Efficacy and Safety of First-Line Immunotherapy Combinations for Advanced NSCLC: A Systematic Review and Network Meta-Analysis

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ABSTRACT

Introduction: A series of randomized controlled trials have investigated different first-line immunotherapy combinations, but the optimal combination strategy is yet to be established.

Methods: We performed a systematic review and Bayesian network meta-analysis by retrieving relevant literature from PubMed, EMBASE, Cochrane Library, ClinicalTrials.gov, and major international conferences. We included published and gray sources of randomized clinical trials comparing immunotherapy combinations with other treatments as first-line treatments for patients with advanced NSCLC. This study was registered in the Prospective Register of Systematic Reviews (CRD42020210501) to ensure transparency.

Results: We analyzed a total of 16 studies involving 8278 patients and including 10 immunotherapy combinations. For patients without programmed death-ligand 1 (PD-L1) selection, pembrolizumab plus chemotherapy was found to be comparable with sintilimab plus chemotherapy in providing the best overall survival (OS) benefit (hazard ratio = 0.96, 95% confidence interval [CI]: 0.72–1.29). Furthermore, atezolizumab plus bevacizumab plus chemotherapy seemed to provide the best progression-free survival (hazard ratio = 0.45, 95% CI: 0.36–0.55) and the best objective response rate (OR = 0.23, 95% CI: 0.12–0.42). Subgroup analysis by PD-L1 suggested that nivolumab plus ipilimumab plus chemotherapy was associated with the best OS in patients with PD-L1 less than 1% and that pembrolizumab plus chemotherapy was associated with the best OS in patients with PD-L1 greater than or equal to 1%. Pembrolizumab and sintilimab were associated with relatively fewer grade greater than or equal to 3 adverse events

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when compared with other immunotherapies combined with chemotherapy.

Conclusions: Our results suggest that antiprogrammed death-1 combinations are associated with potentially higher survival outcomes than anti–PD-L1 combinations with comparable safety profiles. Moreover, pem-chemo and nivo-ipi-chemo seem to be superior first-line immunotherapy combinations for patients with advanced NSCLC with positive and negative PD-L1 expression, respectively. Although atezo-beva-chemo treatment provided the best progression-free survival and objective response rate, the addition of chemotherapy to immunotherapy would increase the toxicity, especially when antiangiogenesis drugs are simultaneously added.

Keywords: Non–-small-cell lung cancer; Immunotherapy combinations; Efficacy; Safety; Network meta-analysis

Introduction

Lung cancer remains to be the leading cause of cancer-related deaths, with NSCLC accounting for approximately 85% of all reported cases.[1,2] Nearly half of all patients with NSCLC are diagnosed only in the advanced or metastatic stages, which limits the treatment options. Historically, platinum-doublet chemotherapy has been the standard first-line care for patients with advanced NSCLC in the absence of targetable genetic alterations.[3] Nevertheless, these interventions provide only limited benefit for the patients and the median overall survival (OS) is less than 1 year.[4,5] This considerable yet marginal benefit is also related to a plethora of side effects that can severely affect quality of life of an individual. Given the prevalence and dismal outcomes associated with advanced NSCLC, global researchers have been working ceaselessly to develop new interventions and combinations to prolong the lifespan of the patients.

Immunotherapy (IO) is one of the most important breakthroughs in cancer treatment, especially immune checkpoint inhibitors (ICIs) that block coinhibitory molecules such as CTLA-4,[6] programmed cell death protein-1 (PD-1), and the related programmed death-ligand 1 (PD-L1).[7,8] Clinical evidence has revealed that pembrolizumab, an anti–PD-1 monoclonal antibody, provides additional benefits in both OS and progression-free survival (PFS) when compared with platinum-based chemotherapy as the first-line treatment for patients with advanced NSCLC.[9,10] Similarly, the anti–PD-L1 antibody atezolizumab also seems to be more effective in prolonging the OS than platinum-based chemotherapy alone for patients with metastatic NSCLC who had previously been treated.[11] Given the encouraging evidence, the U.S. Food and Drug Administration approved a series of ICIs for clinical practice, including pembrolizumab, atezolizumab, nivolumab, ipilimumab, and durvalumab.[12] Nevertheless, this field is still evolving and requires an element of "trial and error" at the clinical level.

The logical next step in the field is to develop combinations that enhance the antitumor activity and offer incremental benefits until a more profound discovery can identify a potentially curative intervention. Cytotoxic agents have been reported to exhibit positive immunomodulatory effects by releasing high levels of tumor antigens and reinstating immunosurveillance, which suggests combining chemotherapy with anti–PD-1 IOs may exhibit a synergistic antitumor effect.[13,14] Recently, a series of randomized controlled trials (RCTs) have investigated different first-line IO combinations, including ICI plus chemotherapy, ICI with antiangiogenesis drugs, and combinations of two types of ICIs. With the increasing number of studies on IO combinations and most trials comparing the results with those from standard chemotherapy, there is an urgent need to establish the optimal combination strategy to help design future clinical studies with head-to-head comparisons.

In this study, we aimed to evaluate the efficacy and safety of all the currently available first-line IO combinations for patients with advanced NSCLC. Systematic review and meta-analysis were performed through adjusted indirect comparisons on the basis of the Bayesian framework approach and subgroup analyses by PD-L1 expression levels, histologic type, and guideline-recommended IO combinations. These studies were intended to identify the optimal IO combinations for specific subpopulations.

Materials and Methods

This network meta-analysis (NMA) was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension statement for network meta-analyses[15] (Supplementary Table 1). The Bayesian approach provides the opportunity to make indirect comparisons between treatments that have not yet been directly compared through trials and offers a more direct method for making probabilistic statements and predictions on treatments and their safety outcomes.[16] The protocol for this study was registered in the Prospective Register of Systematic Reviews to ensure transparency, reliability, and novelty (CRD42020210501).

Data Sources and Search Strategy

PubMed, EMBASE, Cochrane Library, and ClinicalTrials.gov databases were systematically searched for relevant studies conducted until February

1, 2021. To include the updated outcomes, online proceedings from annual conferences that took place from 2018 to 2021 were also sourced. The American Association for Cancer Research, American Society of Clinical Oncology, European Society of Medical Oncology, Chinese Society of Clinical Oncology, and The World Conference on Lung Cancer were included. The keywords for the literature search were "non-small-cell lung cancer, randomized clinical trial, immunotherapy, PD-1, PD-L1, CTLA-4, pembrolizumab, atezolizumab, nivolumab, ipilimumab, durvalumab, tremelimumab, camrelizumab, tislelizumab, and sintilimab" (Supplementary Table 2).

Selection Criteria

Published and gray sources that met the following criteria were included:

(1) RCTs that enrolled patients with advanced NSCLC (stages III–IV) confirmed either histologically or cytologically;
(2) RCTs that used IO combinations as first-line treatment settings;
(3) RCTs comparing IO combinations with other treatment modalities for patients with advanced NSCLC;
(4) Phase II and III trials reporting at least one of the following clinical outcomes:
(5) OS, defined as the time from randomization until death from any cause;
(6) PFS, defined as the time from randomization to disease progression or death from any cause;
(7) Objective response rate (ORR), defined as the proportion of patients who achieved an objective response;
(8) Adverse events (AEs) of any-grade or grade greater than or equal to 3 AEs, which were defined and graded according to the National Cancer Institute Common Terminology Criteria for AEs.

The exclusion criteria were as follows:

(1) RCTs that were based on overlapping patients;
(2) RCTs with ambiguous clinical outcomes.

Titles and abstracts were screened before the assessment of full texts to determine the eligibility. All the included trials were double-checked online to ensure the inclusion of the most recent data.

Data Extraction and Quality Assessment

The data were independently extracted by three investigators (LL, CW, and SL) as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis process, and any discrepancies were resolved through discussions with the other authors (ZW, JD, and PX). The trial name, first author, publication sources, year of publication, trial phase, National Clinical Trials identification number, sample size, patients' age and sex distribution, smoking status, histologic type, PD-L1 expression, and Eastern Cooperative Oncology Group performance status score were extracted from each article. The clinical outcomes extracted included hazard ratios (HRs) with corresponding 95% confidence intervals (95% CIs) for OS and PFS and the incidence of ORR, any-grade AEs, and AEs of grade greater than or equal to 3.

The quality of the included studies was checked using the Cochrane Risk of Bias Tool (2.0) for RCTs, which is based on the following five domains: risk of bias arising from the randomization process, risk of bias owing to deviations from the intended interventions, risk of bias from missing outcome data, risk of bias in the measurement of the outcome, and risk of bias in the selection of the reported result.[17] The included studies were then classified into one of the following three categories: low risk, high risk, and having "some concerns."

Statistical Analysis

The primary outcomes were OS and PFS, and the secondary outcomes were ORR, any-grade AEs, and AEs of grade greater than or equal to 3. HRs with 95% CIs were used as the effect sizes for OS and PFS, and ORs with 95% CIs were used as the effect sizes for ORR, any-grade AEs, and grade greater than or equal to 3 AEs.

Indirect comparisons of IO combinations were firstly performed in a Bayesian framework using a Markov Chain Monte Carlo simulation method with WinBUGS software (version 1.4.3). WinBUGS is part of the Bayesian inference Using Gibbs Sampling project, which aimed to make practical Markov Chain Monte Carlo methods available to applied statisticians. The results were then confirmed by using R software (version 4.0.3) with package gemtc (version 0.8-8) and JAGS software (version 4.3.0) with identical parameter settings. For each outcome measure, a fixed-effects consistency model was used, and three independent Markov chains were established for running 10,000 burn-ins and 15,000 sample iterations per chain simultaneously with one step-size iteration. This process was intended to obtain a posterior distribution, with model convergence of the iterations being evaluated and visualized using trace plots and Brooks-Gelman-Rubin diagnostic. The Bayesian approach also provided overall ranking probabilities for each IO combination, making it possible to rank each outcome measurement from the best to the worst, and were then visualized by calculating the surface under the cumulative ranking curves on the basis of the ranking profiles.

Key assumptions of an NMA include similarity, consistency, and transitivity. The transitivity equation has

the potential to make indirect comparisons.[18] Accordingly, we performed a pairwise meta-analysis on head-to-head comparisons on the basis of the frequentist approach to compare with the corresponding pooled results from the Bayesian framework (Supplementary Table 3). Furthermore, statistical heterogeneity and inconsistency were evaluated using the Q test and the statistic inconsistency index (I^2). An I^2 value greater than 50% is generally considered to indicate a substantial level of heterogeneity, which consequently initiates sensitivity analysis to identify the source[19] (Supplementary Table 4). In addition, similarity and transitivity within the included trials were evaluated with a meta-regression analysis using STATA software (version 15.1). A meta-regression was performed using descriptive statistics for the study and population baselines, including age, sample size, sex, Eastern Cooperative Oncology Group score, smoking status, and presence of liver, brain, or bone metastasis. Four models were then generated on the basis of the covariates of "intervention arms versus control arms," "ICI-chemo combinations versus ICI-ICI combinations," "global studies versus Chinese studies," and "older studies versus recent studies" (Supplementary Table 5).

The Egger regression test with a funnel plot was used to evaluate the publication bias, and a p value of less than 0.10 was considered to indicate significant asymmetry and publication bias. All tests were two-sided, and a p value of less than 0.05 was considered statistically significant.

Results

Systematic Review and Characteristics of the Included Studies

We identified a total of 3985 records from the databases and 112 additional online records from the conference proceedings during the preliminary literature search. After eliminating the duplicates and nonpertinent articles through abstract screening, 150 studies were considered eligible for full-text review and 16 studies finally met our eligibility criteria (Fig. 1).[20–35] A total of 9070 patients were enrolled to receive the following 12 treatments: pembrolizumab plus chemotherapy (pem-chemo), atezolizumab plus chemotherapy (atezo-chemo), atezolizumab plus bevacizumab plus chemotherapy (atezo-beva-chemo), camrelizumab plus chemotherapy (camre-chemo), tislelizumab plus chemotherapy (tisle-chemo), sintilimab plus chemotherapy (sint-chemo), nivolumab plus ipilimumab (nivo-ipi); nivolumab plus ipilimumab plus chemotherapy (nivo-ipi-chemo), durvalumab plus tremelimumab (durva-treme), durvalumab plus tremelimumab plus chemotherapy (durva-treme-chemo), chemotherapy (chemo), and bevacizumab plus chemotherapy (beva-chemo). Detailed information on all the included studies has been presented in Tables 1 and 2, and Supplementary Table 6.

The network plots are depicted in Figure 2. The beva-chemo treatment merely served as a transitivity node to generate indirect comparisons and is therefore not presented in our further analyses. Only wild-type populations from IMpower-130 and IMpower-150 cohorts were included in this study to minimize the heterogeneity. The assessment of risk of bias is presented in Supplementary Fig. 1. The Egger regression test was carried out to determine the publication bias and a p value of 0.59 was obtained, suggesting the absence of publication bias in the included studies (Supplementary Fig. 2).

Comparisons of OS, PFS, and ORR

The primary outcomes were OS and PFS, and the secondary outcome of interest was ORR. NMA included 10 IO combinations for OS, PFS, and ORR in patients with advanced NSCLC without PD-L1 selection (Fig. 2*A*).

Regarding OS (Fig. 3*A*), patients who received IO combinations were more likely to obtain greater OS benefit than those who received standard chemotherapy, and sint-chemo yielded the best OS benefit compared with chemotherapy (HR = 0.59, 95% CI: 0.45–0.77). Pem-chemo was also found to be comparable to sint-chemo in providing OS benefit (HR = 0.96, 95% CI: 0.72–1.29). Treatment regimens containing anti–PD-1 were found to yield superior OS benefit when compared with not only anti–PD-L1 but also anti–CTLA-4 treatments. Furthermore, pem-chemo was discerned to offer marked benefits on comparison with durva-treme (HR = 0.65, 95% CI: 0.53–0.78), atezo-chemo (HR = 0.73, 95% CI: 0.62–0.86), durva-treme-chemo (HR = 0.73, 95% CI: 0.54–0.98), atezo-beva-chemo (HR = 0.76, 95% CI: 0.59–0.99), and nivo-ipi (HR = 0.83, 95% CI: 0.70–0.99).

Regarding PFS (Fig. 3*A*), IO combinations revealed consistently better PFS than standard chemotherapy. The only exception was durva-treme, which was found to have the worst PFS of all treatments. Among the IO combinations, atezo-beva-chemo provided the best PFS benefit versus chemotherapy (HR = 0.45, 95% CI: 0.36–0.55), followed by sint-chemo (HR = 0.51, 95% CI: 0.44–0.60) and pem-chemo (HR = 0.54, 95% CI: 0.49–0.61). Significant differences were also observed when comparing the anti–PD-1 combinations with the anti–PD-L1 combinations, in which pem-chemo (HR = 0.84, 95% CI: 0.72–0.96) and sint-chemo (HR = 0.79, 95% CI: 0.66–0.94) had higher PFS than atezo-chemo. Similar efficacies were noted across the anti–PD-1 plus

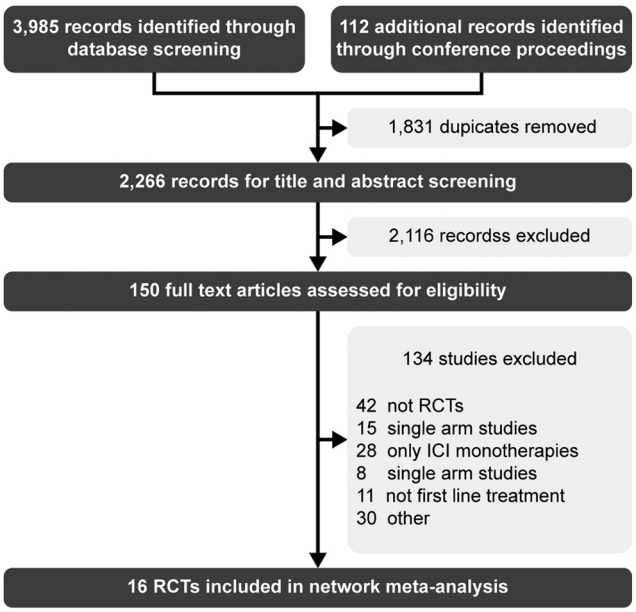

Figure 1. Literature search and selection. The study process followed the PRISMA guidelines. ICI, immune checkpoint inhibitor; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCT, randomized controlled trial.

chemotherapy combinations, including pem-chemo, sint-chemo, camre-chemo, and tisle-chemo, and the HRs ranged from 0.91 to 0.99.

Regarding ORR (Fig. 3*B*), the efficacy results were similar to those of PFS, whereas durva-treme still remained the only IO combination that did not improve the ORR than standard chemotherapy. Atezo-beva-chemo was observed to be the best treatment with regard to the objective response (OR = 0.23, 95% CI: 0.12–0.42), which was followed by pem-chemo (OR = 0.38, 95% CI: 0.26–0.54). Although significant differences were not perceived, anti–PD-1 still exhibited a potential advantage than anti–PD-L1 when combined with chemotherapy.

Safety and Toxicity

Safety and toxicity were determined according to any-grade AEs and grade greater than or equal to 3 AEs. NMA included nine IO combinations for AEs of any-grade and 10 IO combinations for AEs of grade greater than or equal to 3 (Fig. 2*B*).

The toxicity was found to be the lowest for the ICI-ICI combinations across all treatments, including nivo-ipi and durva-treme, with the fewest AEs (Figs. 3*B* and 4*A*). Nevertheless, the addition of chemotherapy to IO elevated the toxicity when compared with standard chemotherapy, especially when antiangiogenesis drugs were simultaneously added, such as atezo-beva-chemo (HR = 5.61, 95% CI: 3.25–9.84). Pem-chemo and sint-chemo were associated with relatively fewer grade greater than or equal to 3 AEs than the other ICI-chemo combinations. No new safety signals were identified with the combinations. The treatment-related AEs that were frequently reported for the IO combinations included fatigue, anemia, vomiting, diarrhea, anorexia, constipation, neutropenia, and asthenia. The immune-mediated AEs were hypothyroidism, hyperthyroidism, rashes, pruritis, pneumonitis, and colitis (Supplementary Table 7).

Differences in the probabilities of these specific AEs were noted across IO combinations. Durva-treme-chemo exhibited the highest probability of causing fatigue, nausea, anemia, vomiting, diarrhea, neutropenia, rashes, pruritus, and colitis. In contrary, nivo-ipi and durva-treme were associated with the least risk of developing fatigue, nausea, anemia, vomiting, constipation, neutropenia, asthenia, and hyperthyroidism (Fig. 4*B*). The incidence of treatment-related AEs, such as anemia, diarrhea, and neutropenia, varied widely across the treatment regimens, whereas immune-mediated AEs, such as hypothyroidism, hyperthyroidism, and pneumonitis, had the most narrow incidence spectrums (Fig. 4*B*).

Rankings

Ranking analysis was performed on the basis of the Bayesian ranking profiles (Supplementary Table 8). The ranking results were consistent with the direct and indirect pooled results obtained using HRs and ORs, implying the stability and reliability of the framework (Fig. 5). For patients with NSCLC without a selection of PD-L1, sint-chemo was most likely to rank first for OS (cumulative probability of 29%), atezo-beva-chemo for both PFS (72%) and ORR (86%), durva-treme for any-grade AEs (58%), and nivo-ipi for AEs of grade greater than or equal to 3 (91%). Atezo-beva-chemo (91%) and camre-chemo (79%) displayed the highest probabilities of ranking last in causing grade greater than or equal to 3 AEs and any-grade AEs, respectively. In case of pem-chemo, an effective balance between efficacy and safety was achieved, and the treatment ranked second for OS (30%) and ORR (28%), third for PFS (31%), and fourth for grade greater than or equal to 3 AEs (24%).

Subgroup Analysis

On the basis of PD-L1 Expression Level. While considering the clinical outcomes of patients with advanced NSCLC with different PD-L1 expression levels, only OS and PFS could be estimated in the subgroup analysis. The patients were divided into the following four subgroups according to the levels of PD-L1 expression: less than 1%, greater than or equal to 1%, 1% to 49%, and greater than or equal to 50%. The

Table 1. Baseline Characteristics of Studies Included in the Network Meta-Analysis

Study (Phase, Design)	Source (y)	Registered ID (Randomization)	Sample Size (Median Age/y)	Stage (Male/Female)	Histology	Ethnicity (%)	Intervention Arm(s)	Control Arm
KEYNOTE-021G (II, open-label)	*JTO* (2019)	NCT02039674 (1:1)	60/63 (62.5/63.2)	IIIB–IV (48/75)	Nonsquamous	White (87.0) Asian (8.1) Black (3.3) Other (1.6)	Pembrolizumab 200 mg Q3W + chemotherapy (carboplatin AUC 5 + pemetrexed 500 mg/m^2 Q3W)	Chemotherapy (carboplatin AUC 5 + pemetrexed 500 mg/m^2 Q3W)
KEYNOTE-189 (III, double-blind)	*ASCO* (2020)	NCT02578680 (2:1)	410/206 (65/63.5)	IV (363/253)	Nonsquamous	White (86.2) Asian (1.6) Black (NR) Other (12.2)	Pembrolizumab 200 mg Q3W + chemotherapy (carboplatin AUC 5 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 Q3W)	Chemotherapy (carboplatin AUC 5 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 Q3W)
KEYNOTE-407 (III, double-blind)	*JTO* (2020)	NCT02775435 (1:1)	278/281 (65/65)	IV (455/104)	Squamous	White (NR) Asian (19.0) Black (NR) Other (NR)	Pembrolizumab 200 mg Q3W + chemotherapy (carboplatin AUC 6 + paclitaxel 200 mg/m^2 Q3W)	Chemotherapy (carboplatin AUC 6 + paclitaxel 200 mg/m^2 Q3W)
IMpower-130[a] (III, open-label)	*Lancet Onco* (2019)	NCT02367781 (2:1)	451/228 (64/65)	IV (400/279)	Nonsquamous	White (90.1) Asian (2.3) Black (3.8) Other (3.8)	Atezolizumab 1200 mg Q3W + chemotherapy (carboplatin AUC 6 Q3W + nab-paclitaxel 100 mg/m^2 QW)	Chemotherapy (carboplatin AUC 6 Q3W + nab-paclitaxel 100 mg/m^2 QW)
IMpower-131 (III, open-label)	*JTO* (2020)	NCT02367794 (1:1:1)	338/343/340 (66/65/65)	IV (835/186)	Squamous	White (85.1) Asian (11.0) Black (1.4) Other (2.5)	Atezolizumab 1200 mg Q3W + chemotherapy (carboplatin AUC 6 Q3W + nab-paclitaxel 100 mg/m^2 Q3W)	Chemotherapy (carboplatin AUC 6 Q3W + nab-paclitaxel 100 mg/m^2 QW)
IMpower-132 (III, open-label)	*JTO* (2018)	NCT02657434 (1:1)	292/286 (64/63)	IV (384/194)	Nonsquamous	White (68.5) Asian (23.5) Black (NR) Other (NR)	Atezolizumab 1200 mg Q3W + chemotherapy (carboplatin AUC 6 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 Q3W)	Chemotherapy (carboplatin AUC 6 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 Q3W)
IMpower-150[a]	*AACR*	NCT02366143	356/350/336	IV	Nonsquamous	White (82.1)	Arm 1: Atezolizumab 1200 mg Q3W + bevacizumab	Bevacizumab 15 mg/kg Q3W

(continued)

Table 1. Continued

Study (Phase, Design)	Source (y)	Registered ID (Randomization)	Sample Size (Median Age/y)	Stage (Male/Female)	Histology	Ethnicity (%)	Intervention Arm(s)	Control Arm
(III, open-label)	(2020)	(1:1:1)	(63/62/63)	(625/417)		Asian (12.5) Black (1.5) Other (3.9)	15 mg/kg Q3W + chemotherapy (carboplatin AUC 6 + paclitaxel 200 mg/m^2 Q3W) Arm 2: Atezolizumab 1200 mg Q3W + chemotherapy (carboplatin AUC 6 + paclitaxel 200 mg/m^2 Q3W)	+ chemotherapy (carboplatin AUC 6 + pemetrexed 200 mg/m^2 Q3W)
CheckMate-9LA	*ASCO*	NCT03215706	361/358	IV	NSCLC	White (89.2)	Nivolumab 350 mg Q3W + ipilimumab 1 mg/kg Q6W	Chemotherapy (carboplatin AUC 6
(III, open-label)	(2020)	(1:1)	(65/65)	(215/504)		Asian (8.3) Black (1.4) Other (1.1)	+ chemotherapy (carboplatin AUC 6 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 Q3W)	or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 Q3W)
CheckMate-227	*ASCO*	NCT02477826	583/583	IV	NSCLC	White (63.3)	Arm 1: Nivolumab 3 mg/kg Q2W	Chemotherapy (carboplatin AUC 6
part 1 (III, open-label)	(2020)	(1:1)	(64/64)	(787/402)		Asian (19.2) Black (NR) Other (17.2)	+ ipilimumab 1 mg/kg Q6W Arm 2: Nivolumab 240 mg Q2W	or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 Q3W)
MYSTIC	*Jama Onco*	NCT02453282	374/372/372	IV	NSCLC	White (66.6)	Arm 1: Durvalumab 20 mg/kg	Chemotherapy (carboplatin AUC 6
(III, open-label)	(2020)	(1:1:1)	(64/65/64.5)	(772/346)		Asian (32.0) Black (1.4) Other (0.0)	+ tremelimumab 1 mg/kg Q4W Arm 2: Durvalumab 20 mg/kg Q4W	or cisplatin 75 mg/m^2) + pemetrexed 500 mg/m^2 Q3W)
CameL	*Lancet Respir Med*	NCT03134872	205/207	IIIB–IV	Nonsquamous	White (0.0)	Camrelizumab 200 mg Q3W	Chemotherapy (carboplatin AUC 5
(III, open-label)	(2020)	(1:1)	(59/61)	(295/117)		Asian (100.0) Black (0.0) Other (0.0)	+ chemotherapy (carboplatin AUC 5 + pemetrexed 500 mg/m^2 Q3W)	+ pemetrexed 500 mg/m^2 Q3W)
CCTG BR-34	*ASCO*	NCT03057106	151/150	IV	NSCLC	White (91.7)	Durvalumab 1500 mg + tremelimumab 75 mg Q4W	Durvalumab 1500 mg
(III, open-label)	(2020)	(1:1)	(65/63)	(162/139)		Asian (4.3)	+ chemotherapy (carboplatin AUC 6	+ tremelimumab 75 mg Q4W

(continued)

Table 1. Continued

Study (Phase, Design)	Source (y)	Registered ID (Randomization)	Sample Size (Median Age/y)	Stage (Male/Female)	Histology	Ethnicity (%)	Intervention Arm(s)	Control Arm
						Black (1.3) Other (2.7)	or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 Q3W)	
RATIONALE-304 (III, open-label)	ESMO (2020)	NCT03663205 (2:1)	223/111 (60/61)	IIIB–IV (247/87)	Nonsquamous	White (0.0) Asian (100.0) Black (0.0) Other (0.0)	Tislelizumab 200 mg + chemotherapy (carboplatin AUC 5 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 Q3W)	Chemotherapy (carboplatin AUC 5 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 Q3W)
RATIONALE-307 (III, open-label)	JAMA Onco (2021)	NCT03594747 (1:1:1)	120/119/121 (60/63/62)	IIIB–IV (330/30)	Squamous	White (0.0) Asian (100.0) Black (0.0) Other (0.0)	Arm 1: Tislelizumab 200 mg + chemotherapy (carboplatin AUC 5 + paclitaxel 175 mg/m^2 Q3W) Arm 2: Tislelizumab 200 mg + chemotherapy (carboplatin AUC 5 Q3W + nab-paclitaxel 100 mg/m^2 QW)	Chemotherapy (carboplatin AUC 5 + paclitaxel 175 mg/m^2 Q3W)
ORIENT-11 (III, double-blind)	*JTO* (2020)	NCT03607539 (2:1)	266/131 (61/61)	IIIB–IV (303/94	Nonsquamous	White (0.0) Asian (100.0) Black (0.0) Other (0.0)	Sintilimab 200 mg + chemotherapy (carboplatin AUC 5 or cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2 Q3W)	Chemotherapy (carboplatin AUC 5 or cisplatin 75 mg/m^2) + pemetrexed 500 mg/m^2 Q3W)
ORIENT-12 (III, double-blind)	*ESMO* (2020)	NCT03629925 (1:1)	179/178 (64/62)	IIIB–IV (327/30)	Squamous	White (0.0) Asian (100.0) Black (0.0) Other (0.0)	Sintilimab 200 mg + chemotherapy (gemcitabine 1 g/m^2, d 1, 8 + carboplatin AUC 5, d 1 or cisplatin 75 mg/m^2 Q3W)	Chemotherapy (gemcitabine 1 g/m^2, d 1, 8 + carboplatin AUC 5, d 1 or cisplatin 75 mg/m^2 Q3W)

Note: Data are presented as intervention/control unless indicated otherwise.

[a]Only wild-type population from IMpower-130 and IMpower-150 cohorts are included.

NR, not reported; AACR, American Association for Cancer Research; ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; WCLC, World Conference on Lung Cancer; *Jama Onco, Jama Oncology; JTO, Journal of Thoracic Oncology; Lancet Onco, Lancet Oncology; Lancet Respir Med, Lancet Respiratory Medicine;* AUC, area under curve; QW, every week; Q3W, every three weeks; Q4W, every four weeks; Q6W, every six weeks.

Table 2. Characteristics of Included Randomized Controlled Trials

			PD-L1 < 1% Patients (%)		PD-L1 1%-49% Patients (%)		PD-L1 ≥ 50% Patients (%)		
Study	Actionable Mutations	PD-L1 Detection	Intervention(s), n (%)	Control	Intervention(s), n (%)	Control, n (%)	Intervention(s), n (%)	Control, n (%)	Reported Outcomes
KEYNOTE-021G	Without *EGFR* or *ALK* alterations	22C3 pharmDx	21 (35.0)	23 (36.5%)	19 (31.7)	23 (36.5)	20 (33.3)	17 (27.0)	OS, PFS, ORR, any-grade AEs, grade ≥3 AEs
KEYNOTE-189	Without *EGFR* or *ALK* alterations	22C3 pharmDx	127 (32.8)	63 (33.0%)	128 (33.1)	58 (30.4)	132 (34.1)	70 (36.6)	OS, PFS, ORR, any-grade AEs, grade ≥3 AEs
KEYNOTE-407	Unselected[a]	22C3 pharmDx	95 (35.1)	99 (35.9%)	103 (38.0)	104 (37.7)	73 (26.9)	73 (26.4)	OS, PFS, ORR, any-grade AEs, grade ≥3 AEs
IMpower-130	Without *EGFR* or *ALK* alterations[b]	SP142	235 (52.1)	121 (53.1%)	128 (28.4)	65 (28.5)	88 (19.5)	42 (18.4)	OS, PFS, ORR, any-grade AEs, grade ≥3 AEs
IMpower-131	Unselected[a]	SP142	160 (46.6)	171 (50.3%)	136 (39.7)	125 (36.8)	47 (13.7)	44 (12.9)	OS, PFS, ORR, any-grade AEs, grade ≥3 AEs
IMpower-132	Without *EGFR* or *ALK* alterations	SP142	88 (50.0)	75 (44.6%)	63 (35.8)	73 (43.5)	25 (14.2)	20 (11.9)	OS, PFS, ORR, any-grade AEs, grade ≥3 AEs
IMpower-150	Without *EGFR* or *ALK* alterations[b]	SP142	331 (46.6)	334 (49.7%)	119 (33.4)	105 (31.3)	71 (19.9)	64 (19.0)	OS, PFS, ORR, any-grade AEs, grade ≥3 AEs
CheckMate-9LA	Without *EGFR* or *ALK* alterations	28-8 pharmDx	144 (40.0)	140 (39.0%)	138 (38.0)	114 (32.0)	79 (22.0)	104 (29.0)	OS, PFS, ORR, any-grade AEs, grade ≥3 AEs
CheckMate-227	Without *EGFR* or *ALK* alterations	28-8 pharmDx	187 (32.1)	186 (31.9%)	191 (32.8)	205 (35.2)	205 (35.1)	192 (32.9)	OS, PFS, ORR, any-grade AEs, grade ≥3 AEs
MYSTIC	Without *EGFR* or *ALK* alterations	SP263	76 (20.4)	83 (22.3%)	188 (50.5)	182 (48.9)	108 (29.0)	107 (28.8)	OS, PFS, ORR, any-grade AEs, grade ≥3 AEs
CameL	Without *EGFR* or *ALK* alterations	22C3 pharmDx	49 (24.3)	69 (37.1%)	108 (58.1)	97 (52.2)	30 (15.6)	20 (10.7)	OS[c], PFS, ORR, any-grade AEs, grade ≥3 AEs
CCTG BR-34	Without *EGFR* or *ALK* alterations	SP263	55 (42.6)	61 (46.2%)	44 (34.1)	44 (33.3)	30 (23.3)	27 (20.5)	OS, PFS, ORR, any-grade AEs, grade ≥3 AEs
RATIONALE-304	Without *EGFR* or *ALK* alterations	SP263	96 (43.0)	48 (43.2%)	53 (23.8)	27 (24.3)	74 (33.2)	36 (32.4)	OS[c], PFS, ORR, any-grade AEs, grade ≥3 AEs
RATIONALE-307	Without *EGFR* or *ALK* alterations	SP263	95 (39.7)	49 (40.5%)	60 (25.1)	31 (25.6)	84 (35.1)	41 (33.9)	PFS, ORR, any-grade AEs
ORIENT-11	Without *EGFR* or *ALK* alterations	22C3 pharmDx	85 (32.0)	44 (33.6%)	74 (27.8)	26 (19.8)	107 (40.2)	61 (46.6)	OS[c], PFS, ORR, any-grade AEs, grade ≥3 AEs
ORIENT-12	Without *EGFR* or *ALK* alterations	22C3 pharmDx	59 (33.0)	63 (35.4%)	NR	NR	NR	NR	OS[c], PFS, ORR, any-grade AEs, grade ≥3 AEs

[a]KEYNOTE-407 and IMpower-131 recruited patients with squamous NSCLC, and testing for *EGFR* and *ALK* status was not mandated.
[b]Only wild-type population from IMpower-130 and IMpower-150 cohorts were included.
[c]OS was continuously followed up.
AE, adverse event; NR, not reported; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

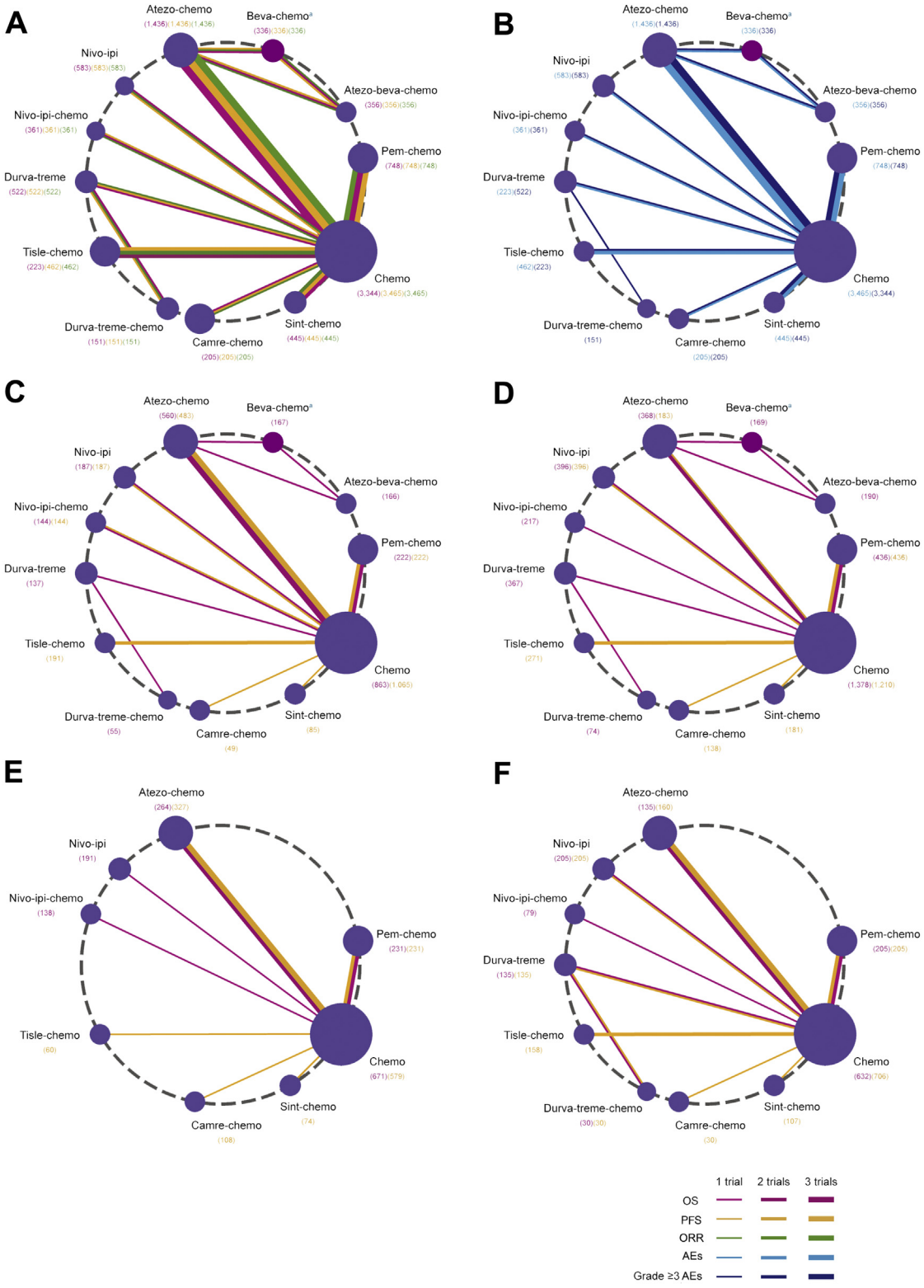

Figure 2. Comparative network plots for efficacy and toxicity of immunotherapy combinations in different populations of patients with advanced NSCLC according to the PD-L1 expression. Comparisons were generated by using the Bayesian framework on (*A*) OS, PFS, ORR, (*B*) any-grade AEs, and AEs of grade $\geq$ 3 in patients without PD-L1 selection. Comparisons of OS and PFS in patients with (*C*) PD-L1 $<$ 1%, (*D*) PD-L1 $\geq$ 1%, (*E*) PD-L1 1%–49%, and (*F*) PD-L1 $\geq$ 50%. Each circle represents an intervention as a node in the network. The size of the circle and the width of the line are proportional to the number of randomized controlled trials and comparisons, respectively. [b]The beva-chemo treatment served only as a transitivity node to generate indirect comparisons. AEs, adverse events; Atezo, atezolizumab; Beva, bevacizumab; Camre, camrelizumab; Chemo, chemotherapy; Durva, durvalumab; Ipi, ipilimumab; Nivo, nivolumab; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; Pem, pembrolizumab; PFS, progression-free survival; Sint, sintilimab; Tisle, tislelizumab; Treme, tremelimumab.

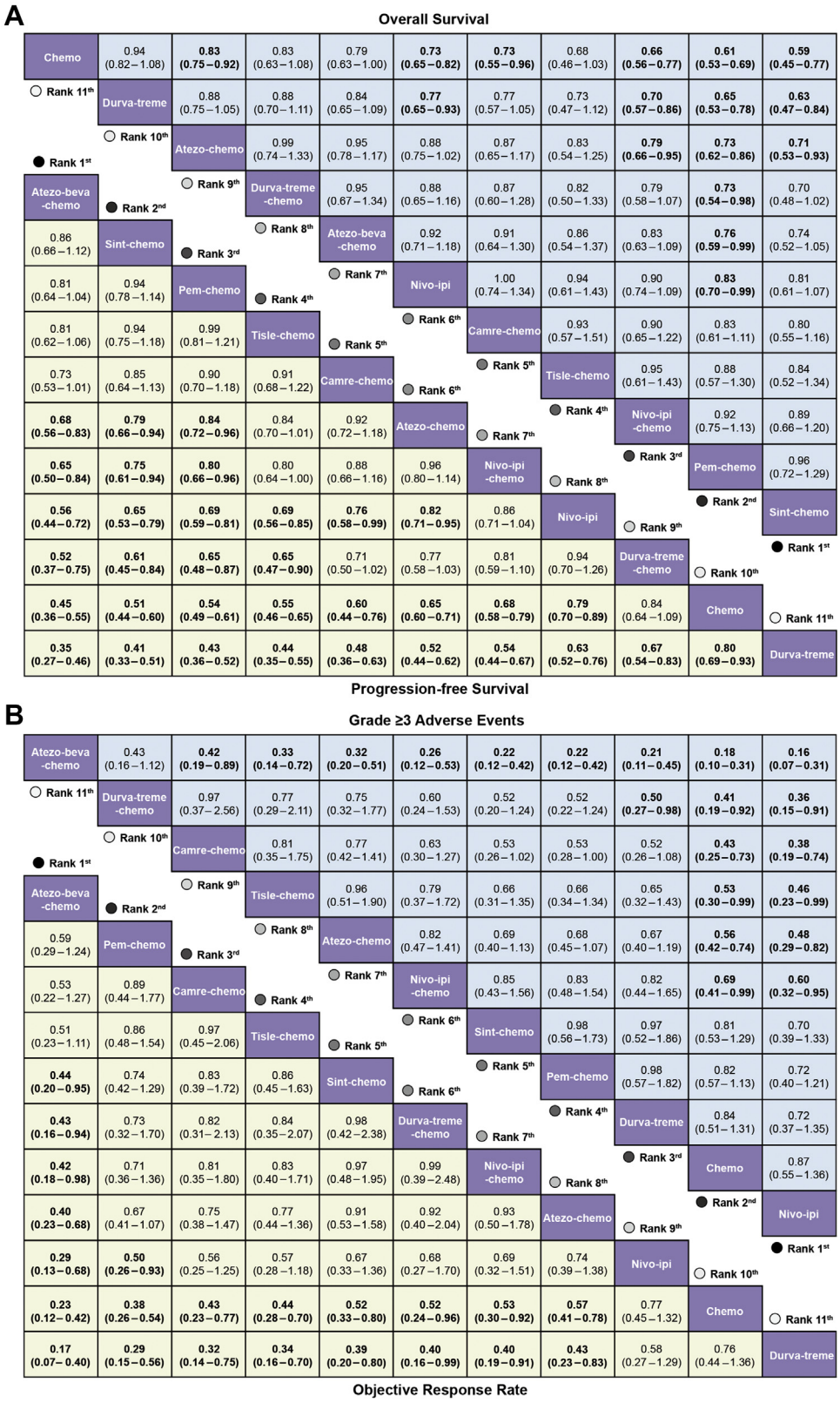

Figure 3. Efficacy and safety profiles of the Bayesian network meta-analysis in patients with advanced NSCLC without PD-L1 selection. (*A*) Hazard ratios and 95% CIs for overall survival (upper triangle in blue) and progression-free survival (lower triangle in yellow), and a hazard ratio < 1.00 provides better survival benefits. (*B*) ORs and 95% CIs for grade ≥ 3 adverse events (upper triangle in blue) and objective response rate (lower triangle in yellow), and an OR < 1.00 indicates a better efficacy or safety. The results are presented as column-defined treatment versus row-defined treatment. Atezo, atezolizumab; Beva, bevacizumab; Camre, camrelizumab; Chemo, chemotherapy; CI, confidence interval; Durva, durvalumab; Ipi, ipilimumab; Nivo, nivolumab; Pem, pembrolizumab; Sint, sintilimab; Tisle, tislelizumab; Treme, tremelimumab.

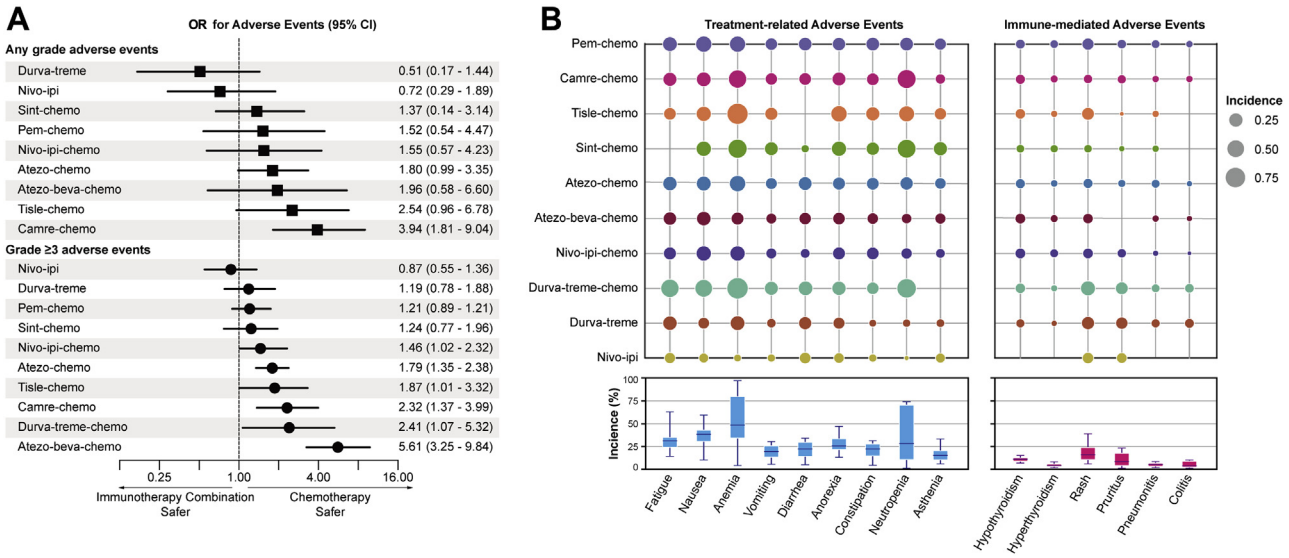

Figure 4. Safety profiles of immunotherapy combinations. (*A*) A forest plot of any-grade adverse events and grade ≥ 3 adverse events for immunotherapy combinations compared with standard chemotherapy, and an OR < 1.00 indicates a better safety. (*B*) Incidence of treatment-related and immune-mediated adverse events. Atezo, atezolizumab; Beva, bevacizumab; Camre, camrelizumab; Chemo, chemotherapy; CI, confidence interval; Durva, durvalumab; Ipi, ipilimumab; Nivo, nivolumab; Pem, pembrolizumab; Sint, sintilimab; Tisle, tislelizumab; Treme, tremelimumab.

optimal IO combination differed across the four subpopulations (Supplementary Fig. 3).

In patients with PD-L1 less than 1%, 10 IO combinations were included in the subgroup analysis (Fig. 2*C*). Regarding OS (Fig. 6*A*), nivo-ipi-chemo (HR = 0.62, 95% CI: 0.47–0.81), nivo-ipi (HR = 0.62, 95% CI: 0.51–0.76), pem-chemo (HR = 0.71, 95% CI: 0.57–0.88), and durva-treme (HR = 0.73, 95% CI: 0.54–0.98) were superior to chemotherapy alone. As for PFS (Fig. 6*B*), nivo-ipi-chemo (HR = 0.62, 95% CI: 0.48–0.81), atezo-chemo (HR = 0.70, 95% CI: 0.61–0.79), tisle-chemo (HR = 0.70, 95% CI: 0.54–0.90), pem-chemo (HR = 0.71, 95% CI: 0.58–0.86), and nivo-ipi (HR = 0.75, 95% CI: 0.61–0.92) were more beneficial than standard chemotherapy.

For patients with PD-L1 greater than or equal to 1%, NMA also included 10 IO combinations in the subgroup analysis (Fig. 2*D*). Pem-chemo (HR = 0.58, 95% CI: 0.49–0.69), nivo-ipi-chemo (HR = 0.64, 95% CI: 0.52–0.79), and nivo-ipi (HR = 0.79, 95% CI: 0.67–0.93) were associated with significantly prolonged OS when compared with chemotherapy (Fig. 6*A*). All IO combinations, especially the anti–PD-1 plus chemotherapy combinations, resulted in significantly improved PFS versus chemotherapy (Fig. 6*B*).

In patients with PD-L1 at 1% to 49%, seven IO combinations were available for comparison (Fig. 2*E*). Pem-chemo provided the best OS when compared with chemotherapy (HR = 0.58, 95% CI: 0.46–0.73), and nivo-ipi-chemo was found to be comparable to pem-chemo in improving OS (HR = 0.94, 95% CI: 0.66–1.36). The IO combinations consistently revealed significant improvements in PFS than chemotherapy (Fig. 6*B*). In addition, tisle-chemo yielded the best benefit of all IO combinations regarding PFS (HR = 0.38, 95% CI: 0.25–0.57).

In patients with PD-L1 greater than or equal to 50%, nine IO combinations were included in the subgroup analysis (Fig. 2*F*). Except for durva-treme, the pooled results suggested that the patients obtained significantly higher OS benefit from IO combinations than from standard chemotherapy (Fig. 6*A*). Among the combinations, pem-chemo (HR = 0.51, 95% CI: 0.37–0.68) and durva-treme-chemo (HR = 0.49, 95% CI: 0.31–0.80) were most likely to be the best treatments in providing OS benefit. Sint-chemo (HR = 0.31, 95% CI: 0.21–0.45), pem-chemo (HR = 0.36, 95% CI: 0.29–0.46), camre-chemo (HR = 0.39, 95% CI: 0.17–0.87), tisle-chemo (HR = 0.41, 95% CI: 0.31–0.54), atezo-chemo (HR = 0.47, 95% CI: 0.37–0.60), and nivo-ipi (HR = 0.62, 95% CI: 0.51–0.76) significantly prolonged PFS when compared with chemotherapy (Fig. 6*B*). Nevertheless, the efficacies of durva-treme and chemotherapy were similar, and the HR was close to 1.00 (HR = 1.05, 95% CI: 0.77–1.43).

On the basis of Histologic Type and National Comprehensive Cancer Network-Recommended IO Combinations. The optimal IO combination differed between the patients with squamous and nonsquamous lung cancer. Sint-chemo and pem-chemo provided the best OS benefit for patients with squamous and nonsquamous lung cancer, respectively, whereas tisle-chemo and atezo-beva-chemo yielded the best PFS benefit for patients with squamous and nonsquamous lung cancer, respectively (Supplementary Fig. 4A).

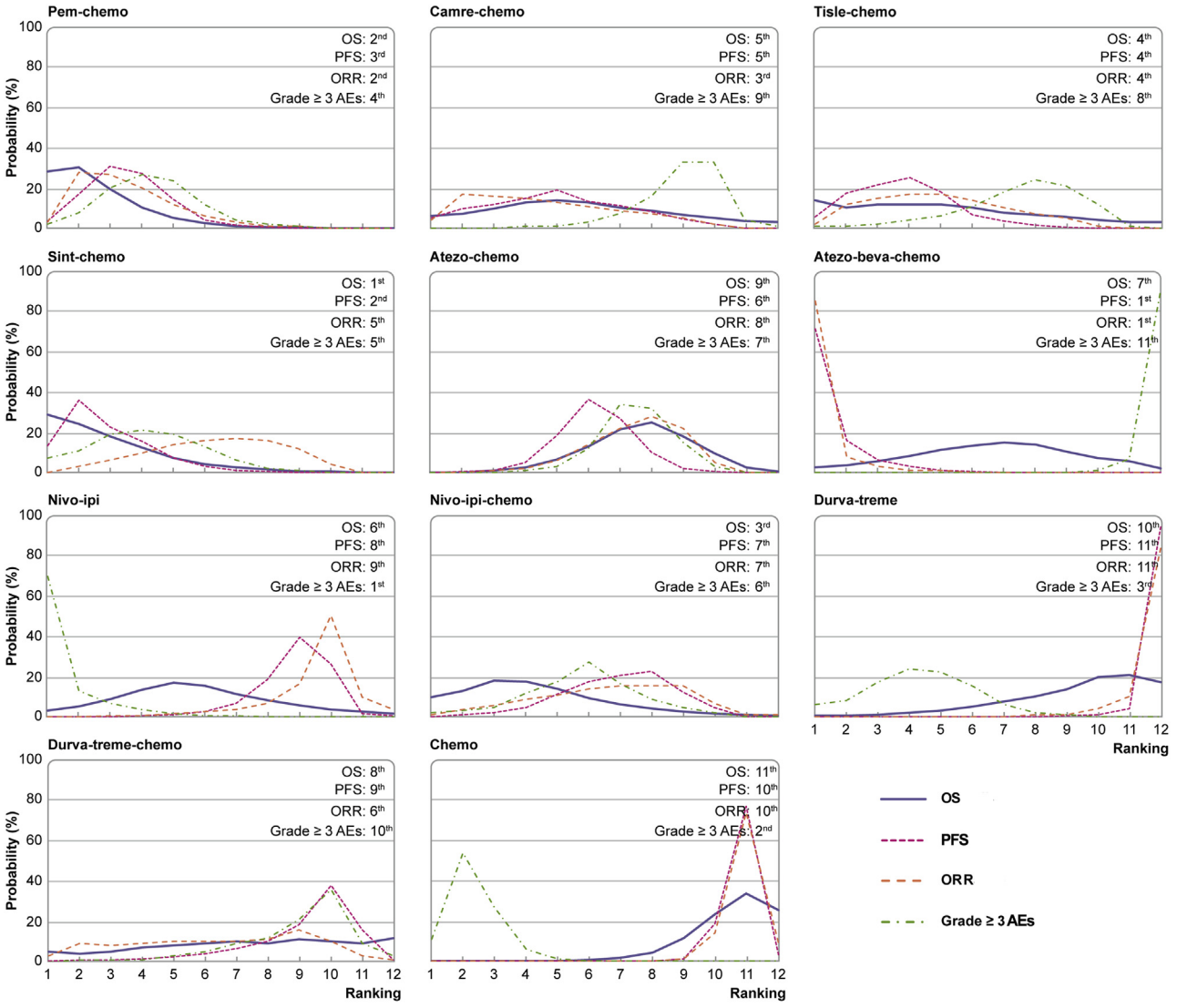

Figure 5. Bayesian ranking profiles for immunotherapy combinations on efficacy and safety for patients with advanced NSCLC without PD-L1 selection. Ranking plots indicate the probability of each comparable immunotherapy combination being ranked from first to last on OS, PFS, objective response rate, and AEs of grade $\geq$ 3. AE, adverse event; Atezo, atezolizumab; Beva, bevacizumab; Camre, camrelizumab; Chemo, chemotherapy; Durva, durvalumab; Ipi, ipilimumab; Nivo, nivolumab; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; Pem, pembrolizumab; PFS, progression-free survival; Sint, sintilimab; Tisle, tislelizumab; Treme, tremelimumab.

Nine studies involving a total of five IO combinations that were recommended by the National Comprehensive Cancer Network (NCCN) clinical practice guidelines were included in a subgroup owing to their high quality and relatively mature data for OS (Supplementary Fig. 5). The pooled results were consistent with those from the original NMA (Supplementary Fig. 4B).

Heterogeneity, Inconsistency, and Transitivity Assessment

The convergence of the calculated model was estimated using the history feature, and Brooks-Gelman-Rubin diagnostic revealed the stability and replicability of the inferential iterations for each Markov Chain Monte Carlo chain (Supplementary Figs. 6 and 7). The results of pairwise meta-analysis on the basis of the frequentist approach were consistent with the corresponding pooled results from the Bayesian framework (Supplementary Table 3). This finding indicates favorable transitivity and consistency among the included trials while generating direct and indirect comparisons. Evaluation of heterogeneity and inconsistency using the Q test and the I^2 statistic also signified minimal ($I^2 = 0\%$) or low heterogeneity ($I^2 < 25\%$) across the included trials (Supplementary Table 4). In addition, according to the meta-regression results, similarity in the clinical characteristics was observed across all the included studies, which implies that the transitivity of the trials was

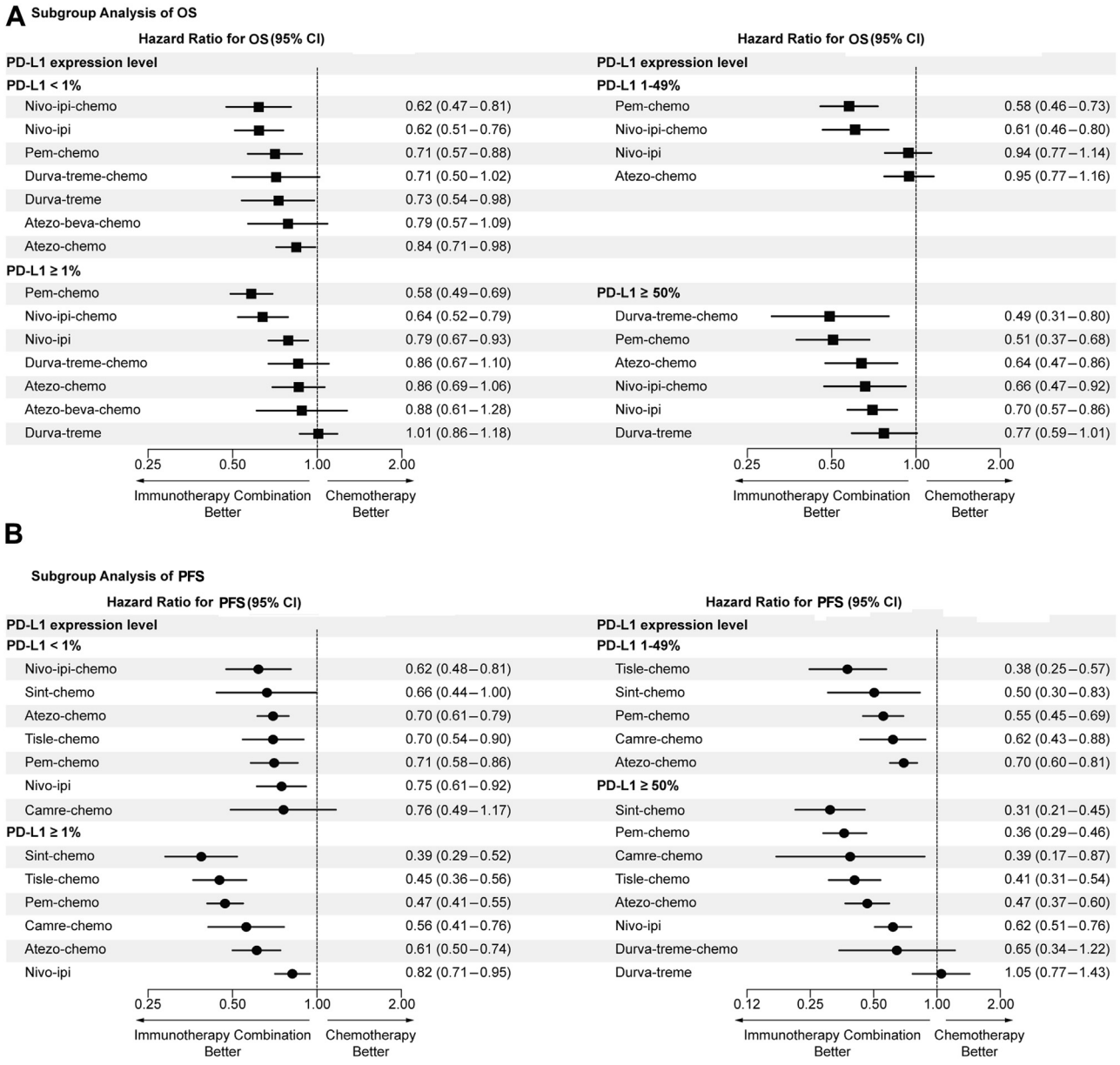

Figure 6. Forest plots of the subgroup analysis in patients with advanced NSCLC according to the PD-L1 expression. Hazard ratios and 95% CIs for overall survival (A) and progression-free survival (B). Hazard ratios < 1.00 provide a better survival benefit. Atezo, atezolizumab; Beva, bevacizumab; Camre, camrelizumab; Chemo, chemotherapy; CI, confidence interval; Durva, durvalumab; Ipi, ipilimumab; Nivo, nivolumab; PD-L1, programmed death-ligand 1; Pem, pembrolizumab; Sint, sintilimab; Tisle, tislelizumab; Treme, tremelimumab.

acceptable and that the risk of bias was minimal (Supplementary Table 5 and Supplementary Fig. 8).

Discussion

Principal Findings

To the best of our knowledge, this is the first systematic review and NMA comparing the efficacy and safety profiles of currently available IO combinations. With a well-designed and comprehensive synthesis, our results provide evidence for clinical practice, including the following:

1. Except for durva-treme, the IO combinations provided survival superiority than standard chemotherapy regarding OS, PFS, and ORR; anti–PD-1 exhibited a potential advantage than anti–PD-L1 when combined with chemotherapy.

2. Pem-chemo and sint-chemo presented the best OS and atezo-beva-chemo consistently offered the best PFS and ORR for patients with advanced NSCLC without PD-L1 selection.
3. Nivo-ipi with or without chemotherapy consistently resulted in the best OS and PFS for patients with advanced NSCLC with PD-L1 less than 1%; pem-chemo and sint-chemo were associated with the best OS and PFS for patients with advanced NSCLC with PD-L1 greater than or equal to 1%, respectively.
4. The addition of chemotherapy to IO increased the toxicity when compared with standard chemotherapy, especially when antiangiogenesis drugs were simultaneously added, such as the atezo-beva-chemo regimen.
5. Efficacy and safety were well balanced in pem-chemo, which ranked second for OS and ORR, third for PFS, and fourth for grade greater than or equal to 3 AEs across all IO combinations.

Interestingly, we observed anti–PD-1 to be advantageous than anti–PD-L1 when combined with chemotherapy. This result agrees with our previous findings establishing that PD-1 antibodies combined with chemotherapy significantly reduced the risk of mortality by 32% when compared with a combination of PD-L1 antibodies and chemotherapy.[36] This observation could be attributed to the fact that PD-1 antibodies can simultaneously block the binding of PD-1 to PD-L1 and PD-L2, thereby inhibiting the immune escape pathway more comprehensively.[37] Nevertheless, we found no statistical difference in the number of AEs caused by PD-1 and PD-L1 antibodies.

Before the advent of immunotherapies, platinum-doublet chemotherapy served as the standard first-line treatment for patients with advanced NSCLC who had no actionable mutations. Nevertheless, the median OS reported for these patients was 8 to 12 months,[4,5] thus making it almost impossible to obtain 5-year OS data. The limited data availability affects clinical decision making and therefore the shared decision-making process. The first 5-year OS data were recently published on the European Society of Medical Oncology (2020) from the KEYNOTE-024 study. The findings revealed that the 5-year OS for patients with PD-L1 greater than or equal to 50% treated with pembrolizumab was 31.9%, which was nearly twice as that observed in the platinum-based chemotherapy-alone group (16.3%).[38] The results from this landmark study suggest that pembrolizumab monotherapy could substantially prolong OS and should be recommended as the first-line care for patients with advanced NSCLC when targetable genetic alterations are not present. Our findings also imply that the pem-chemo can further improve OS than standard chemotherapy.

In this study, we found that atezo-beva-chemo provides the best PFS and ORR for patients with advanced NSCLC. In addition to the known antiangiogenic effects of bevacizumab,[39–42] the inhibition of vascular endothelial growth factor (VEGF) has immunomodulatory effects.[43–47] Hence, the efficacy of atezolizumab might be enhanced through the addition of bevacizumab to reverse VEGF-mediated immunosuppression.[48–50] By modifying the hostile tumor microenvironment (TME), the combination of IO with antiangiogenesis treatment could alter the hostile immune-suppressive TME to an immune-active TME.[51,52] In this scenario, tumor vascular normalization might enhance the immunotherapeutic effect by promoting tissue perfusion and immune cell infiltration.[53,54] Supporting evidence exists for this assertion because studies have revealed that the activation and reprogramming of immune cells can in turn promote normalization of tumor vasculature.[55–57] Therefore, immune reprogramming and tumor vascular normalization exhibit synergistic effects, which could hypothetically be a mutually reinforcing virtuous cycle that improves the efficiency and efficacy of TME. Nevertheless, further research is required to substantiate this theory. Moreover, inhibition of VEGF receptor signaling leads to a reduction in myeloid-derived suppressor cell infiltration,[58] which plays a key immunosuppressive role in various cancer types. In recent years, accumulating evidence has highlighted that myeloid-derived suppressor cell is a major driver of the immunosuppressive TME.[59–61]

The anti–PD-1 plus anti–CTLA-4 combination (nivo-ipi) has been formally approved by the U.S. Food and Drug Administration for the treatment of six cancer types, namely melanoma,[62] renal cancer,[63] colorectal cancer,[64] liver cancer,[65] and NSCLC.[66] This decision is supported by the findings of the CheckMate-227 study which unearthed that adopting nivo-ipi as the first-line treatment prolonged the OS when compared with chemotherapy alone in patients with NSCLC, independent of the PD-L1 expression level. In this study, we found that nivo-ipi provided the best survival benefit, especially for those with negative PD-L1 expression and that the regimen was more effective when combined with chemotherapy. Nivo-ipi is an ICI-ICI intervention, which is potentially synergistic because it simultaneously targets PD-1 and CTLA-4. This strategy might aid in eliminating the tumor cells, that is, ipilimumab encourages the activation and proliferation of T cells, whereas nivolumab supports the existing T cells in identifying and targeting the tumor cells. In addition, some T cells activated by ipilimumab can differentiate into memory T cells that are more likely to produce a long-term immune response.[67] Armed with this knowledge, one might suggest that nivo-ipi supplemented with a limited course of chemotherapy could help patients

achieve early disease control. Further investigations involving head-to-head comparisons between nivo-ipi and nivo-ipi-chemo are required because the inclusion of chemotherapy may significantly increase AEs according to our results.

Nevertheless, as per our findings, the anti–PD-L1 plus anti–CTLA-4 combination (durva-treme) did not significantly improve OS or PFS when compared with standard chemotherapy. We found that the addition of chemotherapy to durva-treme may significantly improve PFS and ORR of patients with advanced NSCLC; however, the approach could elevate the risk of grade greater than or equal to 3 AEs. One possible reason for this negative outcome could be the fact that the primary end points in the MYSTIC study were PFS and OS in patients with PD-L1 greater than or equal to 25%; however, it remains to be found whether PD-L1 expression is an effective predictor of the efficacy of ICI-ICI combinations. When compared with ICI monotherapies in which PD-L1 expression has been established as a useful biomarker for patient selection, studies have revealed that PD-L1 expression is an unreliable biomarker for judging the efficacy of combinations, such as anti–PD-1/PD-L1 plus anti–CTLA-4.[68]

Implications

By consolidating the evidence from RCTs, this review provides clinicians with a reference source to evaluate the strengths and weaknesses of practice choices among multiple promising options. When taking both efficacy and safety into consideration, pem-chemo and nivo-ipi-chemo seem to be superior first-line treatments for patients with advanced NSCLC with positive and negative PD-L1 expression, respectively. Nevertheless, the addition of chemotherapy to IO would exacerbate the toxicity when compared with standard chemotherapy, especially when antiangiogenesis drugs, such as bevacizumab, are simultaneously added. Our results also suggest that anti–PD-1 combinations exhibit potentially better survival outcomes than anti–PD-L1 combinations, with comparable safety profiles. These findings could complement recent guidelines that help answer the question of whether IO combinations have a role in the standard care of patients with advanced NSCLC and which treatments may be optimal for those lacking actionable mutations. Nevertheless, further trials involving head-to-head comparisons, such as pem-chemo versus pem-beva-chemo and nivo-ipi versus nivo-ipi-chemo, are required.

Even though the included studies were all multicenter RCTs involving a mixture of ethnicities, few black people were enrolled in these trials. The prevalence of lung cancer among the male members of black communities is globally higher than that among the white males. This fact raises several issues which ought to be immediately addressed. None of the studies have stipulated ethnicity as a factor in their respective eligibility criteria, and therefore, one must assume that there is an issue with either, offering potential candidates the opportunity to participate with informed consent or withdrawal. There are some unanswered questions, which if addressed, will enable us to understand the nuances of participant selection and responses in a better way. This information may also enable us to develop reliable nomograms for specific patients using biomarker expressions.

Limitations

First of all, patients with NSCLC with sensitizing mutations in *EGFR* or *ALK* alterations are less likely to obtain survival benefit from immunotherapies. In this study, we only included wild-type populations from the IMpower-130 and IMpower-150 cohorts to minimize the heterogeneity. Given the fact that *EGFR* or *ALK* testing is not mandatory for patients with squamous cell lung cancer,[69,70] we conducted subgroup analysis on the basis of histologic types to identify the optimal IO combinations for specific subpopulations. Nevertheless, more well-designed RCTs that record and report histologic information related to patients with NSCLC are needed to improve clinical decision making and devise appropriate treatment strategies.

Second, OS continues to be followed up in CameL, RATIONALE-304, ORIENT-11, and ORIENT-12 studies, which might be a source of heterogeneity and risk of bias. Hence, we performed a subgroup analysis for NCCN-recommended IO combinations because these trials were of high quality with relatively mature OS data. Furthermore, we conducted a series of statistical analyses and did not find significant heterogeneity or risk of bias in the Bayesian framework.

Finally, platinum-doublet chemotherapy has been the standard first-line treatment for patients with advanced NSCLC who lack targetable genetic alterations. In this NMA, the chemotherapeutic strategies differed and included both pemetrexed-based and pemetrexed-free approaches. The efficacy of pemetrexed has been proven to be better than that of other third-generation chemotherapeutics in patients with nonsquamous NSCLC. Therefore, it is not unreasonable to assume that different chemotherapeutic regimens might exert different synergistic effects when combined with immunotherapies. However, this is a tentative assertion because the evidence base for IO combinations is relatively new and the combination strategies are yet to be established.

In conclusions, our study suggested that anti–PD-1 combinations exhibited potentially better survival outcomes than anti–PD-L1 combinations, with comparable safety profiles. Furthermore, pem-chemo and nivo-ipi-chemo seem to be superior first-line IO combinations for patients with advanced NSCLC with positive and negative PD-L1 expression, respectively. Although atezo-beva-chemo treatment provided the best PFS and ORR, the addition of chemotherapy to IO exacerbated the toxicity, especially when antiangiogenesis drugs were simultaneously added. Our findings could complement the current standard of care and aid in future trials making head-to-head comparisons, such as pem-chemo versus pem-beva-chemo and nivo-ipi versus nivo-ipi-chemo, for patients with advanced NSCLC.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2021.03.016.

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