-L1 expression <1%, Pem-PBC and Atezo-Beva-PBC showed the best OS and PFS, respectively. For patients with PD-L1 expression ≥1%, Sint-PBC and Pem-DXT provided the best OS and PFS, respectively. Camre-PBC conferred the best OS and PFS in patients with PD-L1 expression of 1–49%. In patients with PD-L1 expression ≥50%, Durva-Treme-PBC and Atezo-Beva-PBC provided the best OS and PFS, respectively. These findings provide rationale for the current standard of care and future drug combination trials.

### Conflicts of interest

None.

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