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Pembrolizumab plus chemotherapy for first-line treatment of metastatic nonsquamous non-small-cell lung cancer: a network meta-analysis

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Aim: A systematic review and network meta-analysis were conducted to evaluate the efficacy of pembrolizumab + pemetrexed + platinum relative to other regimens in metastatic nonsquamous non-small-cell lung cancer (NSq-NSCLC). **Patients & methods:** Eligible studies evaluated first-line regimens in NSq-NSCLC patients without known targetable mutations. Relative treatment effects were synthesized with random effects proportional hazards Bayesian network meta-analyses. **Results:** The hazard ratio (HR) for overall survival (OS) for pembrolizumab + pemetrexed + platinum was statistically significant over all platinum-doublet (HR range: 0.42–0.61), platinum-doublet + bevacizumab (HR range: 0.44–0.53) and platinum-doublet + atezolizumab regimens (HR range: 0.56–0.62). Additionally, pembrolizumab + pemetrexed + platinum numerically improved OS over atezolizumab + paclitaxel + carboplatin + bevacizumab (HR: 0.65; 95% credible interval: 0.43, 1.01). Pembrolizumab + pemetrexed + platinum had 95.6% probability of being the best treatment regimen for OS. **Conclusion:** Pembrolizumab + pemetrexed + platinum is likely the most efficacious first-line regimen for metastatic NSq-NSCLC.

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Keywords: immunotherapy • nonsquamous • NSCLC • PD-L1 inhibitor • pembrolizumab

The introduction of immunotherapy has led to a rapid transformation in the treatment of metastatic non-small-cell lung cancer (NSCLC). The PD-1/PD-L1 inhibitors, nivolumab, pembrolizumab and atezolizumab were first approved for advanced NSCLC in previously treated disease, based on significantly improved overall survival (OS) compared with docetaxel [1–4]. Pembrolizumab monotherapy was subsequently approved for the first-line treatment of metastatic NSCLC whose tumors have high PD-L1 expression (tumor proportion score [TPS] $\geq 50\%$) and with no *EGFR* mutation or *ALK* gene rearrangement, based on significantly improved OS compared with platinum-based doublet chemotherapy [5].

Recently, several clinical trials evaluating PD-1/PD-L1 inhibitors in combination with traditional chemotherapy regimens have been published. In a randomized, Phase II clinical trial in metastatic nonsquamous NSCLC without actionable mutations, carboplatin plus pemetrexed with pembrolizumab provided significantly better response rates and progression-free survival (PFS) compared with chemotherapy alone, leading to FDA accelerated approval in May 2017 [6]. The subsequent confirmatory Phase III KEYNOTE-189 trial demonstrated patients who received pembrolizumab + pemetrexed + platinum had superior OS compared with patients who received pemetrexed + platinum chemotherapy alone (hazard ratio [HR] for OS: 0.49; 95% CI: 0.38–0.64; $p < 0.001$) [7]. The Phase III IMpower150 study demonstrated carboplatin + paclitaxel + bevacizumab + atezolizumab was superior to carboplatin + paclitaxel + bevacizumab for OS (HR for OS: 0.78; 95% CI: 0.64–0.96; $p = 0.0164$), while carboplatin + paclitaxel + atezolizumab was not superior to carboplatin + paclitaxel + bevacizumab (HR for

OS: 0.88; 95% CI: 0.72–1.08) [8,9]. The Phase III IMpower130 trial results add to evidence that carboplatin + nab-paclitaxel + atezolizumab has superior OS compared with carboplatin + nab-paclitaxel (HR for OS: 0.79; 95% CI: 0.64–0.98; $p = 0.033$) [10]. Finally, the Phase III IMpower132 interim analysis results failed to demonstrate that carboplatin or cisplatin + pemetrexed + atezolizumab had superior OS compared with carboplatin or cisplatin + pemetrexed (HR for OS: 0.81; 95% CI: 0.64–1.03; $p = 0.0797$) [11].

KEYNOTE-021G, a randomized Phase II trial, showed benefit for platinum doublet chemotherapy in combination with immunotherapy compared with chemotherapy alone in metastatic nonsquamous NSCLC without actionable mutations. However, KEYNOTE-189 was the first randomized Phase III trial to show the benefit of adding immunotherapy to a platinum doublet chemotherapy regimen irrespective of PD-L1 expression status. On the basis of this result, the National Comprehensive Cancer Network (NCCN) issued a category 1 recommendation in its guidelines [12]. Additionally, based on findings in KEYNOTE-189, the European Society for Medical Oncology (ESMO) has issued platinum doublet chemotherapy as a category A regimen [13]. Due to KEYNOTE-189's impact on the standard of care, it was of interest to compare the relative efficacy of pembrolizumab + pemetrexed + platinum to additional competing interventions, including other immunotherapy-based regimens for the first-line treatment of metastatic nonsquamous NSCLC patients without tumor *EGFR* mutation or *ALK* translocation by means of a network meta-analysis (NMA). Given a connected network of evidence, NMA provides a valid alternative for simultaneous comparison of all included interventions and estimates relative treatment effects between any pair of interventions in the network [14–16].

Methods

Systematic literature review

A systematic literature review (SLR) was initiated in May 2016 and updated at regular intervals through November 2018. Prespecified selection criteria regarding study population, interventions, comparators, outcomes and study design (PICOS) are enumerated in Table 1. The PICOS captured randomized controlled trials (RCTs) that were conducted in metastatic NSCLC patients who were previously untreated for their disease; evaluated recommended interventions; reported outcomes of interest; were conducted after 1995; and were published in English. Trials employing PD-L1 selection criteria were not included. During each SLR update, searches of MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials were conducted. The Scottish Intercollegiate Guidelines Network (SIGN) filter for RCTs was used to limit study design. Medical subject headings (MeSH) terms and keywords were used to identify studies by population, interventions and comparators. In addition, proceedings from European Society for Medical Oncology, International Association for the Study of Lung Cancer World Conference on Lung Cancer (IASLC WCLC), American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) were searched. Full search strategies are available in the Supplementary Materials.

Two reviewers independently screened titles and abstracts of articles and conference proceedings for potentially eligible studies. Full-text publications corresponding to included studies were then retrieved and screened in duplicate. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagrams for the original SLR and for each update are provided in the Supplementary Materials. Discrepancies were resolved by discussion between the pair of reviewers. Once the list of included studies was finalized, trial characteristics, patient characteristics and study results were extracted in duplicate from all eligible publications.

Study quality was assessed using Cochrane Collaboration's Risk of Bias tool to evaluate six key domains: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias [17]. Specific study characteristics evaluated include: random sequence generation, allocation concealment, blinding/masking status, incomplete outcome data, selective outcome reporting, as well as funding, support or conflicts of interest reported. Each of the study characteristics is assigned a low, medium, high or unclear risk status, and support for the decision is made and reported in tables (Supplementary Information).

Network meta-analysis

NMA is a well-established statistical technique that allows the comparison of treatment effects among interventions that have not been studied in a head-to-head clinical trial [14–16,18]. Indirect treatment comparisons have been in use for >20 years and a recent review found that nearly 800 NMAs were published in over 300 journals between 1997 and 2015 [19,20]. Additionally, health technology assessment bodies in a number of countries recommend Bayesian NMA to synthesize evidence for decision making [18,21]. The methods followed in this analysis match

Table 1. Study selection criteria to identify trials for the systematic literature review.

Criteria	Description
Population	Metastatic NSCLC patients who were previously untreated with systemic therapy for their metastatic nonsquamous disease [†]
Interventions	Pembrolizumab
	Pembrolizumab + platinum + pemetrexed
	Nivolumab
	Nivolumab + ipilimumab
	Nivolumab + platinum (carboplatin + cisplatin) + pemetrexed, followed by pemetrexed maintenance
	Durvalumab
	Durvalumab + tremelimumab
	Atezolizumab
	Atezolizumab + bevacizumab + paclitaxel + carboplatin
	Atezolizumab + paclitaxel + carboplatin
	Atezolizumab + nab-paclitaxel + carboplatin
	Atezolizumab + platinum + pemetrexed
	Avelumab
	Pemetrexed + platinum
	Pemetrexed + platinum, followed by pemetrexed maintenance
	Taxane + platinum (paclitaxel, nab-paclitaxel or docetaxel)
	Docetaxel + platinum followed by pemetrexed maintenance
	Paclitaxel + platinum followed by pemetrexed maintenance
	Gemcitabine + platinum
	Gemcitabine + platinum followed by pemetrexed maintenance
	Vinorelbine + platinum
	Gemcitabine + platinum followed by gemcitabine maintenance
	Etoposide + platinum
	Nonpemetrexed platinum doublet followed by pemetrexed switch maintenance
	Nonerlotinib-containing platinum doublet × 4–6 cycles followed by erlotinib switch maintenance
	Gemcitabine + bevacizumab + platinum
	Paclitaxel + bevacizumab + platinum
	Pemetrexed + bevacizumab + platinum
	Nonplatinum regimens (gemcitabine + docetaxel and gemcitabine + vinorelbine)
Comparisons	Any of the above interventions and placebo
	Between any of the above interventions
Outcomes	Overall survival
	Progression-free survival
	Overall response rate (tabulations only)
	Health-related quality of life (tabulations only)
	Grade 3 or 4 adverse events (tabulations only)
Study design	Randomized controlled trials
Other	English language
	1995 onwards

[†]The population of interest is metastatic nonsquamous NSCLC patients who are *EGFR* mutation and *ALK* translocation negative; however, a broader search was necessary due to anticipated lack of trial data for this specific population.
Nota bene: Platinum is carboplatin or cisplatin.
NSCLC: Non-small-cell lung cancer.

those outlined in the Technical Support Document #2, published by the National Institute for Health and Care Excellence in the UK. In brief, NMA is an extension of pairwise meta-analysis that allows estimation of relative treatment effects between all interventions in a connected network of RCTs by calculating the differences in pooled relative treatment effects between studies. First, a parameter such as an HR is assumed to follow a noninformative (i.e., no prior knowledge of the parameter) probability distribution. Next, the probabilities of different values for the parameters of interest are calculated given the observed data, and the prior probability distribution is updated to yield a posterior probability distribution. This calculation is performed using a Markov chain Monte Carlo

algorithm implemented in the software package OpenBUGS according to the methods described in National Institute for Health and Care Excellence Technical Support Document #2 [18]. The posterior distribution is then summarized as a point estimate for the parameter of interest along with a 95% credible interval (CrI). CrIs are the Bayesian analog of a frequentist CI. Unlike CIs, CrIs are interpreted probabilistically; there is 95% chance that the true value of the parameter lies within the 95% CrI.

A well-designed NMA is dependent upon properly defining both prognostic factors and relative treatment effect modifiers. Prognostic factors are characteristics that affect the outcome of patients with a disease, independent of treatment. Relative treatment effect modifiers are patient characteristics that influence the treatment effects of an intervention relative to the control, and which may introduce between-study heterogeneity if effect modifiers are imbalanced across trials. Only the relative treatment effects of each trial are considered, reducing the degree to which indirect comparisons of interventions are affected by differences in study effects (i.e., known and unknown prognostic factors). Therefore, in order to decrease the likelihood of biased estimates, potential relative treatment effect modifiers must be evaluated in a feasibility assessment prior to conducting an NMA to ensure included trials are reasonably similar.

Before proceeding with an NMA, a feasibility assessment was conducted to determine whether the RCT evidence for the interventions of interest form a single evidence network for each population and outcome of interest; and assess distributions of treatment, outcomes, study and patient characteristics that may influence the treatment effects when performing direct comparisons of the evidence networks [22]. Assessed trial characteristics included study phase, trial initiation, trial completion, trial region(s), eligibility criteria and risk of bias. Heterogeneity of patient characteristics was determined by baseline patient characteristics such as crossover, demographics of the trial (e.g., age, sex, race/ethnicity) and clinical characteristics of the trial (e.g., ECOG performance status, smoking status and disease stage). Histology, a known treatment effect modifier, was accounted for by including only patients with nonsquamous disease in the analysis, as stated in the PICOS eligibility criteria. Trials that enrolled patients of other histologies were included only if outcomes were available for the nonsquamous subgroup and these subgroup outcomes were used in the analysis. After determining that the evidence networks and their respective trials were sufficiently similar, the evidence was synthesized by means of NMAs. Random-effects pairwise meta-analyses were used to determine direct and indirect associated treatment effects for both OS and PFS NMAs. Under the assumption of consistency, the NMA model relates the data from the individual studies to basic parameters reflecting the (pooled) relative treatment effect of each intervention compared with the reference, in this case platinum + pemetrexed. Based on these basic parameters, the relative treatment effects between each of the contrasts in the network were obtained. Under the Bayesian framework, it is possible to calculate the probability of being the best treatment out of all treatments included in the connected network of evidence. It is also possible to calculate which treatments are the second best, third best, etc., treatment out of all interventions included in the connected network [23].

The NMA of reported HRs for PFS and OS, assuming proportional hazards between treatments, was performed using a model with a contrast-based normal likelihood for the log HR (and corresponding standard error) of each trial (or comparison) in the network. Normal noninformative prior distributions for the parameters were estimated with a mean of 0 and a variance of 10,000. In cases where HRs were not reported but Kaplan–Meier curves were available, the Kaplan–Meier curves were digitized (DigitizeIt; www.digitizeit.de/) and constant HRs were estimated using the Guyot algorithm [24].

The results of the NMA for PFS and OS were presented with estimates for treatment effects of each intervention relative to the reference, platinum + pemetrexed. The posterior distributions of relative treatment effects were summarized by the median and 95% CrIs, which were constructed from the 2.5th and 97.5th percentiles of the posterior distributions. Additionally, median rankings and associated probability of being the best treatment for each outcome of interest were presented. All analyses were performed using R version 3.4.0 (R Project for Statistical Computing) with the package R2JAGS version 0.5.7 (OpenBUGS Project Management Group) [25]. R is a widely used, free, open-source programming language and environment for statistical computing as well as graphics [25].

Results

Systematic literature review & feasibility assessment

The original SLR was conducted in May 2016 and updated in March 2017; November 2017; April 2018; June 2018; and November 2018. A total of 14,300 abstracts and 462 full text publications were screened. In all, 65

publications pertaining to 27 trials matching the PICOS criteria were identified. The included trials and their corresponding publications are listed in [Table 2](#).

Outcomes of interest

26 trials reported OS and 23 trials reported PFS. Eleven trials defined OS; of these trials, six defined OS as time from randomization to death from any cause. Two trials, Spigel (2012) and Sun (2015), defined OS as time from enrollment to time of death [81,82]. TRAIL defined OS as time from the first date of treatment to time of death from any cause []. Finally, both IMpower130 and IMpower132 defined OS as from baseline until death [10,11]. PFS was defined in 12 trials, of which eight trials defined PFS as time from randomization to the first documented disease progression or death. Sun (2015) defined PFS as time from enrollment to disease progression or death, and TRAIL defined time to progression (TTP) as time from first date of treatment until disease progression or death [82]. Additionally, both IMpower130 and IMpower132 defined PFS as baseline until disease progression or death, whichever occurred first [10,11]. Two trials reported TTP only, Checkmate 026 and TRAIL; this end point was used as a surrogate for PFS [31]. Additionally, Zhang (2013), Gronberg (2009), and Johnson (2004) reported neither PFS nor TTP and, therefore, were not included in PFS analyses [40,84,85]. One trial did not report any outcomes of interest; Kristensen (2017), reported only patient-reported outcomes [74].

Trial characteristics

Trial characteristics of included RCTs were similar ([Table 3](#)). The earliest study was completed in 2007 and the latest study is scheduled to be completed in 2019. Most trials were open label, had low risk of bias according to the Cochrane Collaboration's tool, and included patients with ECOG performance scores of 0 or 1. However, five trials did permit patients with ECOG scores of 2 (Gronberg (2009), Jang (2017), Johnson (2004), Rodrigues-Pereira (2011) and TRAIL) [40,50,80,85]. Based on eligibility criteria defined in the PICOS table ([Table 2](#)), only patients with nonsquamous histology were of interest. However, six trials were conducted in both nonsquamous and squamous patients. For trials including both nonsquamous and squamous patients, subgroup data in nonsquamous patients was used to maintain a homogeneous population with respect to histology status. Two trials restricted eligibility based on PD-L1 immunohistochemistry status, KEYNOTE-024 and CheckMate-026, which allowed only PD-L1-expressing patients [5,30].

Intervention characteristics

Intervention characteristics of included trials, including dosage and frequency, and planned duration of treatment were reasonably similar across trials. Treatment regimens largely consisted of six planned cycles with each cycle lasting 21 days. However, 17 trials did allow maintenance therapies for patients with complete or partial tumor response, with no progressive disease, and/or at the local physicians' discretion. Maintenance therapies consisted of certain components of the randomized regimen a patient was assigned to. Seven trials allowed for within-trial crossover in treatment following disease progression: CheckMate 026, IMpower130, Johnson 2004, KEYNOTE-189, KEYNOTE-021G, KEYNOTE-024, and TRAIL [5–7,10,30,66,85]. Crossover proportions refer to patients who were eligible and crossed over to interventions upon verified disease progression ([Table 5](#)). Of trials permitting crossover, six out of the seven allowed patients to crossover from the control arm to the crossover therapy. Proportions of patients crossing over from the control arm to the maintenance therapy ranged from 40.8 to 59.4%. The TRAIL trial permitted patients in both the control and intervention arms to crossover; in the control arm, 72.7% crossed over and the comparator arm had 69.0% crossed over []. One trial evaluated nivolumab monotherapy in PD-L1-positive patients, CheckMate 026 [30].

Patient characteristics

Differences identified in the ITT populations with respect to age, sex, ECOG status, smoking status and American Joint Committee on Cancer (AJCC) stage status were assessed and deemed reasonably similar. However, substantial variation was observed for ethnicity ([Table 4](#)).

Ranging from 54 to 77 years, median age at baseline varied little between treatment arms. However, two trials were conducted in exclusively elderly patients, Jang 2017 and Spigel (2012) [50,81]. Similarly, sex distribution across trials had little variation, with all trials being majority male, except for KEYNOTE-021G, which consisted of 39.0% males [6]. Although the between-trial sex distribution was reasonably similar, within-trial sex distributions for three trials were imbalanced. Fewer than half (48%) of the patients in the docetaxel + platinum arm of Rodrigues-Pereira

Table 2. List of publications included after full-text review, arranged by trial.

Trial ID	Trial number	Principal publication	Subsequent publications
AVAIL	NCT00806923	Reck <i>et al.</i> [26]	Reck <i>et al.</i> [27] Mok <i>et al.</i> [28]
BEYOND	NCT01364012	Zhou <i>et al.</i> [29]	–
CheckMate 026	NCT02041533	Carbone <i>et al.</i> [30]	Socinski <i>et al.</i> [31]
CLEAR	–	Koyama <i>et al.</i> [32]	Atagi <i>et al.</i> [33] Harada <i>et al.</i> [34]
ECOG 4599	NCT0021060	Sandler <i>et al.</i> [35]	Sandler <i>et al.</i> [36] Tyagi <i>et al.</i> [37] Gerber <i>et al.</i> [38]
ERACLE	NCT01303926	Galetta <i>et al.</i> [39]	–
Gronberg 2009	–	Gronberg <i>et al.</i> [40]	Brown <i>et al.</i> [41]
IMpower130	NCT02367781	Cappuzzo <i>et al.</i> [10]	–
IMpower132	NCT02657434	Papadimitrakopoulou [11]	–
IMpower150	NCT02366143	Socinski <i>et al.</i> [8]	Socinski [42] Reck [43] Reck <i>et al.</i> [44] Kowanetz <i>et al.</i> [45] Reck <i>et al.</i> [46] Reck <i>et al.</i> [47] Rothenstein <i>et al.</i> [48] Reck <i>et al.</i> [49]
Jang 2017	–	Jang <i>et al.</i> [50]	–
JMDB	NCT00087711	Scagliotti <i>et al.</i> [51]	Novello <i>et al.</i> [52] Syrigos <i>et al.</i> [53] Yang <i>et al.</i> [54]
JMIL	NCT01005680	Wu <i>et al.</i> [55]	Eli Lilly and Company <i>et al.</i> [56]
JO19907	–	Niho <i>et al.</i> [57]	–
Johnson 2004	–	Johnson <i>et al.</i> [58]	–
KEYNOTE-021G	NCT02039674	Langer <i>et al.</i> [6]	Langer <i>et al.</i> [59] Langer <i>et al.</i> [60] Papadimitrakopoulou <i>et al.</i> [61] Borghaei <i>et al.</i> [62] Borghaei <i>et al.</i> [63] Borghaei <i>et al.</i> [64] Gentzler [65]
KEYNOTE-024	NCT02142738	Reck <i>et al.</i> [5]	Reck <i>et al.</i> [66] Brahmer <i>et al.</i> [67] Brahmer <i>et al.</i> [68] Reck <i>et al.</i> [69]
KEYNOTE-189	NCT02578680	Gandhi <i>et al.</i> [7]	Gandhi [70] Garassino <i>et al.</i> [71] Hui <i>et al.</i> [72] Rodriguez <i>et al.</i> [73]
Kristensen 2017	–	Kristensen <i>et al.</i> [74]	–
NAVotrial 01	Eudract 2009-012001	Bennouna <i>et al.</i> [75]	–
PointBreak	NCT00762034	Patel <i>et al.</i> [76]	Spigel <i>et al.</i> [77] Reynolds <i>et al.</i> [78]
PRONOUNCE	NCT00948675	Zinner <i>et al.</i> [79]	–
Rodrigues-Pereira 2011	NCT00520676	Rodrigues-Pereira <i>et al.</i> [80]	–
Spigel 2012	–	Spigel <i>et al.</i> [81]	–
Sun 2015	NCT01401192	Sun <i>et al.</i> [82]	–
TRAIL	NCT01282151	Park <i>et al.</i> [83]	–
Zhang 2013	ChiCTR-TRC-11001194	Zhang <i>et al.</i> [84]	–

Note: Trials are listed in alphabetical order.

Table 3. List of key trial characteristics, arranged by trial.

Trial ID	Phase	Masking	Multicenter	Age (years)	Disease stage	Performance score
AVAIL	III	Double blind	Yes	≥18	IIIB or IV	ECOG ≤1
BEYOND	III	Double blind	Yes	≥18	IIIB or IV	ECOG ≤1
CheckMate 026	III	Open label	Yes	≥18	IV	ECOG ≤1
CLEAR	II	Open label	Yes	20–74	IIIB or IV	ECOG ≤1
ECOG 4599	III	Open label	–	–	IIIB or IV	ECOG ≤1
ERACLE	III	Open label	Yes	18–70	IIIB or IV	ECOG ≤1
Gronberg 2009	III	Open label	Yes	≥18	IIIB or IV	ECOG ≤2
IMpower130	III	Open label	Yes	≥18	IV	ECOG ≤1
IMpower132	III	Open label	Yes	≥18	IV	ECOG ≤1
IMpower150	III	Open label	Yes	≥18	IV	ECOG ≤1
Jang 2017	II	–	Yes	≥65	IIIB or IV	ECOG ≤2
JMDB	III	–	Yes	≥18	IIIB or IV	ECOG ≤1
JMIL	III	Open label	Yes	≥18	IIIB or IV	ECOG ≤1
JO19907	II	Open label	Yes	20–74	IIIB or IV	ECOG ≤1
Johnson 2004	II	–	Yes	≥18	IIIB or IV	ECOG ≤2
KEYNOTE-021G	II	Open label	Yes	≥18	IIIB or IV	ECOG ≤1
KEYNOTE-024	II	Open label	Yes	≥18	IV	ECOG ≤1
KEYNOTE-189	III	Quadruple or double blind	Yes	≥18	IV	ECOG ≤1
Kristensen 2017	–	Open label	No	–	IIIB or IV	WHO 0–2
NAVotrial 01	II	–	Yes	18–75 years	IIIB or IV	Karnofsky ≥80%
PointBreak	III	Open label	Yes	≥18	IIIB or IV	ECOG ≤1
PRONOUNCE	III	Open label	Yes	≥18	IV	ECOG ≤1
Rodrigues-Pereira 2011	III	Open label	Yes	≥18	IIIB or IV	ECOG ≤2
Spigel 2012	II	Open label	Yes	≥70	IIIB or IV	ECOG ≤1
Sun 2015	II	Open label	No	≥18	IIIB or IV (UICCC 6)	ECOG ≤1
TRAIL	III	Open label	Yes	≥18	IIIB or IV	ECOG ≤2
Zhang 2013	II	–	Yes	≥18	IIIB or IV (UICCC 6)	ECOG ≤1

Note: Trials are listed in alphabetical order.
ECOG: Eastern Cooperative Oncology Group.

(2011) were male but 54.3% of the patients in the entire trial were male [80]. In Spigel (2012), 47% of the patients in the pemetrexed + bevacizumab + platinum arm were male; however, 50% of the entire trial was male [81]. Similarly, fewer than half (46%) of the patients in the paclitaxel + bevacizumab (15 mg/kg) + platinum arm of Johnson (2004) were male; however, 60% of the patients in the entire trial were male [85]. Most patients had ECOG performance status (PS) of 0 or 1. Three trials (Gronberg [2009], Rodrigues-Pereira [2011] and TRAIL) reported at least 10% of patients with an ECOG PS of 2 [40,80]. Among trials reporting this information, most (>50%) patients were current and former smokers with the exception of TRAIL, in which slightly fewer than half of patients (48.6%) were current and former smokers []. The proportion of patients with AJCC stage IV lung cancer was reasonably similar between all arms, ranging from 62 to 100%. A minority of patients in some trials had stage IIIB disease, with KEYNOTE-189 containing no stage IIIB patients and Jang 2017 having the highest proportion of stage IIIB patients (31.5%) [7,84]. Although many trials did not report *EGFR* mutation or *ALK* translocation status, six trials were conducted in *EGFR* mutation-negative patients only and five trials were conducted in *ALK* translocation-negative patients only. Three trials reported minimal proportions of patients whose tumors were *EGFR* mutation positive ranging from 10 to 28%. IMpower150, BEYOND and CLEAR reported <8% of patients with *ALK* translocation positive status. Although IMpower150 included some *EGFR*- and *ALK*-positive patients, HRs from the *EGFR* wild-type subgroup were used in the NMAs. Ethnicity varied between trials as six trials (BEYOND; JO19907; JMIL; Sun [2015]; Zhang [2013]; and TRAIL) were conducted among exclusively east Asian patients while seven trials (CheckMate 026, IMpower130, JMDB, KEYNOTE-021G,

Table 4. List of key patient characteristics, arranged by trial.

Trial ID	Treatment	N	Median age (range)	Male N (%)	Asian N (%)	ECOG 0 or 1 (%)	Current or former smoker (%)	Never smoker (%)	Stage IV (%)	EGR positive (%)	ALK positive (%)
AVAL	Gemcitabine + platinum	347	59.0 (29.0–83.0)	223 (64%)	–	347 (100%)	–	–	266 (77%)	–	–
	Gemcitabine + bevacizumab (7.5 mg/kg) + platinum	345	57.0 (26.0–81.0)	223 (65%)	–	345 (100%)	–	–	267 (78%)	–	–
	Gemcitabine + bevacizumab (15 mg/kg) + platinum	351	59.0 (20.0–83.0)	219 (62%)	–	351 (100%)	–	–	269 (77%)	–	–
BEYOND	Paclitaxel + platinum	138	56.0 (23.0–74.0)	77 (56%)	138 (100%)	138 (100%)	–	–	125 (91%)	17 (12%)	–
	Paclitaxel + bevacizumab + platinum	138	57.0 (30.0–75.0)	75 (54%)	138 (100%)	138 (100%)	–	–	126 (91%)	23 (17%)	–
CheckMate 026	Nivolumab	271	62.8 (32.0–89.0)	184 (68%)	30 (11%)	268 (99%)	238 (88%)	30 (11%)	255 (94%)	–	–
	Pemetrexed + platinum	270	63.4 (29.0–87.0)	149 (55%)	17 (6%)	267 (99%)	237 (88%)	29 (11%)	244 (90%)	–	–
CLEAR	Pemetrexed + bevacizumab + platinum	131	66.0 (37.0–74.0)	97 (74%)	–	131 (100%)	109 (83%)	22 (17%)	95 (73%)	0 (0%)	2 (2%)
	Paclitaxel + bevacizumab + platinum	66	67.0 (22.0–74.0)	47 (71%)	–	66 (100%)	54 (82%)	12 (18%)	50 (76%)	0 (0%)	0 (0%)
ECOG 4599	Paclitaxel + platinum	433	–	253 (58%)	–	430 (99%)	–	–	337 (78%)	–	–
	Paclitaxel + bevacizumab + platinum	417	–	210 (50%)	–	414 (99%)	–	–	310 (74%)	–	–
ERACLE	Pemetrexed + platinum	60	60.0 (35.0–72.0)	42 (70%)	–	60 (100%)	42 (70%)	13 (22%)	57 (95%)	–	–
	Paclitaxel + bevacizumab + platinum	58	62.0 (41.0–71.0)	45 (78%)	–	58 (100%)	35 (60%)	16 (28%)	54 (93%)	–	–
Gronberg 2009	Gemcitabine + platinum	217	66.0 (25.0–84.0)	128 (59%)	–	168 (77.4%)	204 (94%)	11 (5%)	156 (72%)	–	–
	Pemetrexed + platinum	219	64.0 (35.0–90.0)	123 (56%)	–	172 (78.5%)	197 (90%)	22 (10%)	156 (71%)	–	–
IMPpower130	Nab-paclitaxel + platinum	228	–	134 (59%)	1 (1%)	91 (40%)	211 (93%)	17 (8%)	228 (100%)	0 (0%)	0 (0%)
	Atezolizumab + nab-paclitaxel + platinum	451	–	266 (59%)	12 (3%)	189 (42%)	403 (89%)	48 (11%)	451 (100%)	0 (0%)	0 (0%)
IMPpower132	Pemetrexed + platinum	286	64.0 (31.0–85.0)	192 (66%)	71 (24%)	126 (43%)	255 (87%)	37 (13%)	292 (100%)	0 (0%)	0 (0%)
	Atezolizumab + pemetrexed + platinum	292	63.0 (33.0–83.0)	192 (67%)	65 (23%)	114 (40%)	256 (90%)	30 (11%)	286 (100%)	0 (0%)	0 (0%)
IMPpower150	Atezolizumab + paclitaxel + bevacizumab + platinum	400	63.0 (31.0–89.0)	240 (60%)	–	–	318 (80%)	82 (21%)	–	34 (9%)	11 (3%)
	Paclitaxel + bevacizumab + platinum	400	63.0 (31.0–90.0)	239 (60%)	–	–	323 (81%)	77 (19%)	–	45 (11%)	20 (5%)
Jang 2017	Atezolizumab + paclitaxel + platinum	402	63.0 (32.0–85.0)	241 (60%)	–	–	325 (81%)	77 (19%)	–	45 (11%)	9 (2%)
	Docetaxel + platinum	50	71.0 (50.0–81.0)	39 (78%)	–	–	–	–	31 (62%)	–	–
JMDB	Gemcitabine + platinum	47	71.0 (40.0–86.0)	32 (68%)	–	–	–	–	35 (75%)	–	–
	Gemcitabine + platinum	634	–	423 (66.7%)	78 (12.3%)	632 (99.7%)	–	–	489 (77%)	–	–
JMIL	Pemetrexed + platinum	618	–	389 (62.9%)	86 (13.9%)	617 (99.8%)	–	–	491 (79%)	–	–
	Gemcitabine + platinum	634	60.0	425 (67%)	634 (100%)	633 (100%)	447 (70%)	105 (17%)	490 (77%)	–	–
JO19907	Pemetrexed + platinum	618	60.6	400 (65%)	618 (100%)	617 (100%)	432 (70%)	111 (18%)	493 (80%)	–	–
	Paclitaxel + platinum	59	60.0 (38.0–73.0)	38 (64%)	59 (100%)	59 (100%)	40 (68%)	19 (32%)	42 (71%)	–	–
	Paclitaxel + bevacizumab + platinum	121	61.0 (34.0–74.0)	77 (64%)	121 (100%)	121 (100%)	83 (69%)	38 (31%)	83 (69%)	–	–

† Mean used in absence of median age.

Nota bene: Platinum is carboplatin or cisplatin.

Table 4. List of key patient characteristics, arranged by trial (cont.).

Trial ID	Treatment	N	Median age (range)	Male N (%)	Asian N (%)	ECOG 0 or 1 (%)	Current or former smoker (%)	Never smoker (%)	Stage IV (%)	EGFR positive (%)	ALK positive (%)
Johnson 2004	Paclitaxel + platinum	32	-	24 (75%)	-	30 (94%)	-	-	26 (81%)	-	-
	Paclitaxel + bevacizumab (7.5 mg/kg) + platinum	32	-	20 (62%)	-	31 (97%)	-	-	30 (94%)	-	-
	Paclitaxel + bevacizumab (15 mg/kg) + platinum	35	-	16 (46%)	-	31 (89%)	-	-	28 (80%)	-	-
KEYNOTE-021G	Pembrolizumab + pemetrexed + platinum	60	62.5 (54.0–70.0)	22 (37%)	5 (8%)	59 (98%)	45 (75%)	15 (25%)	59 (98%)	0 (0%)	0 (0%)
	Pemetrexed + platinum	63	63.2 (58.0–70.0)	26 (41%)	5 (8%)	63 (100%)	54 (86%)	9 (14%)	60 (95%)	0 (0%)	0 (0%)
KEYNOTE-024	Pembrolizumab	154	64.5 (33.0–90.0)	92 (60%)	25 (16%)	153 (100%)	149 (97%)	5 (3%)	153 (99%)	-	-
	Pemetrexed + platinum	151	66.0 (38.0–85.0)	95 (63%)	21 (14%)	151 (100%)	132 (87%)	19 (13%)	150 (99%)	-	-
KEYNOTE-189	Pembrolizumab + pemetrexed + platinum	410	63.5 (34.0–84.0)	254 (62%)	10 (2%)	311 (76%)	362 (88%)	48 (12%)	410 (100%)	0 (0%)	0 (0%)
	Pemetrexed + platinum	206	63.0 (34.0–84.0)	109 (53%)	8 (4%)	205 (99%)	181 (88%)	25 (12%)	206 (100%)	0 (0%)	0 (0%)
Kristensen 2017	Vinorelbine + platinum	25	63.0 (52.0–84.0)	13 (52%)	-	24 (96%)	-	-	20 (80%)	-	-
	Gemcitabine + platinum	27	65.0 (50.0–87.0)	16 (59%)	-	4 (89%)	-	-	24 (89%)	-	-
NAVotrial 01	Pemetrexed + platinum	51	63.8 (40.3–75.5)	33 (65%)	-	-	-	-	45 (88%)	-	-
	Vinorelbine + platinum	100	61.0 (38.4–75.1)	62 (62%)	-	-	-	-	88 (88%)	-	-
PointBreak	Paclitaxel + bevacizumab + platinum	472	64.6	251 (53%)	15 (3%)	472 (0%)	420 (89%)	50 (11%)	424 (90%)	-	-
	Pemetrexed + bevacizumab + platinum	467	64.9	249 (53%)	14 (3%)	466 (0%)	405 (87%)	58 (12%)	420 (90%)	-	-
PRONOUNCE	Paclitaxel + bevacizumab + platinum, followed by bevacizumab	179	65.4 (41.2–86.2)	104 (58%)	0 (0%)	179 (100%)	172 (96%)	-	179 (100%)	-	-
	Pemetrexed + platinum, followed by pemetrexed	182	65.8 (38.4–84.1)	105 (58%)	4 (2%)	181 (99%)	164 (90%)	-	181 (99%)	-	-
Rodrigues-Pereira 2011	Docetaxel + platinum	105	58.9 (31.4–78.4)	50 (48%)	44 (42%)	88 (84%)	62 (59%)	41 (39%)	82 (78%)	-	-
	Pemetrexed + platinum	106	60.1 (27.9–83.1)	64 (60%)	45 (42%)	91 (86%)	72 (68%)	34 (32%)	89 (84%)	-	-
Spigel 2012	Gemcitabine + bevacizumab + pemetrexed	55	76.0 (70.0–89.0)	29 (53%)	-	55 (100%)	-	-	50 (91%)	-	-
	Pemetrexed + bevacizumab + platinum	55	77.0 (70.0–89.0)	26 (47%)	-	55 (100%)	-	-	47 (86%)	-	-
Sun 2015	Gemcitabine + platinum	155	(37.0–79.0)	91 (59%)	155 (100%)	-	90 (58%)	65 (42%)	142 (92%)	47 (30%)	12 (8%)
	Pemetrexed + platinum	160	(29.0–81.0)	87 (54%)	160 (100%)	-	82 (51%)	78 (49%)	144 (90%)	41 (26%)	13 (8%)
TRAIL	Pemetrexed + platinum	77	63.0† (8.9)	53 (69%)	-	69 (90%)	37 (48%)	14 (18%)	72 (94%)	0 (0%)	0 (0%)
	Docetaxel + platinum	71	63.6† (9.7)	50 (70%)	-	64 (90%)	35 (49%)	14 (20%)	68 (96%)	0 (0%)	0 (0%)
Zhang 2013	Gemcitabine + platinum	124	55.0 (26.0–71.0)	77 (62%)	124 (100%)	124 (100%)	-	-	89 (72%)	-	-
	Pemetrexed + platinum	127	54.0 (33.0–73.0)	78 (61%)	127 (100%)	127 (100%)	-	-	82 (65%)	-	-

† Mean used in absence of median age.

Nota bene: Platinum is carboplatin or cisplatin.

Table 5. Trials with treatment crossover permitted.

Trial	Original treatment(s)	N	Crossover allowed	Crossover treatment	Conditions for crossover	% patients crossover
CheckMate 026	Pemetrexed + platinum	270	Yes	Nivolumab	Disease progression	58.0%
	Nivolumab	271	–	–	–	–
IMpower130	Nab-paclitaxel + platinum	228	Yes	Atezolizumab + nab-paclitaxel + platinum	Disease progression	40.8%
	Atezolizumab + nab-paclitaxel + platinum	451	–	–	–	–
Johnson, 2004	Paclitaxel + platinum	32	Yes	Bevacizumab	Disease progression	59.4%
	Paclitaxel + bevacizumab (7.5 mg/kg) + platinum	32	–	–	–	–
	Platinum + paclitaxel + bevacizumab (15 mg/kg)	35	–	–	–	–
KEYNOTE-021G	Pemetrexed + platinum	63	Yes	Pembrolizumab	Disease progression	43.3%
	Pembrolizumab + pemetrexed + platinum	60	–	–	–	–
KEYNOTE-024	Pemetrexed + platinum	151	Yes	Pembrolizumab	Disease progression	43.7%
	Pembrolizumab	154	–	–	–	–
KEYNOTE-189	Pemetrexed + platinum	206	Yes	Pembrolizumab	Disease progression	41.3%
	Pembrolizumab + pemetrexed + platinum	410	–	–	–	–
TRAIL	Pemetrexed + platinum	77	Yes	Docetaxel or EGFR inhibitor	Disease progression	72.7%
	Docetaxel + platinum	71	Yes	Pemetrexed or EGFR inhibitor	Disease progression	69.0%

Nota bene: Platinum is carboplatin or cisplatin.

KEYNOTE-189, PointBreak and PRONOUNCE) reported that fewer than 15% of patients were of Asian/east Asian descent [6,7,29,31,51,55,57,76,79,82,84].

After evaluating heterogeneity of trials included after the SLR in the feasibility assessment, five trials were excluded from NMAs. Two trials were conducted in an exclusively elderly population, Jang (2017) and Spigel (2017) [50,81]. One trial, Kristensen (2017), did not report any outcomes of interest [74]. KEYNOTE-024 and CheckMate 026 only enrolled PD-L1-expressing patients, and were thereby excluded, as no other trials in the network had this criterion and PD-L1 expression is a known effect modifier [30,66]. After exclusion of these five trials, studies were determined to be of good quality and with minimal heterogeneity, although key differences were identified with respect to within-trial crossover, use of maintenance therapies and race/ethnicity. Of trials included in the evidence base that reported subgroup analyses to assess potential effect modifiers, there was no reporting of statistically significant differences in efficacy by subgroup; however, it should be noted that in some instances potential differences by subgroup were reported numerically, but not statistically tested. In absence of individual patient data to adjust for differences identified, there is risk of confounding bias if these differences act as treatment effect modifiers. Thus, differences between the target population and the evidence base should be acknowledged when interpreting results of the NMAs conducted for OS and PFS. After the feasibility assessment, connected networks of evidence were constructed for OS and PFS consisting of 22 trials (Figure 1) and 19 trials (Figure 2), respectively.

Network meta-analysis

For each trial in the OS and PFS networks, the HR, log (HR) and associated standard error are presented in Tables 6 and 8, respectively. Results of the random-effects NMA for OS and PFS are shown in Tables 7 and 9, respectively.

Under the proportional hazards random-effects model, the point estimate of the HR for OS for pembrolizumab + pemetrexed + platinum was statistically significant over all platinum-based doublets (HR range: 0.42–0.61), platinum doublet + bevacizumab regimens (HR range: 0.44–0.53) and both three-drug atezolizumab regimens (HR range: 0.56–0.62). Pembrolizumab + pemetrexed + platinum showed numerical superiority over the four-drug atezolizumab regimen for OS (HR: 0.65; 95% CrI: 0.43, 1.01). However, this difference was not statistically significant. Platinum doublet regimens were statistically equivalent to each other for OS; paclitaxel + bevacizumab + platinum, as well as all atezolizumab-containing regimens were statistically superior to paclitaxel/nab-paclitaxel + platinum. Median ranks of all interventions included in the NMA for OS are provided in Table 10. Pembrolizumab + pemetrexed + platinum is 95.6% most likely to be the best treatment for OS. All treatments were <1% likely to be the best treatment, excluding the four-drug atezolizumab regimen, which had a median rank of the second best treatment and 2.6% probability of being the best treatment for OS.

Figure 1. Network of evidence for overall survival.

Figure 2. Network of evidence for progression-free survival.

Pembrolizumab + pemetrexed + platinum was numerically superior to all competing interventions for PFS and this difference was statistically significant for all treatments except pemetrexed + bevacizumab + platinum (HR: 0.61; 95% CrI: 0.36, 1.01), pemetrexed + atezolizumab + platinum (HR: 0.69; 95% CrI: 0.42, 1.14) and paclitaxel + bevacizumab + atezolizumab + platinum (HR: 0.85; 95% CrI: 0.47, 1.48). For PFS, all interventions included in the network were superior to paclitaxel/nab-paclitaxel + platinum, with the exception

Table 6. Data used for overall survival network meta-analysis.

Study	Reference	Intervention	HR	logHR (SE)
AVAIL	Gem + platinum	Gem + bev + platinum	1.03	0.03 (0.09)
BEYOND	Pac/nab-pac + platinum	Pac + bev + platinum	0.68	-0.39 (0.16)
CLEAR	Pac + bev + platinum	Peme + bev + platinum	0.96	-0.05 (0.22)
ECOG 4599	Pac/nab-pac + platinum	Pac + bev + platinum	0.79	-0.24 (0.08)
ERACLE	Peme + platinum	Pac + bev + platinum	1.08	0.08 (0.22)
Gronberg 2009	Peme + platinum	Gem + platinum	1.04	0.04 (0.13)
IMpower130	Pac/nab-pac + platinum	Pac/nab-pac + atezo + platinum	0.79	-0.24 (0.11)
IMpower132	Peme + platinum	Peme + atezo + platinum	0.81	-0.21 (0.12)
IMpower150	Pac/nab-pac + platinum	Pac/nab-pac + atezo + platinum	0.88	-0.13 (0.10)
IMpower150	Pac/nab-pac + platinum	Pac + bev + atezo + platinum	0.78	-0.25 (0.10)
J019907	Pac/nab-pac + platinum	Pac + bev + platinum	0.99	-0.01 (0.21)
JMDB	Peme + platinum	Gem + platinum	1.23	0.21 (0.08)
JMIL	Peme + platinum	Gem + platinum	1.00	0.00 (0.15)
Johnson 2004	Pac/nab-pac + platinum	Pac + bev + platinum	0.85	-0.16 (0.27)
KEYNOTE-21G	Peme + platinum	Pembro + peme + platinum	0.56	-0.58 (0.28)
KEYNOTE-189	Peme + platinum	Pembro + peme + platinum	0.49	-0.71 (0.13)
NAVotrial01	Peme + platinum	Vin + platinum	1.00	0.00 (0.22)
PointBreak	Pac + bev + platinum	Peme + bev + platinum	1.00	0.00 (0.08)
PRONOUNCE	Peme + platinum	Pac + bev + platinum	0.93	-0.07 (0.13)
Rodrigues-Pereira (2011)	Peme + platinum	Doc + platinum	1.01	0.01 (0.17)
Sun (2015)	Peme + platinum	Gem + platinum	1.14	0.13 (0.17)
TRAIL	Peme + platinum	Doc + platinum	0.68	-0.39 (0.18)
Zhang (2013)	Peme + platinum	Gem + platinum	1.05	0.05 (0.17)

Atezo: Atezolizumab; Bev: Bevacizumab; Doc: Docetaxel; Gem: Gemcitabine; HR: Hazard ratio; Pac: Paclitaxel; Pembro: Pembrolizumab; Peme: Pemetrexed; SE: Standard error; Vin: Vinorelbine.

of vinorelbine + platinum (HR: 0.64; 95% CrI: 0.33, 1.16). Median ranks for interventions included in the NMA for PFS are provided in Table 11. Pembrolizumab + pemetrexed + platinum had a median rank of being the best treatment regimen, and was associated with a 67.3% of being the best treatment. Following pembrolizumab + pemetrexed + platinum, the four-drug atezolizumab regimen was associated with a median rank of second best, and 24.1% likely to be the best treatment regimen. All other treatment regimens had <5% likelihood of being the best treatment regimen for PFS.

Discussion

The objective of this study was to assess the efficacy of pembrolizumab + pemetrexed + platinum relative to alternative interventions for first-line treatment of metastatic NSCLC patients whose tumors had nonsquamous histology and are sensitizing *EGFR* mutation and *ALK* translocation negative. The validity of an NMA depends on the quality of the RCTs and the extent of any violations in the similarity and consistency assumptions across studies. In an NMA of RCTs involving multiple treatment comparisons, randomization holds only within the individual trials and not across trials. If the different direct comparisons show systematic differences in study and patient characteristics, and these differences are treatment-effect modifiers, then the estimates of any indirect comparison as obtained with the NMA will be biased. To assess these risks, a feasibility assessment examining heterogeneity in terms of treatment and outcome characteristics, as well as the study and patient characteristics, was performed [22]. Three trials were excluded from analyses as they differed from the rest of evidence base with respect to age and eligibility criteria. Furthermore, one trial was removed as it only reported patient-reported outcomes and another trial evaluated a treatment that is not approved for the first-line treatment of nonsquamous NSCLC patients. After removal of these five trials, the trials included in the NMAs were largely similar in trial and patient characteristics. It is important to recognize that only trials meeting the prespecified PICOS eligibility criteria and feasibility assessment criteria were included. Extrapolation of results to populations other than nonsquamous NSCLC patients with PS 0-1 and without targetable mutations would not be valid.

Table 7. Results of random effects network meta-analysis; overall survival; results presented as constant hazard ratios between all competing interventions with 95% credible intervals.

Peme + platinum	0.84 (0.63, 1.10)	1.20 (0.92, 1.57)	0.89 (0.78, 1.02)	0.86 (0.67, 1.14)	1.04 (0.82, 1.31)	1.04 (0.77, 1.42)	1.00 (0.64, 1.56)	1.12 (0.82, 1.52)	1.29 (0.92, 1.81)	1.23 (0.93, 1.63)	1.98 (1.52, 2.59)
1.19 (0.91, 1.60)	Pac/nab-pac + platinum	1.43 (0.97, 2.13)	1.06 (0.78, 1.47)	1.03 (0.71, 1.53)	1.24 (1.07, 1.44)	1.25 (0.98, 1.59)	1.19 (0.70, 2.03)	1.34 (1.10, 1.63)	1.55 (1.19, 2.01)	1.47 (0.99, 2.21)	2.38 (1.61, 3.47)
0.83 (0.64, 1.09)	0.70 (0.47, 1.03)	Doc + platinum	0.74 (0.55, 1.00)	0.72 (0.49, 1.06)	0.86 (0.60, 1.24)	0.87 (0.58, 1.29)	0.83 (0.49, 1.40)	0.93 (0.61, 1.39)	1.08 (0.69, 1.65)	1.03 (0.70, 1.52)	1.65 (1.13, 2.40)
1.13 (0.98, 1.28)	0.94 (0.68, 1.28)	1.35 (1.00, 1.83)	Gem + platinum	0.97 (0.76, 1.23)	1.17 (0.88, 1.52)	1.18 (0.84, 1.63)	1.12 (0.70, 1.78)	1.25 (0.89, 1.75)	1.45 (1.00, 2.08)	1.39 (1.00, 1.87)	2.22 (1.64, 3.00)
1.16 (0.88, 1.50)	0.97 (0.65, 1.42)	1.39 (0.94, 2.05)	1.03 (0.81, 1.31)	Gem + bev + platinum	1.20 (0.83, 1.71)	1.21 (0.80, 1.80)	1.16 (0.68, 1.94)	1.30 (0.85, 1.93)	1.50 (0.96, 2.29)	1.43 (0.96, 2.09)	2.29 (1.57, 3.32)
0.97 (0.76, 1.23)	0.81 (0.70, 0.94)	1.16 (0.81, 1.68)	0.86 (0.66, 1.14)	0.83 (0.59, 1.21)	Pac + bev + platinum	1.01 (0.83, 1.22)	0.96 (0.57, 1.60)	1.08 (0.89, 1.32)	1.25 (0.98, 1.59)	1.18 (0.82, 1.72)	1.92 (1.34, 2.72)
0.96 (0.71, 1.30)	0.80 (0.63, 1.02)	1.15 (0.77, 1.73)	0.85 (0.61, 1.19)	0.82 (0.56, 1.25)	0.99 (0.82, 1.20)	Peme + bev + platinum	0.96 (0.55, 1.65)	1.07 (0.82, 1.41)	1.24 (0.91, 1.69)	1.18 (0.78, 1.81)	1.90 (1.26, 2.83)
1.00 (0.64, 1.56)	0.84 (0.49, 1.44)	1.21 (0.71, 2.06)	0.89 (0.56, 1.43)	0.86 (0.51, 1.48)	1.04 (0.63, 1.74)	1.05 (0.61, 1.82)	Vin + platinum	1.13 (0.64, 1.96)	1.30 (0.74, 2.31)	1.24 (0.72, 2.11)	1.98 (1.18, 3.34)
0.90 (0.66, 1.22)	0.75 (0.61, 0.91)	1.08 (0.72, 1.64)	0.80 (0.57, 1.12)	0.77 (0.52, 1.17)	0.93 (0.76, 1.13)	0.93 (0.71, 1.22)	0.89 (0.51, 1.55)	Pac/nab-pac + atezo + platinum	1.16 (0.91, 1.47)	1.10 (0.73, 1.68)	1.77 (1.17, 2.65)
0.77 (0.55, 1.09)	0.64 (0.50, 0.84)	0.93 (0.61, 1.45)	0.69 (0.48, 1.00)	0.67 (0.44, 1.04)	0.80 (0.63, 1.02)	0.80 (0.59, 1.10)	0.77 (0.43, 1.36)	0.86 (0.68, 1.10)	Pac + bev + atezo + platinum	0.95 (0.61, 1.49)	1.53 (0.99, 2.35)
0.81 (0.61, 1.08)	0.68 (0.45, 1.01)	0.97 (0.66, 1.44)	0.72 (0.53, 1.00)	0.70 (0.48, 1.04)	0.84 (0.58, 1.21)	0.85 (0.55, 1.28)	0.81 (0.47, 1.40)	0.91 (0.60, 1.38)	1.06 (0.67, 1.63)	Peme + atezo + platinum	1.60 (1.10, 2.34)
0.51 (0.39, 0.66)	0.42 (0.29, 0.62)	0.61 (0.42, 0.89)	0.45 (0.33, 0.61)	0.44 (0.30, 0.64)	0.52 (0.37, 0.75)	0.53 (0.35, 0.79)	0.51 (0.30, 0.85)	0.56 (0.38, 0.86)	0.65 (0.43, 1.01)	0.62 (0.43, 0.91)	Pembro + peme + platinum

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.

DI: 31.42; Deviance: 18.14; SD: 0.06.

Atezo: Atezolizumab; Bev: Bevacizumab; CrI: Credible interval; Doc: Docetaxel; Gem: Gemcitabine; Pac: Paclitaxel; Pembro: Pembrolizumab; Peme: Pemetrexed; SD: Standard deviation; Vin: Vinorelbine.

Table 8. Data used for progression-free survival network meta-analysis.

Study	Reference	Intervention	HR	logHR(SE)
AVAIL	Gem + platinum	Gem + bev + platinum	0.82	-0.20 (0.09)
BEYOND	Pac/nab-pac + platinum	Pac + bev + platinum	0.40	-0.92 (0.16)
CLEAR	Pac + bev + platinum	Peme + bev + platinum	0.83	-0.19 (0.16)
ECOG 4599	Pac/nab-pac + platinum	Pac + bev + platinum	0.66	-0.42 (0.08)
ERACLE	Peme + platinum	Pac + bev + platinum	1.27	0.24 (0.20)
IMpower130	Pac/nab-pac + platinum	Pac/nab-pac + atezo + platinum	0.64	-0.45 (0.09)
IMpower132	Peme + platinum	Peme + atezo + platinum	0.76	-0.28 (0.10)
IMpower150	Pac/nab-pac + bev + platinum	Pac + bev + atezo + platinum	0.59	-0.53 (0.09)
JMDB	Peme + platinum	Gem + platinum	1.11	0.11 (0.07)
JMIL	Peme + platinum	Gem + platinum	0.95	-0.05 (0.13)
JO19907	Pac/nab-pac + platinum	Pac + bev + platinum	0.61	-0.49 (0.19)
KEYNOTE-021G	Peme + platinum	Pembro + peme + platinum	0.53	-0.63 (0.24)
KEYNOTE-189	Peme + platinum	Pembro + peme + platinum	0.52	-0.65 (0.10)
NAVotrial01	Peme + platinum	Vin + platinum	1.16	0.15 (0.19)
PointBreak	Pac + bev + platinum	Peme + bev + platinum	0.83	-0.19 (0.08)
PRONOUNCE	Peme + platinum	Pac + bev + platinum	0.94	-0.06 (0.12)
Rodrigues-Pereira (2011)	Peme + platinum	Doc + platinum	1.04	0.04 (0.15)
Sun (2015)	Peme + platinum	Gem + platinum	1.33	0.29 (0.12)
TRAIL	Peme + platinum	Doc + platinum	0.97	-0.03 (0.16)

Atezo: Atezolizumab; Bev: Bevacizumab; Doc: Docetaxel; Gem: Gemcitabine; HR: Hazard ratio; Pac: Paclitaxel; Pembro: Pembrolizumab; Peme: Pemetrexed; SE: Standard error; Vin: Vinorelbine.

Notably, trials differed in the proportion of east Asian patients enrolled. Although it is considered a positive prognostic factor in metastatic NSCLC, east Asian ethnicity is not considered a treatment-effect modifier [86]. In addition, there was variation among trials in the proportion of males enrolled. Female sex is associated with improved chemotherapy outcomes in nonsquamous NSCLC [87–89]. Although KEYNOTE-021G had a higher proportion of female patients than any other trial, sex was balanced between the study arms and, consequently, female sex is unlikely to modify the treatment effect in this trial. Imbalances in sex between study arms in Rodrigues-Pereira 2011 and Johnson 2004 may have caused the efficacy of docetaxel + platinum and paclitaxel + bevacizumab + platinum to be overestimated [6].

Five trials permitted within trial crossover following disease progression, potentially biasing the NMA results for OS. In KEYNOTE-021G and KEYNOTE-189, patients could crossover from pemetrexed + platinum to pembrolizumab monotherapy [6,7]. As a result, the efficacy of pembrolizumab + pemetrexed + platinum relative to comparators in the network may be underestimated. Patients randomized to the paclitaxel/nab-paclitaxel + platinum arm could crossover to the paclitaxel/nab-paclitaxel + atezolizumab + platinum arm in IMpower130 protocol versions 1–4 [10]. In Johnson 2004, patients who received platinum + paclitaxel/nab-paclitaxel could crossover to receive bevacizumab monotherapy [58]. This may cause the efficacy of platinum + paclitaxel/nab-paclitaxel relative to alternative interventions to be overestimated. In TRAIL, patients on either arm could crossover to receive the other study drug or an *EGFR* inhibitor []. Because the proportion of patients who crossed over was similar in each arm, crossover was unlikely to bias the estimate of docetaxel + platinum's treatment effect relative to other interventions in the network.

The model relied on the assumptions of random effects and proportional hazards. In networks for both OS and PFS, there were enough trials along each connection to employ the random-effects model reliably. Because the random-effects model assumes that each study has its own true treatment effect and these are assumed to follow a distribution around an overall mean (the meta-analysis mean), the model is more plausible than fixed effects because it is consistent with the presence of effect modifiers. Additionally, the analysis was conducted using a proportional hazards model, which rests on the assumption that the hazard functions of competing interventions for OS and PFS do not cross. Finally, this study did not make comparisons of regimens by PD-L1 expression level due to differences in PD-L1 assays, scoring and cutoff points employed in trials conducted by different study sponsors [90,91]. Comparisons of regimens in PD-L1-expressing patients are an important area for future research.

Table 9. Results of random effects network meta-analysis; progression-free survival; results presented as constant hazard ratios between all competing interventions with 95% credible intervals.

Peme + platinum	0.55 (0.35, 0.79)	0.99 (0.72, 1.36)	0.89 (0.72, 1.11)	1.09 (0.70, 1.69)	0.96 (0.69, 1.29)	1.16 (0.75, 1.72)	0.86 (0.53, 1.42)	0.86 (0.48, 1.42)	1.64 (0.99, 2.56)	1.32 (0.91, 1.93)	1.92 (1.39, 2.61)
1.81 (1.27, 2.83)	Pac/nab-pac + platinum	1.80 (1.13, 3.11)	1.61 (1.07, 2.66)	1.96 (1.13, 3.67)	1.74 (1.41, 2.29)	2.10 (1.51, 3.13)	1.56 (0.86, 3.06)	1.56 (1.08, 2.28)	2.95 (1.96, 4.71)	2.39 (1.45, 4.36)	3.47 (2.19, 5.97)
1.01 (0.74, 1.39)	0.56 (0.32, 0.88)	Doc + platinum	0.90 (0.62, 1.31)	1.09 (0.64, 1.87)	0.97 (0.61, 1.48)	1.17 (0.68, 1.93)	0.87 (0.49, 1.55)	0.87 (0.45, 1.56)	1.65 (0.91, 2.85)	1.33 (0.82, 2.17)	1.93 (1.24, 2.98)
1.12 (0.90, 1.39)	0.62 (0.38, 0.93)	1.12 (0.76, 1.62)	Gem + platinum	1.22 (0.83, 1.78)	1.08 (0.73, 1.55)	1.31 (0.80, 2.06)	0.96 (0.57, 1.67)	0.97 (0.52, 1.67)	1.84 (1.06, 3.03)	1.48 (0.96, 2.31)	2.15 (1.46, 3.13)
0.92 (0.59, 1.42)	0.51 (0.27, 0.88)	0.91 (0.53, 1.57)	0.82 (0.56, 1.20)	Gem + bev + platinum	0.89 (0.51, 1.49)	1.07 (0.58, 1.92)	0.80 (0.41, 1.53)	0.79 (0.38, 1.52)	1.50 (0.77, 2.83)	1.22 (0.69, 2.17)	1.77 (1.02, 2.99)
1.04 (0.78, 1.45)	0.57 (0.44, 0.71)	1.03 (0.68, 1.63)	0.92 (0.64, 1.38)	1.13 (0.67, 1.95)	Pac + bev + platinum	1.21 (0.92, 1.59)	0.89 (0.51, 1.64)	0.90 (0.56, 1.36)	1.70 (1.18, 2.44)	1.37 (0.86, 2.30)	1.99 (1.29, 3.15)
0.86 (0.58, 1.33)	0.48 (0.32, 0.66)	0.85 (0.52, 1.47)	0.76 (0.49, 1.25)	0.93 (0.52, 1.72)	0.83 (0.63, 1.09)	Peme + bev + platinum	0.74 (0.39, 1.44)	0.74 (0.43, 1.21)	1.40 (0.89, 2.23)	1.13 (0.66, 2.05)	1.65 (0.99, 2.79)
1.16 (0.71, 1.89)	0.64 (0.33, 1.16)	1.15 (0.64, 2.03)	1.04 (0.60, 1.74)	1.26 (0.65, 2.42)	1.12 (0.61, 1.97)	1.35 (0.69, 2.54)	Vin + platinum	1.00 (0.46, 1.99)	1.90 (0.94, 3.64)	1.53 (0.83, 2.82)	2.23 (1.22, 3.93)
1.16 (0.71, 2.08)	0.64 (0.44, 0.93)	1.15 (0.64, 2.24)	1.03 (0.60, 1.93)	1.26 (0.66, 2.62)	1.11 (0.74, 1.78)	1.35 (0.82, 2.30)	1.00 (0.50, 2.17)	Pac/nab-pac + atezo + platinum	1.89 (1.08, 3.48)	1.53 (0.84, 3.11)	2.22 (1.25, 4.30)
0.61 (0.39, 1.01)	0.34 (0.21, 0.51)	0.61 (0.35, 1.10)	0.54 (0.33, 0.94)	0.67 (0.35, 1.29)	0.59 (0.41, 0.85)	0.71 (0.45, 1.12)	0.53 (0.27, 1.06)	0.53 (0.29, 0.92)	Pac + bev + atezo + platinum	0.81 (0.45, 1.52)	1.17 (0.68, 2.12)
0.76 (0.52, 1.09)	0.42 (0.23, 0.69)	0.75 (0.46, 1.22)	0.68 (0.43, 1.04)	0.82 (0.46, 1.45)	0.73 (0.43, 1.16)	0.88 (0.49, 1.50)	0.65 (0.35, 1.21)	0.65 (0.32, 1.20)	1.24 (0.66, 2.22)	Peme + atezo + platinum	1.45 (0.88, 2.36)
0.52 (0.38, 0.72)	0.29 (0.17, 0.46)	0.52 (0.34, 0.81)	0.46 (0.32, 0.69)	0.57 (0.33, 0.98)	0.50 (0.32, 0.77)	0.61 (0.36, 1.01)	0.45 (0.25, 0.82)	0.45 (0.23, 0.80)	0.85 (0.47, 1.48)	0.69 (0.42, 1.14)	Pembro + peme + platinum

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment.
All bolded values are statistically meaningful at the 0.05 significance level.

DiC: 34.07; Deviance: 18.88; SD: 0.13.

Atezo: Atezolizumab; Bev: Bevacizumab; CrI: Credible interval; Doc: Docetaxel; Gem: Gemcitabine; Pac: Paclitaxel; Pembro: Pembrolizumab; Peme: Pemetrexed; SD: Standard deviation; Vin: Vinorelbine.

Table 10. Ranking of treatments, overall survival and random effects.

Treatment	Probability of being the best
Pembro + peme + platinum	0.956188
Pac + bev + atezo + platinum	0.025688
Peme + atezo + platinum	0.00675
Vin + platinum	0.005625
Doc + platinum	0.003875
Pac/nab-pac + atezo + platinum	0.001188
Peme + bev + platinum	0.0005
Gem + bev + platinum	0.000188
Peme + platinum	0
Pac/nab-pac + platinum	0
Gem + platinum	0
Pac + bev + platinum	0

Atezo: Atezolizumab; Bev: Bevacizumab; Doc: Docetaxel; Gem: Gemcitabine; Pac: Paclitaxel; Pembro: Pembrolizumab; Peme: Pemetrexed; Vin: Vinorelbine.

Table 11. Ranking of treatments, progression-free survival, random effects.

Treatment	Probability of being the best
Pembro + peme + platinum	0.672750
Pac + bev + atezo + platinum	0.241313
Peme + atezo + platinum	0.045313
Peme + bev + platinum	0.016188
Gem + bev + platinum	0.015625
Vin + platinum	0.004063
Pac/nab-pac + atezo + platinum	0.002875
Doc + platinum	0.001750
Gem + platinum	0.000125
Peme + platinum	0
Pac/nab-pac + platinum	0
Pac + bev + platinum	0

Atezo: Atezolizumab; Bev: Bevacizumab; Doc: Docetaxel; Gem: Gemcitabine; Pac: Paclitaxel; Pembro: Pembrolizumab; Peme: Pemetrexed; Vin: Vinorelbine.

Of all lung cancer diagnoses, NSCLC accounts for 80–85% of cases and has poor survival rates among late-stage NSCLC [92]. In the USA, the 5-year survival rate is 26, 10 and <1% for stage IIIB, stage IVA and stage IVB NSCLC, respectively [92]. This analysis reflects the OS and PFS benefit provided by the pembrolizumab + pemetrexed + platinum regimen for those diagnosed with metastatic, nonsquamous NSCLC. In conclusion, pembrolizumab + pemetrexed + platinum had a better HR for survival compared with alternative interventions. This benefit was statistically significant versus all platinum doublets, platinum doublet + bevacizumab, platinum + paclitaxel/nab-paclitaxel + atezolizumab and pemetrexed + atezolizumab + platinum for the first-line treatment of metastatic nonsquamous NSCLC, with respect to OS. There was a numerical benefit for OS compared with paclitaxel + bevacizumab + atezolizumab + platinum. Additionally, pembrolizumab + pemetrexed + platinum had a statistically significant benefit for PFS over all platinum doublet therapies, as well as paclitaxel + bevacizumab + platinum, gemcitabine + bevacizumab + platinum and paclitaxel/nab-paclitaxel + atezolizumab + platinum.

Future perspective

Providing significant increases in survival, PD-1/PD-L1-directed therapies are an important innovation in the first-line treatment of nonsquamous NSCLC. The accumulation of clinical experience with PD-1/PD-L1 inhibitors in this population over the next 5–10 years will provide opportunities to incorporate new clinical trials as well as real-world evidence into future analyses in order to verify these conclusions.

Executive summary

Background

- Several clinical trials evaluating PD-1/PD-L1 inhibitors in combination with traditional chemotherapy regimens for first-line treatment of nonsquamous non-small-cell lung cancer (NSCLC) have been recently published.
- In order to evaluate the relative efficacy of treatments that have not been studied head-to-head in this population, a systematic literature review and network meta-analysis were conducted in accordance with a prespecified study protocol.

Systematic literature review

- The systematic review, current through November 2018, was used to identify studies evaluating approved first-line treatments in metastatic nonsquamous NSCLC patients without known *EGFR* mutations or *ALK* translocations.
- Fifty-five publications pertaining to 22 trials formed a connected network with 12 interventions (total intent to treat population: 10,826).

Bayesian network meta-analysis methodology

- Bayesian network meta-analysis allows for simultaneous comparison of all included interventions and estimates relative treatment effects between any pair of interventions for a connected network.
- With Bayesian methodology, it is possible to calculate the probability of being the best treatment out of all other interventions included in a connected network.

Feasibility assessment

- The included trials were similar in the distribution of trial characteristics and patient characteristics including Eastern Cooperative Oncology Group performance status, disease stage, and sex distribution.
- Substantial variation in ethnicity was observed between trials. Six trials were conducted exclusively in east Asian patients and five trials reported that fewer than 15% of enrolled patients were east Asian. Although east Asian ethnicity is a prognostic factor for patients with nonsquamous NSCLC, it is not thought to be a relative treatment-effect modifier.

Network meta-analysis results

- This analysis suggests combining pembrolizumab with pemetrexed and platinum results in longer overall survival compared with all platinum doublet chemotherapy regimens as well as platinum doublets combined with atezolizumab or bevacizumab for the first-line treatment of metastatic nonsquamous NSCLC.
- Based on median rankings and probabilities of being the best treatment, pembrolizumab + pemetrexed + platinum had a median rank of 1 and has the highest probability of being the best treatment regimen for both overall and progression-free survivals.

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