Original Article

Comparative Efficacy of Chemoimmunotherapy Versus Immunotherapy for Advanced Non–Small Cell Lung Cancer: A Network Meta-Analysis of Randomized Trials

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BACKGROUND: To the authors' knowledge, in the absence of head-to-head trials, it is unclear whether chemoimmunotherapy provides an additional overall survival (OS) benefit compared with immunotherapy alone in the first-line treatment of patients with advanced non–small cell lung cancer (NSCLC). The authors conducted a systematic literature review and network meta-analysis (NMA) to compare the efficacy of chemoimmunotherapy versus ICI. **METHODS:** MEDLINE, Excerpta Medica dataBASE (EMBASE), Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov were searched from inception to April 2020. Phase 3 trials evaluating the efficacy of first-line ICI or chemoimmunotherapy and reporting efficacy outcomes (OS, progression-free survival [PFS], and the overall response rate [ORR]) stratified by programmed death–ligand 1 (PD-L1) status were included. NMA with a Bayesian random effects model was performed. **RESULTS:** A total of 12 eligible trials comprising 7845 patients were included. In patients who were negative for PD-L1 (tumor proportion score [TPS] <1%), NMA comparing chemoimmunotherapy with dual-agent ICI failed to demonstrate a statistically significant difference with regard to OS, PFS, or the ORR. In patients with low PD-L1 (TPS 1%-49%), there was no statistically significant difference observed between chemoimmunotherapy compared with either single-agent ICI or dual-agent ICI with regard to OS or the ORR. In patients with high PD-L1 (TPS ≥50%), chemoimmunotherapy was found to be associated with an improved PFS and ORR compared with single-agent ICI, but not with dual-agent ICI. No differences in OS were observed with chemoimmunotherapy when compared with either single-agent or dual-agent ICIs. **CONCLUSIONS:** Although chemoimmunotherapy appears to improve the ORR and PFS in patients with PD-L1–high tumors when compared with single-agent ICI, it does not appear to confer an OS benefit over single-agent or dual-agent ICI for patients with advanced NSCLC regardless of PD-L1 status. Prospective trials are needed to validate these findings. ***Cancer* 2020;0:1-11**.

KEYWORDS: combination, drug therapy, immunotherapy, meta-analysis, network, non–small cell lung carcinoma, programmed cell death protein 1 receptor/antagonists and inhibitors, systematic review, survival analysis.

INTRODUCTION

With the introduction of immune checkpoint inhibitors (ICIs), the treatment paradigms for patients with advanced non–small cell lung cancer (NSCLC) have changed drastically.[1] In 2016, the anti–programmed cell death protein 1 (PD-1) antibody pembrolizumab was demonstrated to have a superior overall survival (OS) compared with platinum-based doublet chemotherapy when used as a first-line therapy for patients with advanced NSCLC with a programmed death–ligand 1 (PD-L1) tumor proportion score (TPS) ≥50%, leading to US Food and Drug Administration (FDA) approval in this setting.[2] In April 2019, based on the results of the KEYNOTE-042 trial, the indication for pembrolizumab monotherapy was expanded to include patients whose tumors express a PD-L1 TPS ≥1%.[3] More recently, dual-checkpoint blockade with ipilimumab (anti–cytotoxic T-lymphocyte–associated protein 4 [CTLA-4] antibody) and nivolumab (anti–PD-1

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See companion article on pages 1-10, this issue.

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Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.33269, **Received:** May 27, 2020; **Revised:** August 25, 2020; **Accepted:** September 9, 2020, **Published online** Month 00, 2020 in Wiley Online Library (wileyonlinelibrary.com)

antibody) has been shown to be superior to chemotherapy independent of PD-L1 status, leading to an FDA approval for patients with a PD-L1 Tumor proportion score (TPS ≥1% and heralding further changes in the landscape of the first-line treatment of patients with advanced NSCLC.[4,5]

Chemotherapy plus ICI (ie, chemo-ICI) has emerged as another first-line treatment option based on the results of recent trials demonstrating an OS benefit with chemo-ICI over platinum-based doublet chemotherapy, regardless of PD-L1 expression.[6-9] Other chemo-ICI trials similarly have reported promising preliminary survival data compared with platinum doublets.[10,11] Based on the available data, both ICI (single-agent or dual-agent) and combination chemo-ICI appear to be efficacious first-line treatments, as reflected in the current guideline recommendations.[12] However, in the absence of head-to-head trials comparing chemo-ICI with immunotherapy, it is unclear which regimen is superior.

Therefore, the objective of the current study was to evaluate the relative efficacy of first-line chemo-ICI versus single-agent or dual-agent ICI in patients with non–oncogene-driven advanced NSCLC by performing a systematic review and network meta-analysis (NMA).

MATERIALS AND METHODS

The current systematic review and NMA was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for NMAs.[13,14] The study protocol was prospectively registered with the National Institute for Health Research PROSPERO registration site (CRD42019145192).

Literature Search

A systematic literature review using MEDLINE, Excerpta Medica dataBASE (EMBASE), Cochrane Central Register of Controlled Trials, Scopus, Web of Science, and ClinicalTrials.gov was performed from database inception to April 2020 by a professional librarian (K.S.F). Key search terms included "non–small cell lung cancer," "immune checkpoint inhibitors," and "randomized clinical trial." References from review articles, commentaries, editorials, included studies, and conference publications were hand searched and cross-referenced to ensure a comprehensive search.[15] A full search strategy is presented in Supporting Table 1.

Study Selection

We included phase 3 randomized clinical trials (RCTs) that evaluated the efficacy of first-line ICI (anti–PD-1 or anti–PD-L1 or anti–CTLA-4 antibodies) or chemo-ICI in the treatment of patients with non–oncogene-driven, advanced NSCLC and reported outcomes according to various PD-L1 expression levels (<1% [negative], 1%-49% [low], and ≥50% [high]). Phase 1 or 2 trials and observational studies were excluded. When >1 publication resulting from the same study population was available, data from the most recent publication were used.

A specialized screening and data extraction tool (Covidence systematic review software; Veritas Health Innovation, Melbourne, Victoria, Australia) was used to remove duplicates and perform study selection. Two authors performed study selection independently (R.P. and M.R.A.) and disagreements were resolved by consensus. Full-text review was performed in cases in which abstracts were believed to be insufficient to determine whether the study met the inclusion criteria.

Outcomes and Data Extraction

The primary efficacy outcome of interest was progression-free survival (PFS) and the secondary outcomes were OS and the overall response rate (ORR). Study characteristics were tabulated. Efficacy outcomes (percentage for the ORR and hazard ratios [HRs] and 95% confidence intervals [95% CIs] for OS and PFS) were extracted for different PD-L1 cohorts. Although the IMpower150 trial included patients with mutated tumors (*EGFR* and *ALK*), efficacy outcomes for the study were restricted to patients with wild-type tumors. Data abstracted by one author (R.P.) was independently verified by a second author (M.R.A.) to ensure accuracy.

Evaluation of PD-L1 status was performed centrally using fresh or archival tissues in all the trials using different assays.[3,4,6-11,16-19] For the KEYNOTE studies, PD-L1 immunohistochemistry (IHC) expression in tumor cells was assessed using the 22C3 pharmDx assay (Agilent Technologies, Santa Clara, California).[20] PD-L1 status was evaluated in the CheckMate-227 and MYSTIC trials using the 28-8 pharmDx assay (Agilent Technologies) and SP263 assay (Ventana Medical Systems, Tucson, Arizona), respectively.[21,22] For the IMpower studies, PD-L1 expression was evaluated using the PD-L1 (SP142) IHC assay (Ventana Medical Systems).[23] All the included trials reported PD-L1 TPS except for the IMpower studies, which used a different reporting system using either tumor cells or immune cell staining. These groups were reclassified into the corresponding TPS cohorts according to the PD-L1 expression in the tumor cells.[24] A recent real-world collaborative effort evaluating the performance of these platforms demonstrated comparable staining characteristics on tumor cells among the 22C3 pharmDx assay, 28-8 pharmDx assay, and SP263 assay, with a lower

sensitivity noted with SP142 for the detection of PD-L1.[25] However, all 4 PD-L1 IHC assays demonstrated high overall agreement in scoring PD-L1 on tumor cells. Further details of the methods used for PD-L1 testing in different trials are summarized in Supporting Table 2.

Risk of Bias

We assessed the risk of bias for all included RCTs using the Cochrane Collaboration tool.[26]

Statistical Analysis

We performed a study-level NMA based on Bayesian random effects regression models. In contrast to the frequentist approach, Bayesian NMA was used due to its flexibility in accommodating complex scenarios and offering a straightforward method for conducting probabilistic statements and predictions regarding the treatment effects.[27] We used a logit link function for the ORR and a complementary log-log link function for OS and PFS. The model preserved randomized treatment comparisons within trials. Analyses were performed using Markov chain Monte-Carlo methods. A vague prior uniform distribution was chosen for the between-trial variances, which we assumed to be equal across comparisons. To ensure that the prior distribution was sufficiently vague, uniform distribution was chosen as $U(0, S)$, in which S was selected heuristically based on the outcome scale following the approach by Valkenhoef et al in which S was the maximum of the effect sizes reported in selected studies for the outcomes of interest.[28] Convergence was assessed by checking plots of the Gelman-Rubin statistics, which indicated that the width of pooled runs and individual runs stabilized around the same value and their ratio was approximately 1.[29] Potential selection biases were adjusted using the meta-regression approach as described by Trinquart et al.[30]

For each pairwise comparison of the ORR, we used odds ratios (ORs) with 95% credible intervals (95% CrIs) as a measure of the association between the treatment used and its efficacy. HRs with 95% CrIs were used for OS and PFS. Within the Bayesian framework, the NMA estimated the overall rankings of treatments by calculating their posterior probabilities (which equals 1 when a treatment is certain to be the best and 0 when a treatment is certain to be the worst). Given the lack of loops in the networks, assessments of inconsistency (consistency describes the agreement between estimates of various studies for a specific comparison) and coherence (coherence describes the agreement between direct and indirect estimates for a specific comparison) were irrelevant in this study.

Random effects models were used due to inherent clinical heterogeneity in the current study data. Heterogeneity was assessed using the I^2 statistic (percentage of variance in a meta-analysis that is attributable to study heterogeneity), with values of 25%, 50%, and 75%, respectively, indicating low, moderate, and high heterogeneity.[26] Two-tailed P values $<.05$ were considered to indicate statistical significance.

Subgroup and Sensitivity Analyses

We performed subgroup analyses by stratifying ICIs into single-agent ICI and dual-agent ICI (eg, ipilimumab plus nivolumab) given their different mechanisms and biology.[31] We planned several sensitivity analyses to assess the reliability and robustness of the results. The first analysis excluded trials that used the anti–vascular endothelial growth factor (VEGF) antibody bevacizumab with ICI (IMpower150).[8] The second analysis excluded CheckMate-026, which did not prespecify different PD-L1 subsets and had imbalanced intervention and control arms.[18] The third analysis stratified chemo-ICI according to the type of PD-1 axis inhibition (anti–PD-1–based and anti–PD-L1–based chemo-ICI). All analyses were repeated using random effects models.

RESULTS

Study Selection

The literature search identified 7971 unique references. After a full-text review of 27 articles, we identified 12 trials for qualitative and quantitative synthesis (Fig. 1).[3,4,6-11,16-19] Three of the included studies were available solely as conference abstracts and/or presentations.[10,11,17] Some of the RCTs were reported in >1 publication.[16,32]

Study Characteristics

Twelve relevant RCTs with 7845 patients were included. Of the 12 RCTs, 2 trials compared pembrolizumab with chemotherapy,[3,16] 1 trial compared atezolizumab with chemotherapy,[17] 1 trial compared nivolumab with chemotherapy,[18] 1 trial compared the combination of ipilimumab and nivolumab with chemotherapy or nivolumab plus chemotherapy with chemotherapy,[4] 1 trial compared the combination of durvalumab and tremelimumab with chemotherapy or durvalumab with chemotherapy,[19] and 6 trials compared chemo-ICI with chemotherapy (see Supporting Fig. 1).[6-11] ICIs included either single-agent ICI (nivolumab, pembrolizumab, durvalumab, or atezolizumab)[3,16,17,19] or dual-agent ICI (ipilimumab plus

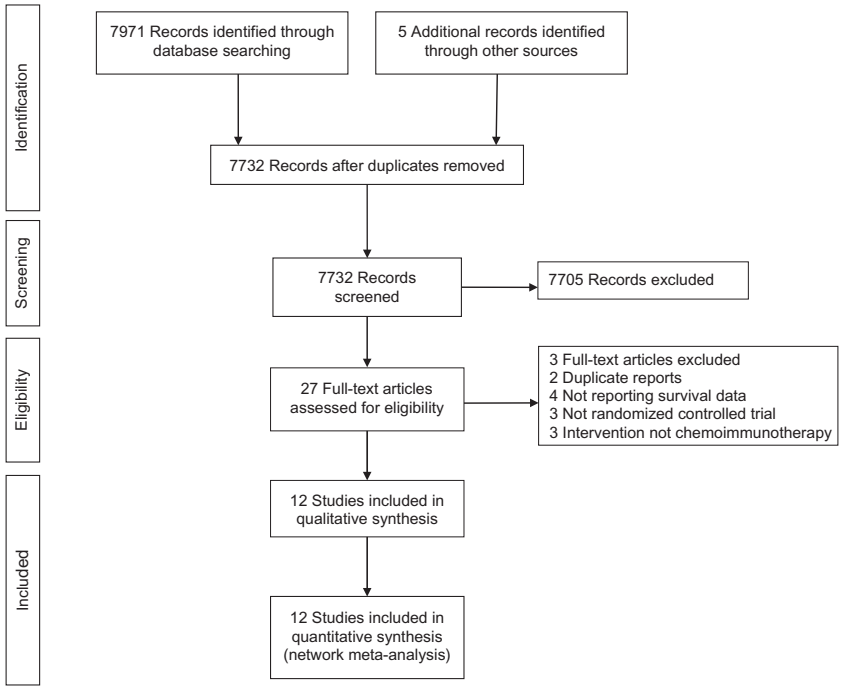

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

nivolumab and durvalumab plus tremelimumab).[4,19] The chemo-ICI regimens included pembrolizumab-based platinum doublets,[6,7] nivolumab-based platinum doublets,[4] and atezolizumab-based platinum doublets,[8-11] with one trial in the latter group including bevacizumab in both the chemo-ICI and chemotherapy arms (see Supporting Table 3).[8] The majority of the trials reported efficacy outcomes stratified by PD-L1 levels (Table 1). The assumption of transitivity (the assumption that included studies are similar enough to build a network) was accepted because no significant variability was identified in the study and population baselines (see Supporting Table 4).

Risk of Bias

The majority of trials included random sequence generation with intermittent reporting of allocation concealment. Overall, the studies were deemed to be at low risk of biases (see Supporting Table 5).

Efficacy of Chemo-ICI in PD-L1–Negative Patients

Similar efficacy was found between chemo-ICI and ICI in terms of OS, PFS, and the ORR for patients with a PD-L1 TPS <1% (Fig. 2) (Table 2).

Efficacy of Chemo-ICI in PD-L1–Positive Patients

PD-L1–low subset

In the PD-L1–low subset (TPS 1%-49%), no significant difference was observed between chemo-ICI and ICI in terms of OS or the ORR. In subset analyses, there were no statistically significant OS differences noted between chemo-ICI and either form of immunotherapy. The PFS estimate could not be obtained due to missing data (Fig. 2) (Table 2).

PD-L1–high subset

Among patients in the PD-L1–high subset (TPS ≥50%), a significantly improved PFS (HR, 0.59; 95% CrI, 0.41-0.85 [$P < .001$]) and ORR (OR, 2.25; 95% CrI, 1.35-3.78 [$P < .001$]) was observed with chemo-ICI when compared with ICI. However, no significant difference in OS was observed with chemo-ICI compared with ICI. The PFS and ORR differences were noted only between chemo-ICI and single-agent ICI and not between chemo-ICI and dual-agent ICI (Fig. 2) (Table 2).

Rank Probabilities

Bayesian ranking results were similar to those of the pooled analyses using HRs and ORs (Fig. 3). For patients with PD-L1–negative tumors, dual-agent ICI was most

TABLE 1. Abstracted Endpoints From Randomized Controlled Trials Included in the Network Meta-Analysis

Study	ICI or Chemo-ICI No.	Chemotherapy No.	OS HR (95% CI)	PFS HR (95% CI)	ORR, %
PD-L1 negative					
Single-agent ICI					
MYSTIC[a]	95	83	1.18 (0.86-1.62)	NA	NA
Dual-ICI					
CheckMate-227[b]	187	186	0.62 (0.48-0.78)	0.75 (0.59-0.96)	27.30 vs 23.10
MYSTIC[c]	76	83	0.73 (0.51-1.04)	NA	NA
Chemo-ICI					
CheckMate-227[d]	177	186	0.78 (0.62-1.02)	0.73 (0.56-0.95)	37.90 vs 23.10
IMpower130	235	121	0.81 (0.61-1.08)	0.72 (0.56-0.91)	NA
IMpower131	170	171	0.86 (0.65-1.15)	0.81 (0.64-1.03)	44.00 vs 42.00
IMpower132	88	75	NA	0.45 (0.31-0.64)	44.00 vs 27.00
IMpower150	167	172	0.82 (0.62-1.08)	0.77 (0.61-0.99)	51.00 vs 36.00
KEYNOTE-189	127	63	0.52 (0.36-0.74)	0.64 (0.47-0.89)	32.30 vs 14.30
KEYNOTE-407	95	99	0.61 (0.38-0.98)	0.68 (0.47-0.98)	NA
PD-L1 Low					
Single-agent ICI					
KEYNOTE-042	338	337	0.92 (0.77-1.11)	NA	16.60 vs 21.7.00
Dual-ICI					
CheckMate-227[b]	191	205	0.94 (0.75-1.18)	NA	NA
Chemo-ICI					
IMpower130	128	65	0.70 (0.45-1.08)	0.61 (0.43-0.85)	NA
IMpower131	129	121	1.34 (0.95-1.90)	0.70 (0.53-0.92)	51.90 vs 43.80
IMpower132	63	73		0.80 (0.56-1.16)	38.00 vs 38.00
IMpower150	121	105	0.80 (0.55-1.15)	0.56 (0.41-0.77)	58.00 vs 41.00
KEYNOTE-189	128	58	0.62 (0.42-0.92)	0.55 (0.36-0.73)	49.20 vs 20.70
KEYNOTE-407	103	104	0.57 (0.36-0.90)	0.56 (0.39-0.80)	49.50 vs 41.30
PD-L1 High					
Single-agent ICI					
CheckMate-026	88	126	0.90 (0.63-1.29)	1.07 (0.77-1.49)	34.00 vs 39.00
IMpower110	107	98	0.59 (0.40-0.89)	0.63 (0.45-0.88)	38.30 vs 28.60
KEYNOTE-024	154	151	0.63 (0.47-0.86)	0.50 (0.37-0.68)	44.8.00 vs 27.80
KEYNOTE-042	299	300	0.69 (0.56-0.85)	0.81 (0.67-0.99)	39.00 vs 32.00
MYSTIC[a]	118	107	0.76 (0.55-1.04)	NA	NA
Dual-ICI					
CheckMate-227[b]	205	192	0.70 (0.55-0.90)	0.62 (0.49-0.79)	44.40 vs 35.40
MYSTIC[c]	108	107	0.77 (0.56-1.07)	NA	NA
Chemo-ICI					
IMpower130	88	42	0.84 (0.51-1.40)	0.51 (0.34-0.77)	
IMpower131	53	48	0.56 (0.32-0.99)	0.44 (0.27-0.71)	60.40 vs 33.30
IMpower132	25	20	NA	0.46 (0.22-0.96)	72.00 vs 55.00
IMpower150	71	65	0.70 (0.43-1.13)	0.39 (0.25-0.60)	69.00 vs 49.00
KEYNOTE-189	132	70	0.59 (0.39-0.88)	0.36 (0.26-0.51)	62.10 vs 24.30
KEYNOTE-407	73	73	0.64 (0.37-1.10)	0.37 (0.24-0.58)	60.30 vs 32.90

Abbreviations: 95% CI, 95% confidence interval; chemo-ICI, chemoimmunotherapy; dual-ICI, combination immunotherapy (eg, ipilimumab and nivolumab); HR, hazard ratio; ICI, immunotherapy; single-agent ICI, single-agent immunotherapy (eg, pembrolizumab or atezolizumab alone); NA not available; ORR, overall response rate; OS, overall survival; PD-L1, programmed death–ligand 1; PD-L1 negative, high and low indicate tumor proportion score levels (<1% [negative], 1%-49% [low], and ≥50% [high]); PFS, progression-free survival.
[a]Durvalumab versus chemotherapy.
[b]Ipilimumab plus nivolumab versus chemotherapy.
[c]Durvalumab plus tremelimumab versus chemotherapy.
[d]Nivolumab plus chemotherapy versus chemotherapy.

likely to be ranked first for OS (cumulative probability, 86%), whereas chemo-ICI was found to have the highest probability of being ranked first in terms of PFS and the ORR. In PD-L1–positive patients (those in both the PD-L1–low and PD-L1–high subsets), chemo-ICI was most likely to be ranked first for all 3 efficacy endpoints (see Supporting Table 6).

Heterogeneity Assessment

We generated forest plots of the pairwise comparisons with heterogeneity estimates for each efficacy endpoint. Our assessment suggested low heterogeneity in all comparisons (Fig. 2).

Sensitivity Analyses

The findings of the current study remained robust on sensitivity analyses performed by excluding the IMpower150 and CheckMate-026 trials. The results also were similar when chemo-ICI regimens were stratified based on the type of PD-1 axis inhibition. All the analyses that were repeated using fixed effect models demonstrated similar results (data available upon request).

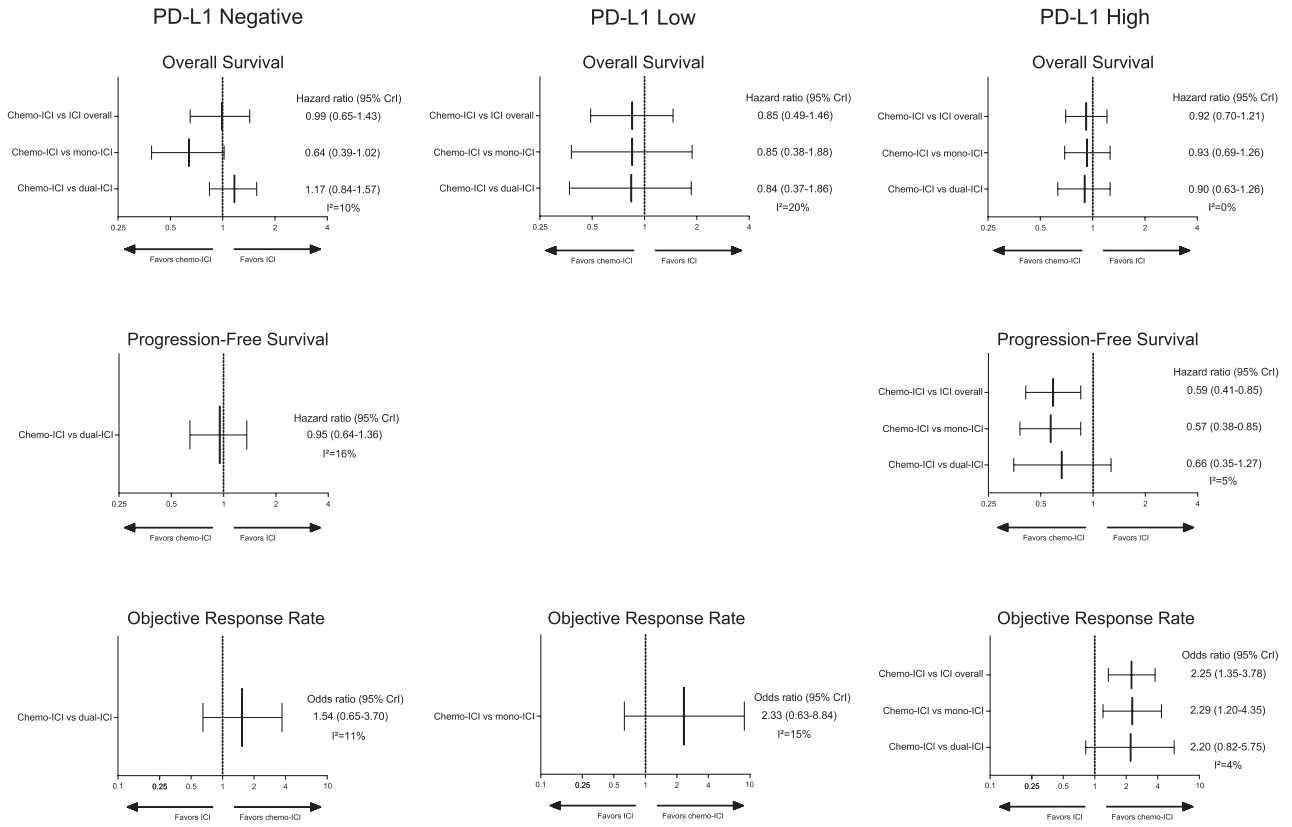

Figure 2. Forest plots for overall survival, progression-free survival, and the overall response rate with chemoimmunotherapy (chemo-ICI) versus immunotherapy (ICI) alone in programmed death–ligand 1 (PD-L1)–negative, PD-L1–low, and PD-L1–high subsets. Hazard ratios <1 for overall survival and progression-free survival suggest that chemo-ICI is superior to ICI and an odds ratio >1 for the overall response rate suggests that chemo-ICI is superior to ICI. 95% CrI indicates 95% credible interval; dual-ICI, combination immunotherapy (eg, ipilimumab and nivolumab); I^2, the percentage of variance in a meta-analysis that is attributable to study heterogeneity; PD-L1 negative, high and low indicate tumor proportion score levels (<1% [negative], 1%-49% [low], and ≥50% [high]); single-agent ICI, single-agent immunotherapy (eg, pembrolizumab or atezolizumab alone).

DISCUSSION

The results of the current NMA, involving 12 RCTs with 7845 patients with advanced NSCLC, found that chemo-ICI yielded a high probability of a superior PFS and ORR in patients with PD-L1–high tumors compared with single-agent ICI. However, we did not observe any statistically significant differences with regard to OS between chemo-ICI and ICI (either single-agent or dual-agent) in the front-line treatment of patients with advanced NSCLC regardless of PD-L1 status. To our knowledge, the current study represents the most extensive NMA comparing chemo-ICI with ICI performed to date.

NMA represents an extension of the principles of conventional meta-analysis and allows for an indirect comparison of interventions across RCTs using a common comparator.[33] In the absence of head-to-head clinical trials comparing the efficacy of chemo-ICI with ICI in patients with advanced NSCLC, the use of such an approach to the best of our knowledge offers the only method of understanding the relative efficacy of these 2 treatments to assist in clinical decision making.

Chemo-ICI represents an important advance in the field of lung cancer treatment, with significant improvements in survival noted compared with chemotherapy in the first-line treatment of patients with advanced NSCLC.[34] Chemo-ICI has been argued to offer a higher response rate and thus to have a potential role in rapid cytoreduction in patients with a large-volume tumor with progressive clinical deterioration.[34] Although the results of the current study demonstrated a statistically significant ORR benefit with chemo-ICI when compared with single-agent ICI in patients with PD-L1–high tumors, no statistically significant differences were observed between chemo-ICI and dual-ICI in any of the PD-L1 groups.

TABLE 2. Pooled Estimates (Pooled HRs [95% CrIs]) for PFS and OS and Pooled ORs (95% CrIs) for ORR of the Network Meta-Analysis

OS				
PD-L1 negative	Chemo-ICI	1.17 (0.84-1.57)	0.64 (0.39-1.02)	**0.76 (0.62-0.90)**[a]
	Dual-ICI		**0.55 (0.32-0.94)**[a]	**0.64 (0.49-0.85)**[a]
	Single-agent ICI			1.17 (0.76-1.86)
	Chemotherapy			
PD-L1 low	Chemo-ICI	0.84 (0.37-1.86)	0.85 (0.38-1.88)	0.79 (0.55-1.12)
	Dual-ICI		1.02 (0.36-2.89)	0.94 (0.45-1.97)
	Single-agent ICI			0.92 (0.45-1.90)
	Chemotherapy			
PD-L1 high	Chemo-ICI	0.90 (0.63-1.26)	0.93 (0.69-1.26)	**0.65 (0.51-0.84)**[a]
	Dual-ICI		1.04 (0.76-1.39)	**0.73 (0.57-0.93)**[a]
	Single-agent ICI			**0.70 (0.60-0.83)**[a]
	Chemotherapy			
PFS				
PD-L1 negative	Chemo-ICI	0.95 (0.64-1.36)	NA	**0.70 (0.58-0.82)**[a]
	Dual-ICI		NA	0.73 (0.50-1.07)
	Single-agent ICI			—
	Chemotherapy			
PD-L1 low	Chemo-ICI	NA	NA	**0.63 (0.52-0.75)**[a]
	Dual-ICI		NA	NA
	Single-agent ICI			NA
	Chemotherapy			
PD-L1 high	Chemo-ICI	0.66 (0.35-1.27)	0.57 (0.38-0.85)	**0.41 (0.31-0.55)**[a]
	Dual-ICI		0.85 (0.44-1.63)	0.62 (0.35-1.09)
	Single-agent ICI			0.73 (0.54-0.98)
	Chemotherapy			
ORR				
PD-L1 negative	Chemo-ICI	1.54 (0.65-3.70)	NA	**1.79 (1.17-1.94)**[a]
	Dual-ICI		NA	1.17 (0.49-2.86)
	Single-agent ICI			NA
	Chemotherapy			
PD-L1 low	Chemo-ICI		2.33 (0.63-8.84)	1.66 (0.97-2.97)
	Dual-ICI		NA	NA
	Single-agent ICI			0.71 (0.21-2.34)
	Chemotherapy			
PD-L1 high	Chemo-ICI	2.20 (0.82-5.75)	**2.29 (1.20-3.35)**[a]	**3.22 (1.95-5.16)**[a]
	Dual-ICI		1.04 (0.41-2.72)	1.45 (0.64-3.39)
	Single-agent ICI			1.40 (0.90-2.14)
	Chemotherapy			

Abbreviations: 95% CrI indicates 95% credible interval; chemo-ICI, chemoimmunotherapy; dual-ICI, combination immunotherapy (eg, ipilimumab and nivolumab); HR, hazard ratio; Single-agent ICI, single-agent immunotherapy (eg, pembrolizumab or atezolizumab alone); NA not available; OR, odds ratio; ORR, overall response rate; OS, overall survival; PD-L1, programmed death–ligand 1; PD-L1 negative, high and low indicate tumor proportion score levels (<1% [negative], 1%-49% [low], and ≥50% [high]); PFS, progression-free survival.

Data in each cell are shown as the HR or OR (95% CrI) for the comparison of row-defining treatment versus column-defining treatment. HRs <1 and ORs >1 favor row-defining treatment.

[a]Bold type indicates statistically significant result.

Studies previously have demonstrated a synergy between platinum-based chemotherapy and ICI across various levels of PD-L1 expression, resulting in enhanced T-cell stimulation and cytotoxic T-cell–mediated killing, which could explain the higher response rates reported with chemo-ICI.[35,36] The current study results have suggested that chemo-ICI may indeed produce a higher response rate when compared with ICIs and potentially could achieve greater cytoreduction. However, the difference in the ORR did not translate into a difference in OS in any of the PD-L1 subsets examined.

In PD-L1–negative patients, although dual-agent ICI had the highest probability of being ranked the most efficacious therapy in terms of OS, there was no clear trend favoring it over chemo-ICI in the pooled analyses. In the absence of head-to-head comparisons, to our knowledge it remains unclear as to which approach yields a superior OS benefit. It should be noted that as of the time of this writing, dual-ICI had been approved by the FDA only for patients with PD-L1–positive (TPS≥1%) disease.[5]

Similarly, among PD-1–positive patients, chemo-ICI did not appear to confer any survival benefit when compared with either form of immunotherapy. This suggests that these patients may be best treated with upfront ICIs (either single-agent or dual-agent ICIs) with chemotherapy saved for salvage therapy, unless a rapid cytoreduction is desired. However, these findings should be considered as hypothesis-generating and

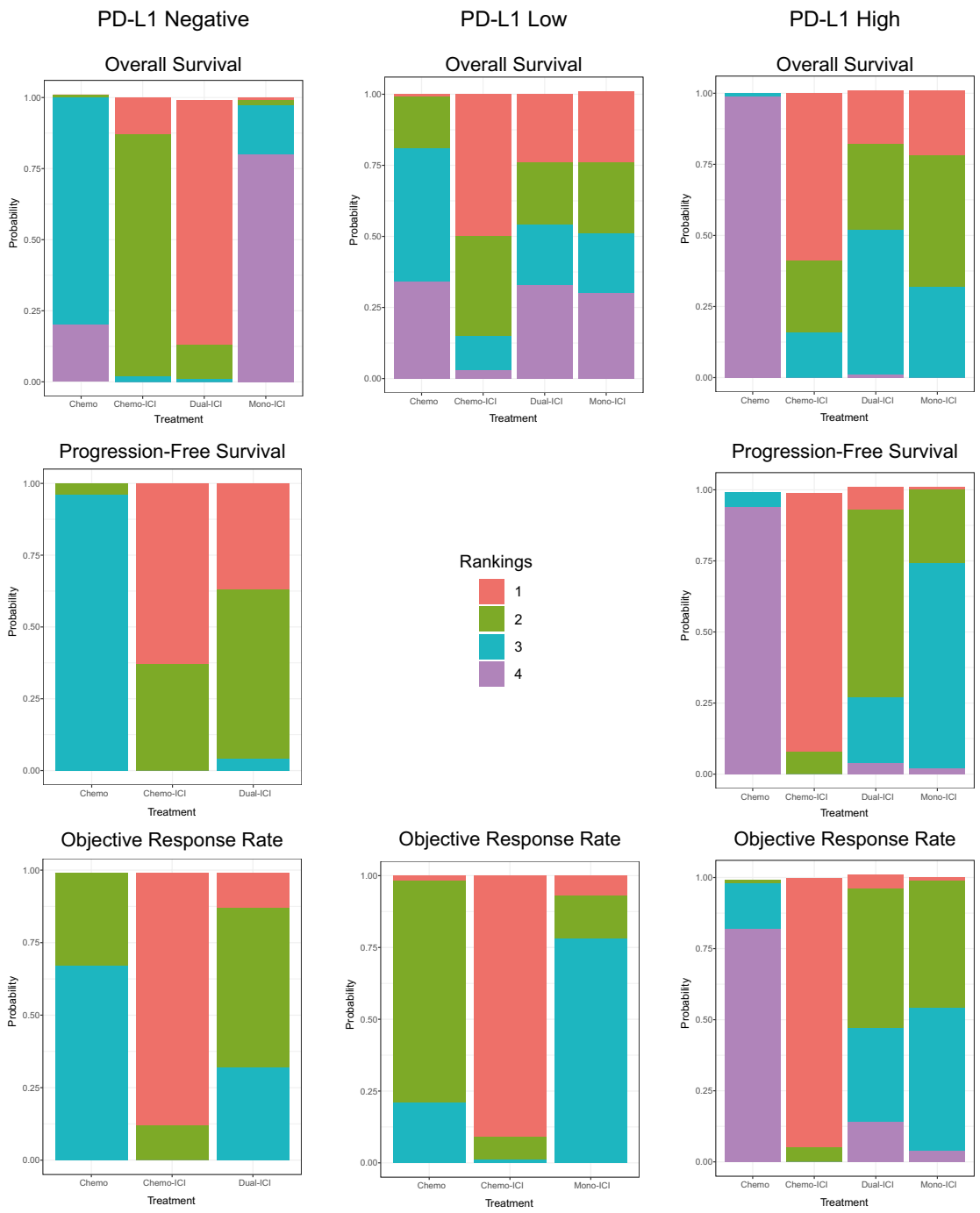

Figure 3. Bayesian ranking profiles of treatments with regard to efficacy for the first-line treatment of patients with advanced non–small cell lung cancer stratified by programmed death–ligand 1 (PD-L1) subsets. Profiles indicate the probability of each treatment being ranked from first to last with regard to overall survival, progression-free survival, and the overall response rate. Ranking curves are described according to the Bayesian ranking results presented in Supporting Table 6. Chemo indicates chemotherapy; chemo-ICI, chemoimmunotherapy; dual-ICI, combination immunotherapy (eg, ipilimumab and nivolumab); PD-L1 negative, high and low indicate tumor proportion score levels (<1% [negative], 1%-49% [low], and ≥50% [high]); single-agent ICI, single-agent immunotherapy (eg, pembrolizumab or atezolizumab alone)

should encourage prospective validation with head-to-head comparisons among chemo-ICI, single-agent ICI, and dual-agent ICI.

Until direct prospective trial results are available, the decision to offer chemo-ICI versus immunotherapy alone for patients with advanced NSCLC without a

driver mutation should be made on a case-by-case basis, with careful attention paid to disease burden, functional status, comorbidities, and patient preference. Ongoing trials such as the Eastern Cooperative Oncology Group 5163/INSIGNA study (ClinicalTrials.gov identifier NCT03793179) hopefully will shed more light on this clinically important question.[37] This phase 3 trial aims to understand the optimum sequencing of chemotherapy and ICI in patients with advanced, PD-L1–positive, nonsquamous NSCLC by randomizing patients into treatment with: 1) frontline pembrolizumab followed by chemotherapy in the second line; 2) frontline pembrolizumab followed by pembrolizumab plus chemotherapy in the second line; or 3) the control arm of induction therapy with combination chemotherapy and pembrolizumab with maintenance pembrolizumab and pemetrexed.

The strengths of the current study included the comparison of the efficacy of chemo-ICI with immunotherapy stratified by clinically relevant PD-L1 subsets. In contrast with previously reported NMAs, the current analysis ensured the homogeneity of the study population by exclusively including only phase 3 trials. In particular, the current study included a PD-L1–negative cohort and a significantly larger patient population.[38] Moreover, multiple sensitivity analyses were performed, including the application of both fixed and random effects models to further assess the robustness of the results.

The current study also had several limitations. Although we attempted an exhaustive literature search, we did not assess publication bias given the small number of trials included in each comparison. NMAs are based on the assumption of transitivity, whereby included studies are considered to be similar enough to build a network. Although we tried to minimize transitivity by including only phase 3 RCTs with similar patient populations, the influence of factors such as differences in outcomes (eg, not all trials reported OS as the primary endpoint), ICIs, and chemotherapy regimens could have introduced some intransitivity. In particular, the included trials used different assays to define PD-L1 status, including the use of immune and tumor cell staining in the IMpower studies. Although we used PD-L1 expression in tumor cells to reclassify patients in the IMpower trials into their corresponding TPS cohorts, we recognized the potential for the misclassification of some patients using this approach (eg, lower sensitivity of the SP142 assay to measure PD-L1 expression in tumor cells).[25] The introduction of some inadvertent misclassification bias could have led to both underestimation or overestimation of benefit (or a lack of) with chemo-ICI in various PD-L1 cohorts. Furthermore, endpoints such as OS and PFS are subject to heterogeneity due to variations in follow-up and data maturity, especially in studies incorporating ICI, because the potential for long-term survival and an extended "tail" of the curve may necessitate adjustments for nonproportional hazards.[39,40] Similarly, an assessment of coherence (ie, agreement of the estimates of treatment effects from direct and indirect evidence) was not possible in the current study given the lack of trials directly comparing chemo-ICI and immunotherapy. In the PD-L1–negative group, patients receiving Single-agent ICI were derived only from the MYSTIC trial, which used treatment with durvalumab (and did not include patients from the KEYNOTE and other trials). This resulted in substantially fewer patients in the PD-L1–negative group compared with the PD-L1–positive groups, thus limiting the robustness of network analysis among PD-L1–negative patients. Last, due to the use of the study-level data, we were unable to examine the impact of individual patient characteristics such as smoking status or histology on the efficacy outcomes.

Conclusions

In the current NMA, it was found that the addition of chemotherapy to ICI might improve the ORR and PFS in patients with PD-L1–high (TPS ≥50%) tumors. However, there does not appear to be an OS benefit for chemo-ICI compared with ICI alone regardless of PD-L1 status. These findings could inform current practice and enhance the design of future clinical trials in the first-line treatment of patients with advanced NSCLC.

FUNDING SUPPORT

No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURES

Gilberto De Lima Lopes has received grants to his institution from Merck (MSD), Bristol-Myers Squibb, AstraZeneca, and Roche for work performed outside of the current study. Sarah B. Goldberg has received grants and personal fees from AstraZeneca and Boehringer Ingelheim and personal fees from Eli Lilly, Genentech, Bristol-Myers Squibb, Blueprint Medicine, Amgen, and Spectrum for work performed outside of the current study. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Ranjan Pathak: Conceptualization, methodology, and writing–original draft. **Gilberto De Lima Lopes:** Writing–review and editing. **Han Yu:** Formal analysis and methodology. **Madan Raj Aryal:** Data curation and writing–review and editing. **Wenyan Ji:** Formal analysis and methodology. **Katherine Stemmer Frumento:** Data curation. **Christopher J. D. Wallis:** Writing–review and editing. **Zachary Klaassen:** Writing–review and editing. **Henry S. Park:** Methodology, supervision, and writing–review and editing. **Sarah B. Goldberg:** Methodology, supervision, and writing–review and editing.

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