First-line Pembrolizumab Versus Pembrolizumab Plus Chemotherapy Versus Chemotherapy Alone in Non–small-cell Lung Cancer: A Systematic Review and Network Meta-analysis

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Abstract

Immunotherapy has revolutionized lung cancer management. Our study focused on the efficacy of first-line pembrolizumab for treatment of non–small-cell lung cancer by summarizing 4 phase III clinical trials. This analysis revealed that pembrolizumab in combination with chemotherapy exhibited better survival outcome than pembrolizumab monotherapy.

Background: This study aimed to comprehensively review the available evidence regarding the efficacy of first-line pembrolizumab for advanced/metastatic non–small-cell lung cancer (NSCLC), and to compare pembrolizumab monotherapy versus pembrolizumab plus chemotherapy versus chemotherapy alone. **Materials and Methods:** A search of the PubMed, EMBASE, and Cochrane Library databases was performed in July 2018, and abstracts from the American Society of Clinical Oncology meetings (2015-2018) were reviewed. Summaries of the results were pooled using a random-effect model to determine the pooled hazard ratio (HR) for progression-free survival (PFS), overall survival (OS), and their 95% confidence intervals (CIs). A network meta-analysis was used to indirectly compare pembrolizumab monotherapy with pembrolizumab plus chemotherapy. **Results:** A total of 4 relevant phase III trials comprising 2754 patients were identified. Pembrolizumab (with or without chemotherapy) led to significant improvements in OS and PFS, irrespective of the programmed cell death ligand 1 (PD-L1) tumor proportion score (TPS). In particular, for the subgroup with PD-L1 TPS $\geq$ 50%, the HR of PFS was 0.49 (95% CI, 0.32-0.76; $P = .001$), and that of OS was 0.57 (95% CI, 0.45-0.73; $P < .001$). In terms of PFS, pembrolizumab plus chemotherapy was superior to pembrolizumab monotherapy with an HR of PFS 0.52 (95% CI, 0.27-0.99; $P = .048$) for the subgroup with PD-L1 TPS $\geq$ 50%. **Conclusions:** For patients with NSCLC with PD-L1 TPS $\geq$ 50%, pembrolizumab plus chemotherapy has a better PFS than pembrolizumab monotherapy in this meta-analysis. To confirm this finding, a prospective phase III trial that directly compares the treatments is warranted.

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Keywords: Immunotherapy, Meta-analysis, Network meta-analysis, Non-small cell lung cancer, Pembrolizumab

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide.[1] The choice of first-line treatment for advanced non–small-cell lung cancer (NSCLC) depends on the presence of genetic aberrations, such as mutations of epidermal growth factor receptor (EGFR) and translocations of anaplastic lymphoma kinase (ALK). However, only 10% to 20% of patients with NSCLC have these actionable mutations.[2] For the remaining patients, treatment options are limited to platinum-based cytotoxic chemotherapy, with a response rate ranging between 15% and 30%.[3,4] The recent

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development of immune checkpoint inhibitors targeting the programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1) axis has revolutionized our approach to treating NSCLC in first-line as well as second-line treatments.

Pembrolizumab, an IgG4-engineered humanized anti-PD-1 antibody, was approved by the United States Food and Drug Administration for second-line treatment of NSCLC,[5,6] and has recently been rigorously evaluated as a first-line therapy for advanced NSCLC. Based on the safety and superior survival outcomes reported in the phase III KEYNOTE-024 trial,[7-9] the United States Food and Drug Administration approved pembrolizumab monotherapy as a first-line treatment for patients with advanced NSCLC whose tumors express a PD-L1 tumor proportion score (TPS) $\geq$ 50%. In recent reports of the KEYNOTE-189 and KEYNOTE-407 studies, first-line pembrolizumab, in combination with standard platinum doublet chemotherapy, showed improved survival outcome compared with chemotherapy alone for metastatic non-squamous NSCLC as well as squamous NSCLC, irrespective of PD-L1 expression.[10-12] Subsequent to these studies, results of a randomized phase III KEYNOTE-042 trial that compared pembrolizumab monotherapy with chemotherapy in PD-L1 TPS $\geq$ 1% were presented.[13] In the KEYNOTE-042 trial, pembrolizumab alone significantly improved overall survival (OS) compared with chemotherapy for first-line NSCLC with PD-L1 TPS $\geq$ 50, 20%, $\geq$ 1%.

According to these prospective randomized trials, pembrolizumab plus chemotherapy was found to be better than chemotherapy alone, regardless of PD-L1 expression. Pembrolizumab monotherapy was better than chemotherapy in PD-L1−positive NSCLC, especially PD-L1 TPS $\geq$ 50%. However, there have been no reported trials that directly compare pembrolizumab monotherapy versus pembrolizumab plus chemotherapy in the first-line treatment setting of advanced/metastatic NSCLC. In this meta-analysis, we aimed to compare pembrolizumab monotherapy versus pembrolizumab plus chemotherapy by comprehensively summarizing the current available evidence of the therapeutic efficacy of pembrolizumab as a first-line treatment for advanced/metastatic NSCLC.

Material and Methods

Inclusion Criteria of Studies

All phase III clinical trials that reported the outcomes of first-line pembrolizumab with or without platinum doublet chemotherapy compared with those of first-line platinum doublet chemotherapy alone for patients with advanced/metastatic NSCLC were considered eligible for inclusion in this meta-analysis. The study participants were patients with untreated, histologically or cytologically confirmed, locally advanced or metastatic NSCLC with no sensitizing *EGFR* mutations or *ALK* translocations. Patients had adequate organ and bone marrow function and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were randomly assigned to receive either pembrolizumab with or without chemotherapy or platinum-based chemotherapy alone. Studies concerning pembrolizumab not used as a first-line treatment, and studies not published in English were excluded.

Literature Search Strategy

The initial literature search was conducted through PubMed, EMBASE, and the Cochrane Library. The following trial databases were also searched for ongoing and unpublished trials: the Meta-Register of controlled clinical trials (available at: http://www.controlled-trials.com/) and the National Institutes of Health Clinical Trials Registry (available at: http://clinicaltrials.gov/). In addition, we performed an individual search of abstract listings from the annual meetings of the American Society of Clinical Oncology, the European Society of Medical Oncology, and the World Conference of Lung Cancer (2015-2018) to identify potentially relevant studies. The detailed search strategy is shown in Supplemental Table 1 (in the online version). Two independent reviewers (R.K., B.K.) performed an independent review of all of the obtained abstracts to assess their eligibility according to the inclusion criteria in July 2018. For abstracts that were inconclusive for eligibility, the entire article was thoroughly reviewed by 2 reviewers (R.K., B.K.). Each trial that fulfilled the inclusion criteria was assessed for methodological quality using the Cochrane Collaboration tool.[14] All disagreements between reviewers were resolved by consensus.

Data Extraction

The following items were extracted from the articles: name of the first author, title and phase of each trial, year of publication, characteristics of the treatments used in each arm, number of patients, proportion of non-squamous NSCLC, proportion of East Asians, median follow-up duration, hazard ratio (HR) for OS and progression-free survival (PFS) with corresponding 95% confidence intervals (CIs), rate of treatment-related adverse events (AEs), and rate of immune-related AEs. To avoid errors in the data extraction process, 2 independent reviewers (R.K., B.K.) extracted data and compared their results. All data were checked for internal consistency, and disagreements were resolved by discussion.

Statistical Analysis

The primary outcome was PFS, defined as the time from random assignment to disease progression or death from any cause, whichever occurred first. Secondary outcomes were OS and treatment-related and immune-related AEs. OS was defined as the time from random assignment to death from any cause.

Because the treatment strategies of the experimental arm in each study was slightly different (eg, pembrolizumab plus chemotherapy or pembrolizumab alone), a random-effect model using the Mantel-Haenzel method was used for calculating pooled HRs, 95% CIs, and P values in subgroups with PD-L1 TPS $\geq$ 50%, 1% to 40%, and $<$ 1%. Relative risks (RRs) for developing AEs were estimated by using available statistical information from relevant trials. Two-sided P values less than .05 were considered statistically significant. Statistical heterogeneity was assessed using a formal statistical test that used the χ^2 test and I^2 statistic.[15,16]

To compare pembrolizumab monotherapy versus pembrolizumab with platinum-based chemotherapy, network meta-analyses within a frequentist framework were carried out to identify indirect evidence from relevant trials.[17,18] This is a novel approach for network meta-analysis that follows the graph-theoretical methodology. This method exploits the analogy

between treatment networks and electrical networks to construct the network meta-analysis. This analysis yields a P-score that measures the extent of certainty that a treatment is better than another treatment, averaged over all competing treatments.[19]

Statistical analyses were performed using STATA software (version 13.0; StataCorp LP, College Station, TX), and R (version 3.5.0; http://www.r-project.org) with the netmeta package. The present study adhered to the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses report (PRISMA Statement).[20]

Results

Study Selection

The search of electronic databases and meeting abstracts resulted in a total of 270 citations (Figure 1). The abstracts of all the citations were examined for relevance to the inclusion criteria. For all of the abstracts that were not excluded based on the initial review, the entire article was reviewed in detail for suitability of inclusion. Based on this review process, 4 articles from 4 phase III clinical trials (KEYNOTE-024, KEYNOTE-407, KEYNOTE-189, and KEYNOTE-042) met the inclusion criteria (Table 1).[8,10,12,13]

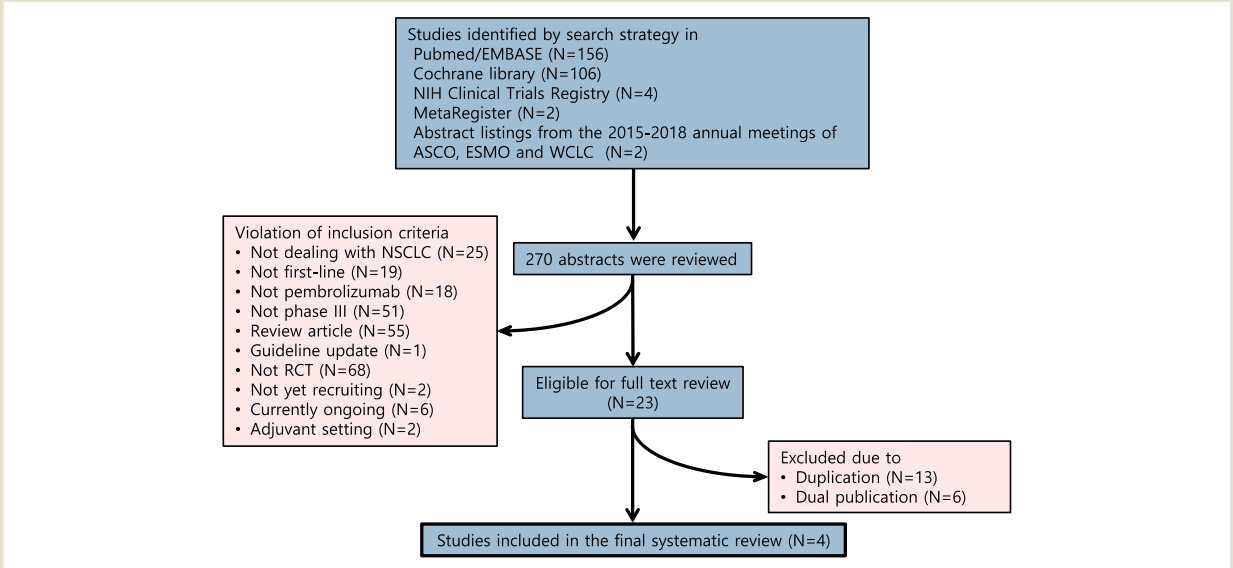
Description of Studies

The KEYNOTE-024 and KEYNOTE-042 trials targeted advanced/metastatic NSCLC with any histology with PD-L1 TPS $\geq$ 50% and $\geq$ 1%, respectively.[8,13] Irrespective of PD-L1 expression, the other 2 trials exclusively enrolled patients with stage IV non-squamous NSCLC (KEYNOTE-189) or squamous NSCLC (KEYNOTE-407).[10,12] Patients assigned to the pembrolizumab group in the KEYNOTE-024 and KEYNOTE-042 trials received pembrolizumab monotherapy. On the other hand, the pembrolizumab group in the KEYNOTE-189 and KEYNOTE-407 trials received pembrolizumab in combination with platinum-based doublet chemotherapy. For all 4 trials, pembrolizumab was administered intravenously at a dose of 200 mg every 3 weeks for 35 cycles, whereas there were differences in the chemotherapeutic agents between trials (see Supplemental Table 2 in the online version). For all studies except the KEYNOTE-042 trial, crossover from the chemotherapy group to the pembrolizumab group was permitted in the event of disease progression. Chemotherapy alone showed similar treatment effects in the 4 trials in terms of median PFS and OS, implying control arms in the 4 studies were comparable (see Supplemental Table 3 in the online version).

Survival Outcomes

The 4 studies included a total of 2754 individual patients, 1479 of whom received pembrolizumab (with or without chemotherapy), and 1275 patients received platinum doublet chemotherapy alone. The HRs of PFS and their 95% CIs in each subgroup with different PD-L1 TPS were extracted from the 4 studies.[8,10,12,13] For a total of 1252 patients with PD-L1 TPS $\geq$ 50%, the pooled HR of PFS was 0.49 (95% CI, 0.32-0.76; $P = .001$) (Figure 2A). The PFS data of patients with PD-L1 TPS 1% to 49% or < 1% were extractable from 2 of the 4 trials, comprising a total of 777 patients,[10,12] resulting in an HR of 0.56 (95% CI, 0.43-0.72; $P < .001$) and 0.72 (95% CI, 0.56-0.92; $P = .009$), respectively. For a total of 1252 patients with PD-L1 TPS $\geq$ 50%, the pooled HR of OS was 0.57 (95% CI, 0.45-0.73; $P < .001$) (Figure 2B). The updated OS data of the KEYNOTE-024 trial, which was recently reported, was used for this analysis.[9] The pooled HR of OS for patients with PD-L1 TPS 1% to 49% and < 1% were 0.70 (95% CI, 0.47-1.02; $P = .065$) and 0.60 (95% CI, 0.43-0.83; $P = .002$), respectively.

Figure 1 Flow Diagram for Study Review and Inclusion. This Search was Performed in July 2018



Abbreviations: ASCO = American Society of Clinical Oncology; ESMO = European Society of Medical Oncology; NIH = National Institutes of Health; NSCLC = non–small-cell lung cancer; RCT = randomized controlled trial; WCLC = World Conference of Lung Cancer.

Table 1 Characteristics of Studies Included in the Meta-analysis

Source	Trial	Histology	Primary Endpoint	Characteristics of Treatment in Each Arm	East Asian, N (%)	Non-squamous, N (%)	No. Patients		No. Patients With PD-L1 TPS ≥ 50%		Median Follow-up Duration, (Range), mos
							Pembrolizumab	Control	Pembrolizumab	Control	
Reck et al[8] 2016 and 2017	KEYNOTE-024 (NCT02142738)	Non-squamous Squamous	PFS	Pembrolizumab vs. chemotherapy	40 (13.1)	249 (81.6)	154	151	154	151	19.1 (14.3-27.6)
Gandhi et al[10] 2018	KEYNOTE-189 (NCT02578680)	Non-squamous	OS PFS	Pembrolizumab + chemotherapy vs. chemotherapy	10 (1.6)	616 (100)	410	206	132	70	10.5 (0.2-20.4)
Paz-Ares et al[12] 2018	KEYNOTE-407 (NCT02775435)	Squamous	OS PFS	Pembrolizumab + chemotherapy vs. chemotherapy	106 (19.0)	0 (0)	278	281	73	73	7.8 (0.1-19.1)
Lopes et al[13] 2018	KEYNOTE-042 (NCT02228094)	Non-squamous Squamous	OS	Pembrolizumab vs. chemotherapy	370 (29.0)	782 (61.4)	637	637	299	300	12.8 (0.1-38.3)

Abbreviations: OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; TPS = tumor proportion score.

The 4 trials analyzed for PFS in patients with PD-L1 TPS ≥ 50% exhibited significant heterogeneity ($\chi^2 = 22.53$, degrees of freedom = 3 [$P < .001$]; $I^2 = 86.7\%$). We noted that this heterogeneity stemmed from different treatment strategies for the experimental arm in the 4 trials. The KEYNOTE-189 and KEYNOTE-402 trials, which treated patients in the experimental arm with pembrolizumab in combination with chemotherapy, showed a better pooled HR of PFS 0.36 (95% CI, 0.27-0.48; $P < .001$) (see Supplemental Figure 1 in the online version) than the other 2 trials (HR of PFS 0.65; 95% CI, 0.40-1.04; $P = .069$) that administered pembrolizumab alone for the experimental arm. Collectively, this heterogeneity implies that pembrolizumab plus chemotherapy and pembrolizumab monotherapy are different in terms of therapeutic effect.

Indirect Comparison Between Pembrolizumab Plus Chemotherapy Versus Pembrolizumab Monotherapy

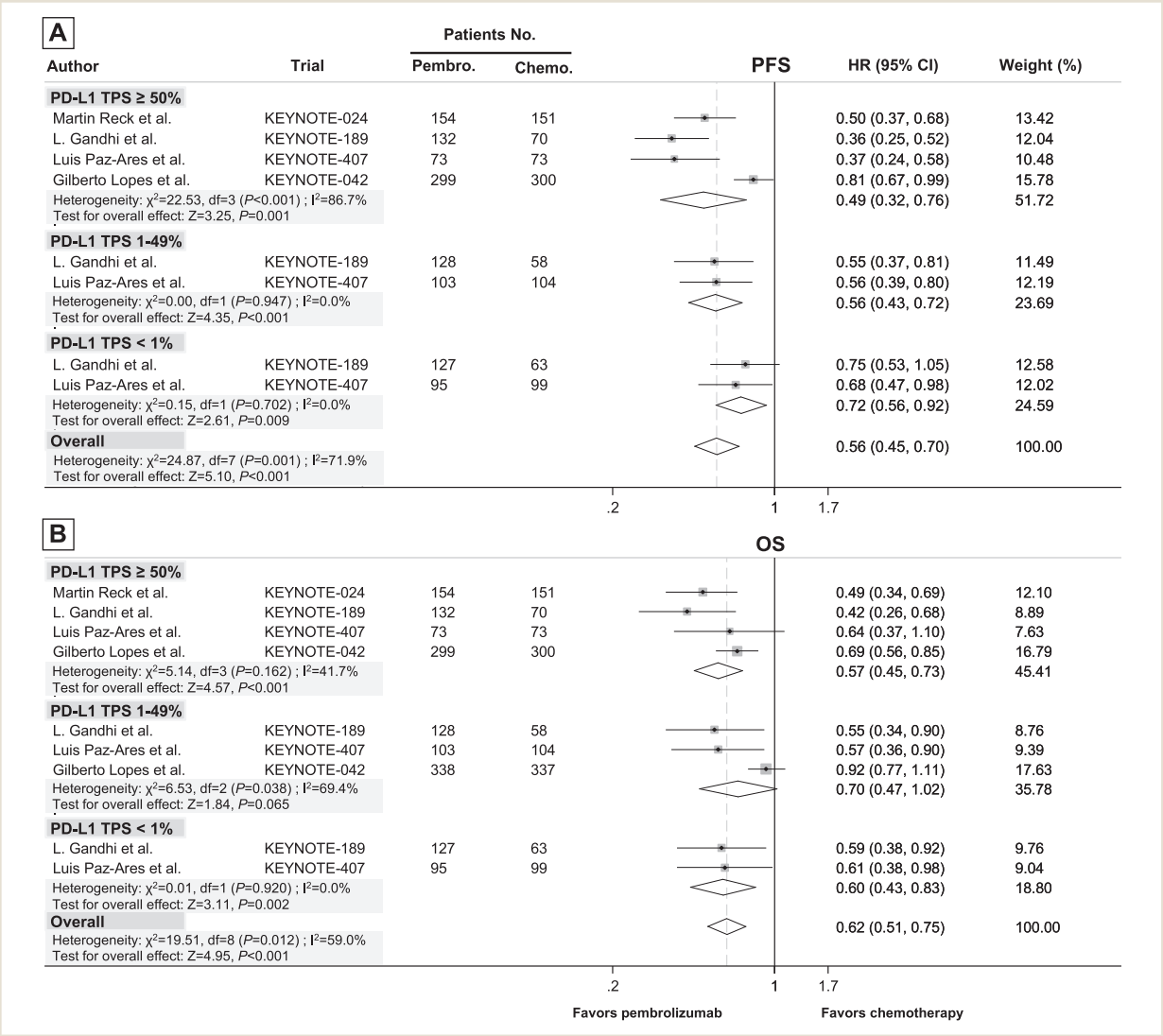
To address the different therapeutic effect of pembrolizumab plus chemotherapy and pembrolizumab monotherapy, a network meta-analysis was performed within a frequentist framework, as there were no studies directly comparing these 2 treatments.[17,18] Survival data for this analysis in patients with PD-L1 TPS ≥ 50% were eligible from all 4 trials.[8,10,12,13] A recently reported HR of OS in KEYNOTE-024 trial was used for this analysis.[9] Compared with pembrolizumab monotherapy, pembrolizumab plus chemotherapy showed an HR of PFS 0.52 (95% CI, 0.27-0.99; $P = .048$) (Figure 3A), and an HR of OS 0.80 (95% CI, 0.36-1.79; $P = .485$) (Figure 3B). There were no significant heterogeneities for PFS ($I^2 = 0.0\%$; $P = .425$) and OS ($I^2 = 0.0\%$; $P = .610$). In terms of P-score, pembrolizumab plus chemotherapy had the highest extent of certainty, being better than any other treatment for first-line treatment in advanced NSCLC with PD-L1 ≥ 50%. A network meta-analysis for other subgroups (ie, not PD-L1 TPS ≥ 50%) could not be performed because of paucity of data.

RRs of treatment-related and immune-related AEs of pembrolizumab plus chemotherapy compared with pembrolizumab were estimated using available statistical information from all four trials.[9,10,12,13] Grade 3 to 5 treatment-related AEs were significantly prevalent in pembrolizumab plus chemotherapy, with RR 2.14 (95% CI, 1.50-3.05; $P < .001$) (Figure 4A), which was similar to chemotherapy alone (RR, 2.09; 95% CI, 1.53-2.87; $P < .001$). The RR of grade 3 to 5 immune-related AEs of pembrolizumab plus chemotherapy was 0.41 (95% CI, 0.08-2.16; $P = .293$) with a P-score of 0.44 (Figure 4B).

Toxicity Profile

The treatment-related and immune-related AEs were assessed in the 4 trials using random effects analysis because of the heterogeneities (see Supplemental Figure 2 in the online version).[8,10,12,13] The updated AE data of the KEYNOTE-024 trial was used for this analysis.[9] The difference in the rates of treatment-related AEs in the pembrolizumab and chemotherapy arms was not significantly different. On the other hand, patients who had received pembrolizumab had a higher risk of developing immune-related AEs (RR, 3.38; 95% CI, 2.22-5.14; $P < .001$) and grade 3 to 5 immune-related AEs (RR, 3.90; 95% CI, 2.00-7.59; $P < .001$) compared with the patients who received chemotherapy alone.

Figure 2 Forest Plots of Survival Outcomes: Progression-free Survival (A) and Overall Survival (B). HRs Were Pooled From 4 Subgroups With Different PD-L1 TPS: ≥ 50%, 1% to 49%, and < 1%. A Random-effects Model Using the Mantel-Haenzel Method was Applied



Abbreviations: Chemo = chemotherapy group; CI = confidence interval; df = degrees of freedom; HR = hazard ratio; NSCLC = non–small-cell lung cancer; OS = overall survival; PD-L1 = programmed death-ligand 1; Pembro = pembrolizumab group; PFS = progression-free survival; TPS = tumor proportion score.

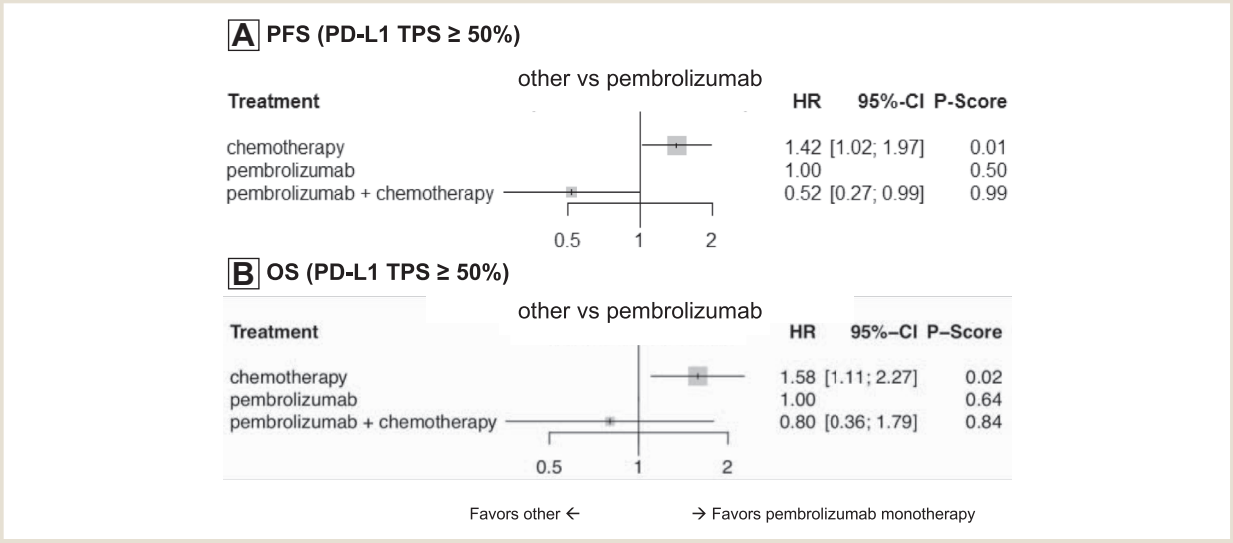
Assessment of Risk of Bias

The risk of bias in the 4 eligible studies was assessed using the risk assessment tool provided by the Cochrane Collaboration Tool (see Supplemental Table 4 in the online version).[14] The adequacy of blinding was one of the most important aspects in the assessment of survival outcome. For 2 of the included studies,[8,13] the study participants and staff were not blinded with regard to whether or not a participant had received pembrolizumab because of the open-label design of these trials. Results from the most recent trial, KEYNOTE-042, have not yet been published.[13] Therefore, the possibility of selective reporting cannot be excluded. Because only 4 trials were analyzed in this meta-analysis, the risk of publication bias in the included studies cannot be rigorously assessed.

Discussion

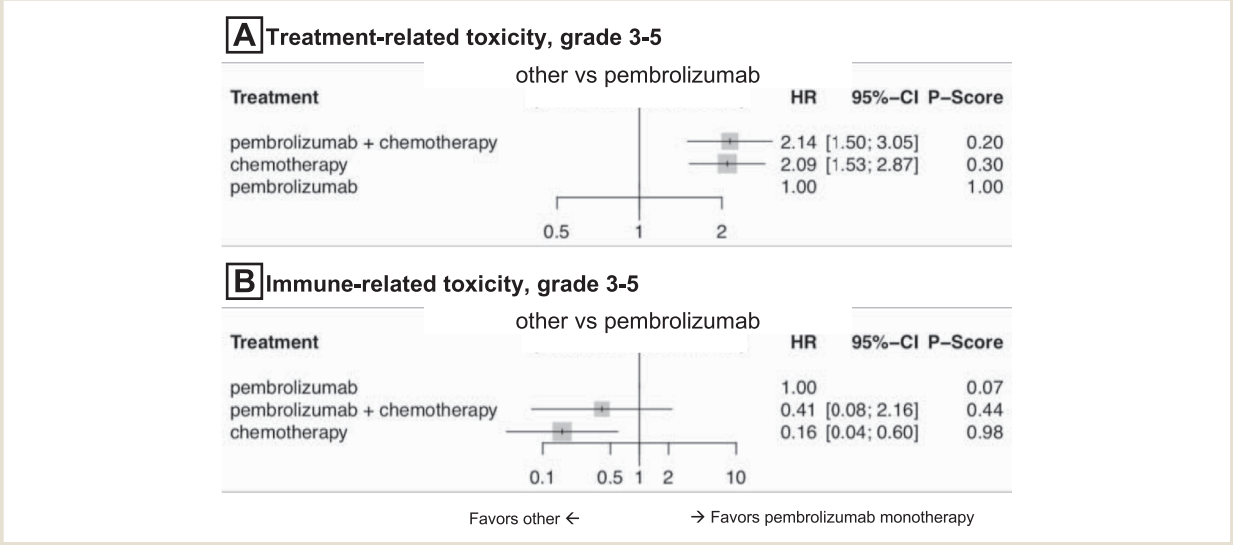
Pembrolizumab has emerged as the standard first-line treatment for patients with advanced/metastatic NSCLC without any sensitizing *EGFR* mutations or *ALK* translocations on the basis of recent randomized controlled studies that compared pembrolizumab with/without platinum-based chemotherapy versus chemotherapy.[8,10,12,13] This meta-analysis of 4 trials provides the first comprehensive systematic review of all available phase III clinical trials assessing first-line pembrolizumab for advanced/metastatic NSCLC. Our analysis summarized comprehensive to suggest that pembrolizumab was better than platinum-based chemotherapy. Additionally, indirect comparison using network analysis revealed that pembrolizumab plus chemotherapy had better PFS than

Figure 3 Forest Plots Comparing Chemotherapy or Pembrolizumab Plus Chemotherapy With Pembrolizumab Monotherapy for Previously Untreated Patients With Advanced Non–small-cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50%: Progression-free Survival (A) and Overall Survival (B). A Network Meta-analysis Within a Frequentist Framework Was Performed With Random-effects Model. "Others" Means Chemotherapy Alone or Pembrolizumab Plus Chemotherapy. The P-score Measures the Extent of Certainty that a Treatment is Better than Another Treatment, Averaged Over all Competing Treatments



Abbreviations: CI = confidence interval; df = degrees of freedom; HR = hazard ratio; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival.

Figure 4 Relative Risks for Adverse Events: Grade 3 to 5 Treatment-related Adverse Events (A); Grade 3 to 5 Immune-related Adverse Events (B). A Network Meta-analysis Within a Frequentist Framework was Performed to Indirectly Compare Pembrolizumab Plus Chemotherapy With Pembrolizumab Monotherapy. "Others" Means Chemotherapy Alone or Pembrolizumab Plus Chemotherapy. The P-score Measures the Extent of Certainty that a Treatment is Better than Another Treatment, Averaged Over all Competing Treatments



Abbreviations: CI = confidence interval; HR = hazard ratio.

pembrolizumab monotherapy in patients with PD-L1 TPS $\geq$ 50%, which has never been addressed in previous studies.

The expression of PD-L1 on the surface of tumor cells has been considered to be a potential biomarker for predicting responses to immunotherapy in NSCLC.[21] However, the 4 phase III trials reported recently, and our systematic review thereof, raise questions about the predictive role of PD-L1. Front-line pembrolizumab, in combination with platinum-based chemotherapy, showed excellent survival benefits in patients with advanced/metastatic NSCLC irrespective of histology as well as PD-L1 expression in the KEYNOTE-189 and KEYNOTE-407 trials.[10,11] Although front-line pembrolizumab monotherapy is recommended for metastatic NSCLC with high PD-L1 expression (TPS $\geq$ 50%) and negative for *EGFR* mutations or *ALK* rearrangement by current National Comprehensive Cancer Network guidelines,[22] this indication will be expanded by the recent reports from the KEYNOTE-042 trial, which showed that pembrolizumab monotherapy significantly improved OS compared with platinum-based chemotherapy as a first-line therapy for patients with advanced/metastatic NSCLC with PD-L1 TPS $\geq$ 1%.[13]

The remaining question is to compare pembrolizumab monotherapy with pembrolizumab plus chemotherapy as a first-line treatment. However, there have been no reports directly comparing these 2 treatments. To compare these 2 treatments with the best current available evidence, a network meta-analyses within a frequentist framework was employed in the present study. This novel concept of meta-analysis aims to combine information from all randomized comparisons among a set of treatments for a given condition, and allows ranking of treatments in order to identify the best and/or worst treatments.[17,18] By summarizing the 4 relevant trials, this approach demonstrated that pembrolizumab plus chemotherapy had a significantly superior PFS compared with pembrolizumab monotherapy for previously untreated patients with advanced/metastatic NSCLC whose tumors express PD-L1 TPS $\geq$ 50%. The chemo-immunotherapy combination showed slightly better OS than pembrolizumab monotherapy with a marginal significance. This is consistent with previous preclinical evidence that demonstrated that platinum agents may exert immune-potentiating effects and increase the sensitivity of cancer cells to $CD8^+$ T-cell-dependent immunosurveillance and rejection,[23-26] by increasing the potential for antigen cross-presentation by dendritic cells after destruction of tumor cells,[27] inhibiting myeloid-derived suppressor cells,[28] and increasing the ratio of cytotoxic lymphocytes to regulatory T cells.[29] According to current evidence, both first-line pembrolizumab and pembrolizumab plus chemotherapy can be administered in PD-L1 TPS $\geq$ 50% NSCLC. For obtaining longer PFS, pembrolizumab plus chemotherapy is advantageous over pembrolizumab monotherapy. Recently, a randomized trial (INSIGNA-EA5163/S1709) has been initiated for directly comparing pembrolizumab plus chemotherapy with pembrolizumab monotherapy in patients with NSCLC with PD-L1 TPS $\geq$ 1%.

This study has several limitations. First, this meta-analysis did not include data on individual patients; therefore, it was not possible to adjust treatment effects according to differences of doses and schedules of chemotherapeutic regimens, and patient variables such as smoking history and Eastern Cooperative Oncology Group performance status. Second, only a small number of trials were included in our analysis. Therefore, the statistical power of this analysis was relatively low. Third, only patients with PD-L1 TPS $\geq$ 50% were included for network meta-analysis. Considering patients included in each of 4 trials were heterogenous in terms of PD-L1 expression status, the stratification of patients according to PD-L1 TPS reduced heterogeneity, and thereby, improve the reliability of pooling results. Fourth, the KEYNOTE-042 trial, which is the most recent and largest, have not yet been formally published.[13] Therefore, the final results should be checked against the results in their preliminary reports. Finally, there were differences in the chemotherapeutic agents between trials, which might impair transitivity and consistency of the results of this network meta-analysis.[17] However, consistent with previous reports,[4] different chemotherapy regimens offered similar treatment effects in all 4 trials in terms of median PFS and OS. Therefore, the network could reasonably be assumed to maintain transitivity and consistency.

Conclusions

This study summarized all of the current evidence, and, to the best of our knowledge, is the largest meta-analysis—to date—that has addressed an important clinical issue, the effect of first-line pembrolizumab on patients with treatment-naive advanced/metastatic NSCLC. In PD-L1 TPS $\geq$ 50% NSCLC, pembrolizumab plus chemotherapy significantly improved PFS compared with pembrolizumab monotherapy. Therefore, pembrolizumab plus chemotherapy could be better than pembrolizumab for obtaining a longer PFS in NSCLC with PD-L1 TPS $\geq$ 50%. Based on this result, a prospective randomized phase III study such as INSIGNA-EA5163/S1708 (NCT03793179) is warranted for directly comparing pembrolizumab monotherapy and pembrolizumab plus chemotherapy for patients with NSCLC as a first-line treatment.

Clinical Practice Points

- According to several phase III trials, pembrolizumab plus chemotherapy was found to be better than chemotherapy alone. However, there have been no reported trials that directly compare pembrolizumab monotherapy versus pembrolizumab plus chemotherapy in first-line treatment setting of advanced/metastatic NSCLC.
- In this meta-analysis, we comprehensively summarized the current available evidence of the therapeutic efficacy of pembrolizumab and compared pembrolizumab monotherapy versus pembrolizumab plus chemotherapy.
- Our findings revealed that pembrolizumab plus chemotherapy resulted in significantly improved PFS compared with pembrolizumab monotherapy in patients with PD-L1 TPS $\geq$ 50%.
- This study provides the first comprehensive systematic review and meta-analysis of all available phase III clinical trials assessing first-line pembrolizumab for advanced/metastatic NSCLC.

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Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental data, tables and figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2019.05.009.

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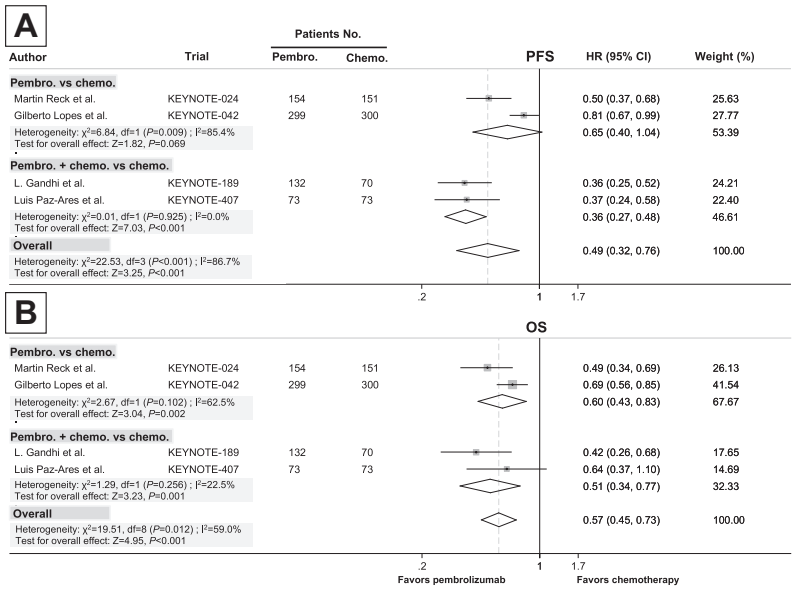
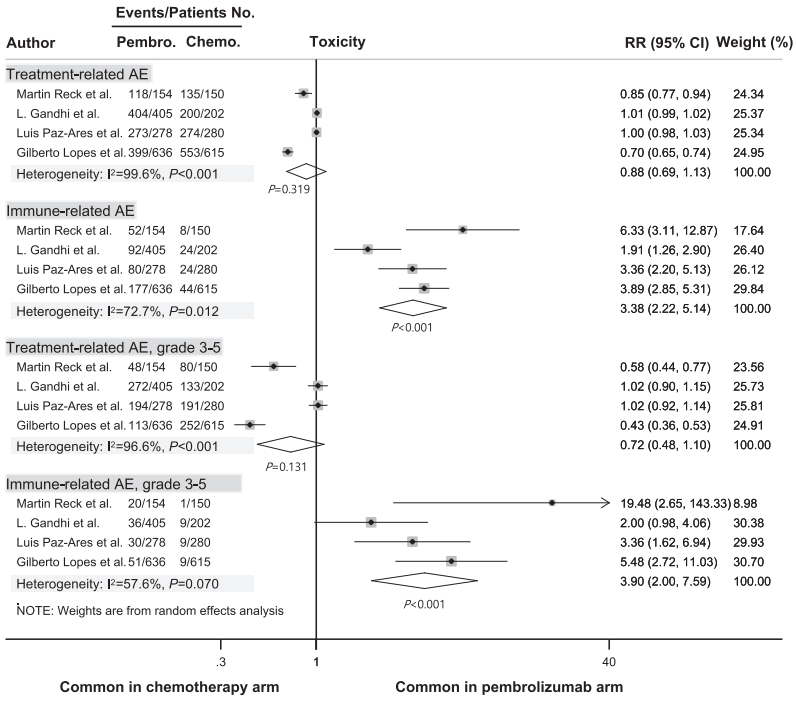
Supplemental Data

Supplemental Figure 1 **Pairwise Comparison Between Pembrolizumab Plus Chemotherapy Versus Chemotherapy and Pembrolizumab Monotherapy Versus Chemotherapy in Terms of Progression-fee Survival (A) and Overall Survival (B). Patients With PD-L1 TPS ≥ 50% Were Analyzed Here**



Abbreviations: Chemo = chemotherapy group; CI = confidence interval; df = degrees of freedom; HR = hazard ratio; OS = overall survival; PD-L1 = programmed death-ligand 1; Pembro = pembrolizumab group; PFS = progression-free survival; TPS = tumor proportion score.

Supplemental Figure 2 Forest Plots of Relative Risks for Treatment-related and Immune-related Adverse Events



Abbreviations: AE = adverse event; Chemo = chemotherapy group; CI = confidence interval; Pembro = pembrolizumab group; RR = relative risk.

Supplemental Table 1 Initial Search Strategies Performed in July 2018

Database	Syntax	Retrieval
PubMed	(((((lung cancer[Title/Abstract] AND non-small cell[Title/Abstract]))) AND pembrolizumab[Title/Abstract]) AND random*[Title/Abstract]	42
EMBASE	TITLE-ABSTR-KEY("lung cancer") and TITLE-ABSTR-KEY(non-small cell) and TITLE-ABSTR-KEY(pembrolizumab) and TITLE-ABSTR-KEY(random*)	114
Cochrane	Lung cancer in Title, Abstract, Keywords and pembrolizumab Title, Abstract, Keywords and random* in Title, Abstract, Keywords	106
National Institutes of Health Clinical Trials Registry	Condition or disease: non-small cell lung cancer Recruitment status: terminated or completed Intervention/treatment: pembrolizumab	4
MetaRegister of controlled clinical trials	"lung cancer" AND pembrolizumab AND non-small cell	2

Supplemental Table 2 Treatment Protocols of Each Study Included in the Meta-analysis

	Reck et al[1]	Gandhi et al[2]	Paz-Ares et al[3]	Lopes et al[4]
Pembrolizumab	200 mg every 3 weeks for 35 cycles			
Chemotherapy regimen	[a]1. Carboplatin AUC 5 to 6 + pemetrexed[b] 500 mg/m^2 [a]2. Cisplatin 75 mg/m^2 + pemetrexed[b] 500 mg/m^2 3. Carboplatin AUC 5 to 6 + gemcitabine 1250 mg/m^2 4. Cisplatin 75 mg/m^2 + gemcitabine 1250 mg/m^2 5. Carboplatin AUC 5 to 6 + paclitaxel[c] 200 mg/m^2	1. Cisplatin 75 mg/m^2 + pemetrexed[d] 500 mg/m^2 2. Carboplatin AUC 5 + pemetrexed[d] 500 mg/m^2	1. Carboplatin AUC 6 + paclitaxel 200 mg/m^2 2. Carboplatin AUC 6 + nab-paclitaxel[e] 100 mg/m^2	1. Carboplatin AUC 5 or 6 + paclitaxel[f] 200 mg/m^2 2. Carboplatin AUC 5 or 6 + pemetrexed[f] 500 mg/m^2
	every 3 weeks for 4-6 cycles	every 3 weeks for 4 cycles	every 4 weeks for 4 cycles	for up to 6 cycles

All the drugs were administered at day 2 of every 3-week cycle, except for gemcitabine which was administered at day 1 and 8 of every 3-week cycle.
Abbreviation: AUC = area under the curve.
[a]Permitted for patients with non-squamous histology only.
[b]Followed by optional pemetrexed maintenance therapy given at a dose of 500 mg/m^2 every 3 weeks.
[c]Followed by optional pemetrexed maintenance therapy given at a dose of 500 mg/m^2 every 3 weeks (patients with non-squamous histology only).
[d]Followed by optional pemetrexed maintenance therapy given at a dose of 500 mg/m^2 every 3 weeks.
[e]Every 3 weeks.
[f]Pemetrexed maintenance therapy was optional but strongly encouraged for patients with non-squamous histology.

Supplemental Table 3 Median PFS and OS of Chemotherapy Arm in Each Study Included in the Meta-analysis

Trials	Median PFS, (95% CI), mos	Medan OS, (95% CI), mos
KEYNOTE-024	6.0 (4.2-6.2)	14.5 (9.8-19.6)
KEYNOTE-189	4.9 (4.7-5.5)	11.3 (8.7-15.1)
KEYNOTE-407	4.8 (4.3-5.7)	11.3 (9.5-14.8)
KEYNOTE-042	6.5 (6.3-7.0)	12.1 (11.3-13.3)

Abbreviations: CI = confidence interval; OS = overall survival; PFS = progression-free survival.

Supplemental Table 4 Methodological Assessments of Studies Included in the Meta-analysis Using the Cochrane Collaboration Tool

Trials	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting
Reck et al (2016)[a]	Low	High (open-label trial)	High (open-label trial)	Low	Low
Gandhi et al (2018)	Low	Low (double-blind)	Low (double-blind)	Low	Low
Paz-Ares et al (2018)	Low	Low (central allocation)	Low (double-blind)	Unclear	Unclear
Lopes et al (2018)[b]	Low	High (open-label trial)	High (open-label trial)	Unclear	Unclear

[a]This trial was stopped early because pembrolizumab was found to be superior to chemotherapy with respect to overall survival at the second interim analysis.
[b]These trials have not yet been published.

Supplemental References

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