ORIGINAL ARTICLE

Efficacy and Safety of Anti–Programmed Cell Death Protein 1/Programmed Death-Ligand 1 Antibodies Plus Chemotherapy as First-Line Treatment for NSCLC in the People's Republic of China: a Systematic Review and Meta-Analysis

Qi-An Chen, M.B.B.S.,[a] Kai Ma, MD, PhD,[b] Lin Zhang, PhD,[b] Wei-Hao Lin, M.B.B.S.,[a] Xian-Xian Wu, PhD,[b] Yi-Bo Gao, MD, PhD[c,d,e,*]

[a]*Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China*
[b]*Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, People's Republic of China*
[c]*Central Laboratory & Shenzhen Key Laboratory of Epigenetics and Precision Medicine for Cancers, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, People's Republic of China*
[d]*State Key Laboratory of Molecular Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China*
[e]*Laboratory of Translational Medicine, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China*

Received 25 January 2024; revised 10 April 2024; accepted 19 April 2024
Available online - 29 April 2024

ABSTRACT

Introduction: The available approved anticancer drugs for Chinese patients are relatively limited because of China's low participation rate in international clinical trials. Therefore, a focus on approved anti–programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) drugs in China is needed. This study aims to assess the heterogeneity of anti–PD-1/PD-L1 antibodies manufactured in China (domestic PD-1/PD-L1) and overseas (imported PD-1/PD-L1) when combined with chemotherapy as the first-line treatment of NSCLC.

Methods: A systematic search was performed using PubMed, EMBASE, and Cochrane Library of publications up to July 13, 2023. Meta-analysis was applied to compare the efficacy and safety profile between anti–PD-1/PD-L1 antibodies plus chemotherapy (PD-1/PD-L1+Chemo) and chemotherapy alone using STATA software. Pooled hazard ratios for progression-free survival and overall survival, odds ratios for objective response rate, and incidence rate of grade greater than or equal to three treatment-related adverse events with 95% confidence intervals were calculated in the domestic group and imported group by a random-effects model, and the heterogeneity between the two estimates was assessed.

Results: There were 14 eligible clinical studies with a total of 3951 patients involved in this analysis, including eight studies of domestic PD-1/PD-L1+Chemo and six studies of imported PD-1/PD-L1+Chemo. The study revealed that there was no significant difference between domestic and imported PD-1/PD-L1+Chemo in overall survival ($p = 0.80$), progression-free survival ($p = 0.53$), and incidence rate of grade greater than or equal to three treatment-related adverse events ($p = 0.10$). Nevertheless, the objective response rate of imported PD-1/PD-L1+Chemo was

*Corresponding author.

Ms. Chen and Dr. Ma contributed equally to this work.

Address for correspondence: Yi-Bo Gao, MD, PhD, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, 518000, People's Republic of China. E-mail: gaoyibo@cicams.ac.cn

Cite this article as: Chen Q.A, Ma K, Zhang L, et al. Efficacy and Safety of Anti-Programmed Cell Death Protein 1/Programmed Death-Ligand 1 Antibodies Plus Chemotherapy as First-Line Treatment for NSCLC in the People's Republic of China: a Systematic Review and Meta-Analysis. *JTO Clin Res Rep* 2024;5:100678

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2024.100678

significantly higher than that of domestic PD-1/PD-L1+Chemo ($p = 0.03$).

Conclusions: Domestic anti–PD-1/PD-L1 antibodies plus chemotherapy were found to have comparable efficacy and safety to those combined with imported anti–PD-1/PD-L1 antibodies based on current evidence.

Keywords: Anti–PD-1/PD-L1 antibody; Non–small cell lung cancer; Efficacy; Safety; China

Introduction

Lung cancer is still one of the leading causes of cancer morbidity and mortality worldwide. It is also prevalent in China, accounting for 29.71% and 22.92% of cancer deaths for males and females, respectively.[1,2] NSCLC is the most common histologic subtype of lung cancer, contributing to more than 85% of the cases.[3] Owing to the late diagnosis related to advanced disease and drug resistance, the prognosis for patients with NSCLC is poor, with a 5-year overall survival (OS) rate of merely 24%.[4] Recently, the excellent progress in immune checkpoint inhibitors (ICIs) has resulted in a considerable improvement in patient outcomes. Among the ICIs, anti–programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) antibodies are the most studied ones. For driver gene-negative advanced NSCLC, anti–PD-1/PD-L1 treatment with or without platinum-based chemotherapy as the first-line strategy has been found to have great benefits.[5] Currently, four anti–PD-1/PD-L1 antibodies, nivolumab, pembrolizumab, atezolizumab, and durvalumab, have been approved by the China National Medical Products Administration (NMPA) to treat NSCLC.[6] Nevertheless, there is still a huge unmet need for anti–PD-1/PD-L1 antibodies in this country owing to its largest population in the world.[7] On the basis of GLOBOCAN 2020, China is estimated to have approximately 37% of the global annual burden of lung cancer incidence and 39.8% of lung cancer deaths[8] (Supplementary Fig. 1). Despite these, there is lagging access of China to cancer drugs caused by a backlog of applications or delays in the approval process. The obvious gap in participation rates in international clinical trials between China and the United States means a lack of clinical data on Chinese patients in international clinical trials.[9] The unique needs in China related to its specific cancer spectrum, ethnic diversity, genetic mutation profile, and clinical practices were not visible and well presented.[10,11]

As a result of a series of health care reform policies, China has seen its drug research and development accelerate in the past decade.[12] Since the launch of the first domestic PD-1 antibody, toripalimab, at the end of 2018,[13] studies on domestic anti–PD-1/PD-L1 drugs in China have exploded. In NCT03594747, the addition of tislelizumab improved progression-free survival (PFS) in patients with squamous NSCLC receiving chemotherapy, which laid the foundation for its indication in squamous NSCLC.[14] Camrelizumab, in combination with carboplatin and pemetrexed, was approved by the NMPA as a first-line therapy to treat advanced or metastatic NSCLC that is EGFR negative and ALK negative, based on the phase 3 CameL study.[15] To date, toripalimab, sintilimab, camrelizumab, tislelizumab, and sugemalimab have been approved by the NMPA for the treatment of patients with unresectable, locally advanced or metastatic, non–oncogene-addicted NSCLC.[6] The relevant studies involved only Chinese patients, and the five medications had not only superior antitumor effects in clinical trials with manageable adverse effects but also economic advantages over imported drugs, which are of great significance to patients affected by cancer in China. Therefore, whether domestic drugs' efficacy is comparable to imported drugs is a matter of concern. The effective and affordable domestic medications available in China can benefit more patients affected by cancer than those imported.

In this study, we focused on anti–PD-1/PD-L1 antibodies available for Chinese patients and assessed the efficacy and safety profile of the combination treatment of chemotherapy and anti–PD-1/PD-L1 antibodies approved by NMPA in the first-line treatment of NSCLC. Considering the potential ethnic differences that would affect results, outcome data from Chinese or Asian patients were retrieved and synthesized to ensure specificity to the Chinese population.

Methods

This study was conducted following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline (see Supplementary Data 1). The protocol was registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42022347563).

Search Strategy and Selection Criteria

A systematic search of the literature was conducted in PubMed, Embase, and Cochrane Library up to July 13, 2023. The following keywords were adopted: "non-small-cell lung cancer, clinical trial, sintilimab, camrelizumab, tislelizumab, sugemalimab, toripalimab, pembrolizumab, atezolizumab, nivolumab, durvalumab." The detailed search strategies are listed in Supplementary Table 1.

The inclusion criteria for published studies were as follows: (1) Enrolled patients with histologically or cytologically confirmed NSCLC without known EGFR and ALK

alteration, having received no previous systemic treatment; (2) Phase III randomized controlled trials (RCTs) comparing chemotherapy alone or in combination with anti–PD-1/PD-L1 antibodies approved by NMPA as first-line therapy; (3) Reported at least one of the following clinical outcomes: PFS, OS, objective response rate (ORR), and the incidence rate of grade greater than or equal to three treatment-related adverse events (trAEs) for Chinese or Asian cohort. The exclusion criteria were as follows: (1) studies only in the form of conference abstracts, posters, and presentations of ongoing trials; (2) reviews, letters, case reports, or commentaries; (3) studies of quality-of-life outcomes or cost-effectiveness analyses only.

Three investigators (QC, KM, and LZ) screened the identified articles to select studies that meet the eligibility criteria outlined previously. The disagreements regarding the eligibility of specific studies were resolved through discussions with the other authors (YG).

Data Collection and Risk of Bias Assessment

Data are extracted using a predefined data extraction form. The following information was extracted: trial name, National Clinical Trials identification number, number of patients, treatment compound, age, gender, histologic type, PD-L1 expression, Eastern Cooperative Oncology Group performance status (ECOG PS), smoking status, and median follow-up time. QC and KM independently did the data extraction. Any discrepancies were resolved through discussion with a third reviewer (LZ).

The Cochrane risk of bias tool 2.0 was used to assess the quality of each included study. The risk of bias was assessed by two investigators (QC and KM) independently, and the discrepancies were resolved through discussion with a third reviewer (LZ).

Statistical Analysis

The primary outcomes of interest were PFS and OS, and the secondary outcomes were ORR, incidence rate of all-grade trAEs, and grade greater than or equal to three trAEs. Hazard ratios (HRs) for PFS and OS, odds ratios (ORs) for ORR, incidence rate of all-grade trAEs, and grade greater than or equal to three trAEs with 95% confidence intervals (CIs) were calculated separately for domestic anti–PD-1/PD-L1 antibody plus chemotherapy and imported anti–PD-1/PD-L1 antibody plus chemotherapy using a random effects model. We assessed the differences between-group using a test for heterogeneity between groups.

Meta-analyses were performed with RevMan (version 5.3), and the effect size was summarized within the forest plot. Heterogeneity was assessed by Cochrane's Q test and the inconsistency test (I^2). An I^2 value of less than 50% suggests a low probability of heterogeneity, whereas I^2 greater than 50% indicates significant heterogeneity.

The publication bias was evaluated by Egger's test and visualized through funnel plots. Predefined subgroup analyses were performed based on histologic type, PD-L1 expression level, target of intervention agents, blinding of participants and personnel, and median follow-up duration. Sensitivity analysis was performed to verify the stability of results by omitting studies one by one.

Informed Consent Statement

No informed consent is required.

Results

Study Selection and Characteristics

We identified 548 relevant articles by searching PubMed, Embase, and Cochrane Central databases according to the search strategy found in Supplementary Table 1. After the removal of duplicate records, 303 records were excluded following a screening of titles and abstracts. The remaining 24 full-text articles were assessed for eligibility. Finally, a total of 14 studies involving 3951 patients were eligible for this meta-analysis (Fig. 1). Update analyses of the incorporated studies were manually searched to ensure that the latest results were included.

Table 1 and Table 2 reveal the baseline characteristics of the included studies and patients. All included studies were phase III RCTs, eight of which evaluated anti–PD-1/PD-L1 antibodies manufactured in China plus chemotherapy (domestic PD-1/PD-L1+Chemo) versus chemotherapy alone[14–26] and six evaluated anti–PD-1/PD-L1 antibodies manufactured overseas plus chemotherapy (imported PD-1/PD-L1+Chemo) versus chemotherapy.[27–32] Domestic PD-1/PD-L1 used in eligible studies included camrelizumab, sintilimab, sugemalimab, tislelizumab, and toripalimab; imported PD-1/PD-L1 included atezolizumab, pembrolizumab, and durvalumab (Supplementary Table 2). Of the included studies, five RCTs involved only patients with squamous NSCLC (CameL-sq, ORIENT-12, RATIONALE-307, KEYNOTE-407, and IMPOWER-131) and six RCTs involved only patients with nonsquamous NSCLC (CameL, ORIENT-11, RATIONALE-304, IMPOWER-132 with China cohort, IMPOWER-132 with Japan cohort, and KEYNOTE-189 with Japan cohort), whereas the remaining three involved mixed histology types (GEMSTONE-302, CHOICE-01, and POSEIDON).

The details of the bias assessment are found in Supplementary Figure 2.

Efficacy Analysis

Overall, PD-1/PD-L1+Chemo significantly improved PFS (HR = 0.51, 95% CI: 0.45–0.58, I^2 = 55%), OS (HR = 0.69, 95% CI: 0.62–0.77, I^2 = 29%), and ORR (OR = 2.61,

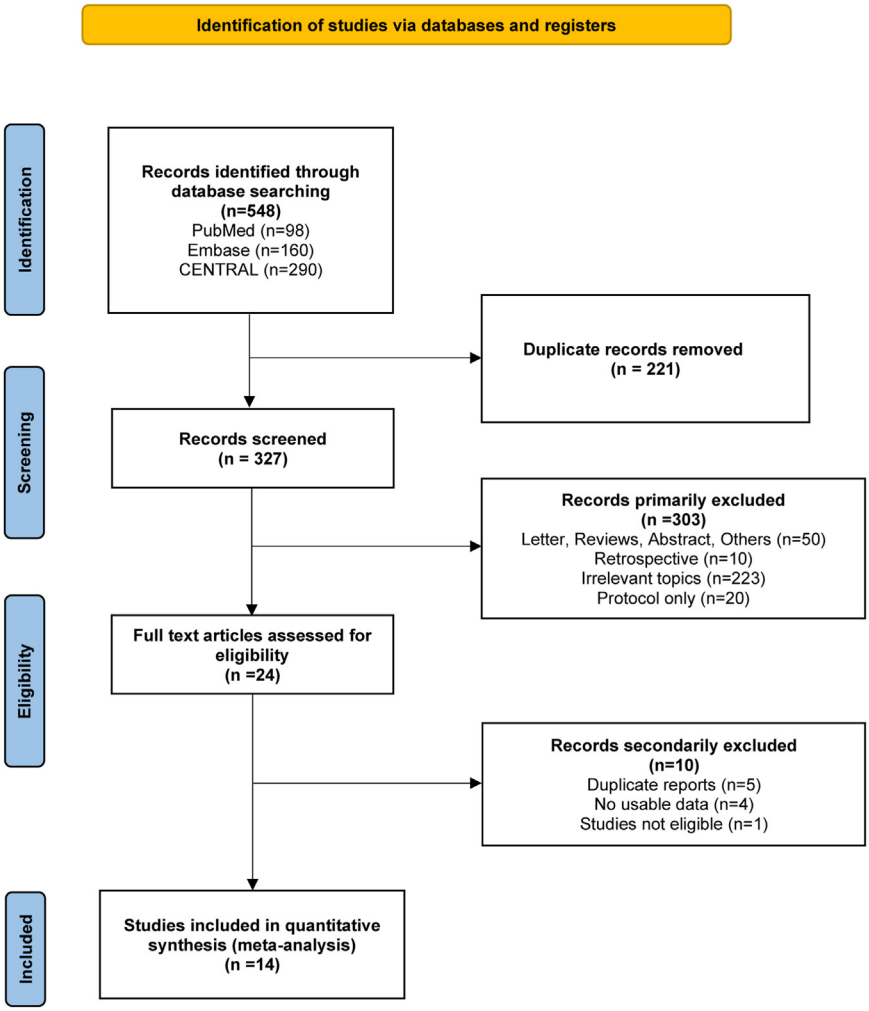

Figure 1. PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis.

95% CI: 2.21–3.08, I^2 = 23%) in comparison to chemotherapy (Fig. 2*A*–*C*). Domestic PD-1/PD-L1+Chemo and imported PD-1/PD-L1+Chemo were found to provide clinically comparable survival in terms of PFS ([HR = 0.49, 95% CI: 0.45–0.55, I^2 = 28%] versus [HR = 0.55, 95% CI: 0.40–0.77, I^2 = 70%], test for subgroup difference: p = 0.53) and OS ([HR = 0.67, 95% CI: 0.61–0.75, I^2 = 0%] versus [HR = 0.71, 95% CI: 0.50–1.00, I^2 = 60%], test for subgroup difference: p = 0.80). Nevertheless, imported PD-1/PD-L1+Chemo yielded better ORR benefits than domestic PD-1/PD-L1+Chemo ([OR = 4.01, 95% CI: 2.66–6.06, I^2 = 0%] versus [OR = 2.42, 95% CI: 2.06–2.85, I^2 = 12%], test for subgroup difference: p = 0.03).

Safety Analysis

As for safety, ICIs added to chemotherapy were associated with higher toxicity as the OR of the incidence rate of all-grade trAEs and grade greater than or equal to three trAEs for PD-1/PD-L1+Chemo were 3.18 (95% CI: 1.34–7.53, I^2 = 0%) (Supplementary Fig. 3) and 1.43 (95% CI: 1.14–1.81, I^2 = 50%) (Fig. 2*D*), respectively. There was no significant difference in the incidence rate of all-grade trAEs and grade greater than or equal to three trAEs between domestic and imported immunochemotherapies (all-grade trAEs, p = 0.98; grade ≥3 trAEs, p = 0.10). The incidences of frequently described organ-specific immune-related adverse events (colitis, hepatitis, pneumonitis, and hypothyroidism)[33] in domestic PD-1/PD-L1+Chemo and imported PD-1/PD-L1+Chemo were also analyzed (Supplementary Table 3).

Subgroup Analysis by Histologic Type

For the squamous NSCLC, domestic PD-1/PD-L1+Chemo significantly prolonged PFS (HR = 0.43, 95% CI: 0.37–0.52, I^2 = 44%) and OS (HR = 0.65, 95% CI: 0.53–0.80, I^2 = 36%). Similar improvements were observed with imported PD-1/PD-L1+Chemo in PFS (HR = 0.48, 95% CI: 0.25–0.94, I^2 = 77%) but not in OS (HR = 0.74, 95% CI: 0.26–2.16, I^2 = 87%) (Fig. 3*A* and *B*).

Table 1. Baseline Characteristics of Included Studies

Trial Name	Registered ID	Blinding	Number (Treatment/ Control)	Histology	Intervention Arm	Control Arm	Median Follow-Up Time (Month)
CameL-sq	NCT03668496	Double-blind	389 (193/196)	Squamous	Camrelizumab + chemotherapy	Chemotherapy	13.5 for PFS and 23.7 for OS
CameL	NCT03134872	Open-label	412 (205/207)	Nonsquamous	Camrelizumab + chemotherapy	Chemotherapy	11.9 for PFS and 19.3 for OS
ORIENT-11	NCT03607539	Double-blind	397 (266/131)	Nonsquamous	Sintilimab + chemotherapy	Chemotherapy	8.9 for PFS and 22.9 for OS
ORIENT-12	NCT03629925	Double-blind	357 (179/178)	Squamous	Sintilimab + chemotherapy	Chemotherapy	12.9 for PFS and 8.0 for OS
GEMSTONE-302	NCT03789604	Double-blind	479 (320/159)	Nonsquamous (287) Squamous (192)	Sugemalimab + chemotherapy	Chemotherapy	17.8
RATIONALE-304	NCT03663205	Open-label	334 (223/111)	Nonsquamous	Tislelizumab + chemotherapy	Chemotherapy	9.8
RATIONALE-307	NCT03594747	Open-label	360 (120/119/121)	Squamous	Tislelizumab + chemotherapy	Chemotherapy	8.6
CHOICE-01	NCT03856411	Double-blind	465 (309/156)	Nonsquamous (245) Squamous (220)	Toripalimab + chemotherapy	Chemotherapy	7.1 for PFS and 16.2 for OS
IMPOWER-131	NCT02367794	Open-label	78	Squamous	Atezolizumab + chemotherapy	Chemotherapy	—
IMPOWER-132 China cohort	NCT02657434	Open-label	163 (82/81)	Nonsquamous	Atezolizumab + chemotherapy	Chemotherapy	11.7
IMPOWER-132 Japan cohort	NCT02657434	Open-label	101 (48/53)	Nonsquamous	Atezolizumab + chemotherapy	Chemotherapy	17.5 for PFS and 31.7 for OS
KEYNOTE-189 Japan cohort	NCT02775435	Double-blind	40 (25/15)	Nonsquamous	Pembrolizumab + chemotherapy	Chemotherapy	—
KEYNOTE-407 China cohort	NCT02775435	Double-blind	125 (65/60)	Squamous	Pembrolizumab + chemotherapy	Chemotherapy	28.1
POSEIDON	NCT03164616	Open-label	251 (123/128)	Mix	Arm A: Tremelimumab + durvalumab + chemotherapy	Chemotherapy	—
					Arm B: Durvalumab + chemotherapy		

PFS, progression-free survival; OS, overall survival.

Table 2. Patient Characteristics of Included Trials

Trial Name	Arm	Age (Median)	Male, n (%)	Smoking Status, n (%)		PD-L1 TPS, n (%)			ECOG PS, n (%)	
				Current/Former	Never	<1%	1%–49%	≥50%	0	1
CameL-sq	Intervention	64	179 (93)	171 (89)	22 (11)	91 (47.2)	58 (30.1)	37 (19.2)	38 (19.7)	155 (80.3)
	Control	62	180 (92)	173 (88)	23 (12)	97 (49.5)	49 (25.0)	44 (22.5)	43 (21.9)	153 (78.1)
CameL	Intervention	59	146 (71)	127 (62)	78 (38)	49 (23.9)	108 (52.7)	30 (14.6)	48 (23.4)	157 (76.6)
	Control	61	149 (72)	130 (63)	77 (37)	69 (33.3)	97 (46.9)	20 (9.7)	36 (17.4)	171 (82.6)
ORIENT-11	Intervention	61	204 (76.7)	171 (64.3)	95 (35.7)	85 (32.0)	74 (27.8)	107 (40.2)	76 (28.6)	190 (71.4)
	Control	61	99 (75.6)	87 (66.4)	44 (33.6)	44 (33.6)	26 (19.8)	61 (46.6)	34 (26.0)	97 (74.0)
ORIENT-12	Intervention	64	163 (91.1)	155 (86.6)	24 (13.4)	59 (33.0)	62 (34.6)	58 (32.4)	30 (16.8)	149 (83.2)
	Control	62	164 (92.1)	147 (82.6)	31 (17.4)	63 (35.4)	52 (29.2)	63 (35.4)	22 (12.4)	156 (87.6)
GEMSTONE-302	Intervention	62	254 (79)	232 (73)	88 (27)	124 (38.8)	92 (28.8)	104 (32.5)	59 (18.4)	261 (81.6)
	Control	64	129 (81)	119 (75)	40 (25)	64 (40.3)	48 (30.2)	47 (29.9)	25 (15.7)	134 (84.3)
RATIONALE 304	Intervention	60	168 (75.3)	147 (65.9)	76 (34.1)	96 (43.0)	53 (23.8)	74 (33.2)	54 (24.2)	169 (75.8)
	Control	61	79 (71.2)	66 (59.4)	45 (40.5)	48 (43.2)	27 (24.3)	36 (32.4)	24 (21.6)	87 (78.4)
RATIONALE 307	Intervention	60	107 (89.2)	96 (80.0)	24 (20.0)	48 (40.0)	30 (25.0)	42 (35.0)	31 (25.8)	89 (74.2)
	Control	62	111 (91.7)	98 (81.0)	23 (19.0)	49 (40.5)	31 (25.6)	41 (33.9)	32 (26.4)	89 (73.6)
CHOICE-01	Intervention	63	247 (79.9)	213 (68.9)	96 (31.1)	108 (35.0)	—	—	66 (21.4)	243 (78.6)
	Control	61	130 (83.3)	107 (68.6)	49 (31.4)	53 (34.0)	—	—	36 (23.1)	120 (76.9)
IMPOWER-131	Intervention	—	—	—	—	—	—	—	—	—
	Control	—	—	—	—	—	—	—	—	—
IMPOWER-132 China	Intervention	61	60 (73.2)	52 (63.4)	30 (36.6)	—	—	—	22 (26.8)	60 (73.2)
	Control	61	59 (72.8)	54 (66.7)	27 (33.3)	—	—	—	22 (27.2)	59 (72.8)
IMPOWER-132 Japan	Intervention	65	31 (64.6)	39 (81.3)	9 (18.8)	13 (27.1)	—	7 (14.6)	21 (43.8)	27 (56.3)
	Control	66	39 (73.6)	48 (90.6)	5 (9.4)	14 (26.4)	—	1 (1.9)	22 (41.5)	31 (58.5)
KEYNOTE-189 Japan	Intervention	64	19 (76)	18 (72)	7 (28)	14 (56)	—	—	15 (60)	10 (40)
	Control	66	12 (80)	12 (80)	3 (20)	6 (40)	—	—	9 (60)	6 (40)
KEYNOTE-407 China	Intervention	63	62 (95.4)	60 (92.3)	5 (7.7)	25 (38.5)	15 (23.1)	22 (33.8)	20 (30.8)	45 (69.2)
	Control	63	57 (95.0)	54 (90.0)	6 (10.0)	23 (38.3)	20 (33.3)	15 (25.0)	11 (18.3)	49 (81.7)
POSEIDON	Intervention	—	—	—	—	—	—	—	—	—
	Control	—	—	—	—	—	—	—	—	—

PD-L1, programmed death-ligand 1; TPS, tumor cell proportion score; ECOG PS, Eastern Cooperative Oncology Group performance status.

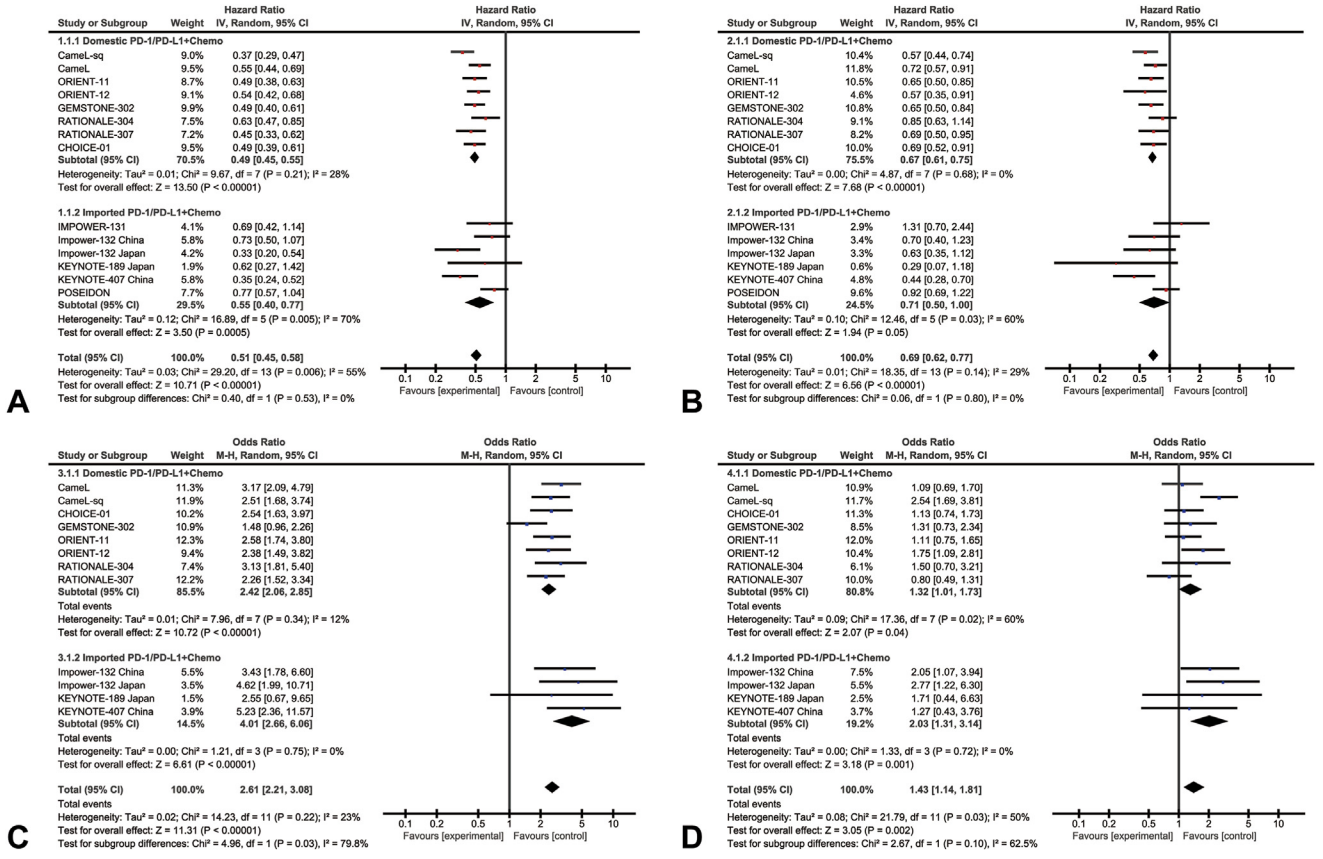

Figure 2. Pooled results of (*A*) PFS, (*B*) OS, (*C*) ORR, and (*D*) incidence rate of grade greater than or equal to three trAEs as per treatment group. CI, confidence interval; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; trAEs, treatment-related adverse events.

For the nonsquamous NSCLC, the domestic PD-1/PD-L1+Chemo yielded a statistically significant improvement in PFS (HR = 0.54, 95% CI: 0.48–0.61, I^2 = 0%) and OS (HR = 0.69, 95% CI: 0.59–0.81, I^2 = 27%) compared with chemotherapy, respectively. Similar improvements in PFS (HR = 0.53, 95% CI: 0.30–0.92, I^2 = 68%) and OS (HR = 0.62, 95%CI: 0.42–0.92, I^2 = 0%) were observed with imported PD-1/PD-L1+Chemo compared with chemotherapy alone (Fig. 3*C* and *D*).

Furthermore, both domestic and imported immunochemotherapies had clinical comparability to each other in squamous (PFS, p = 0.77; OS, p = 0.82) and nonsquamous NSCLC (PFS, p = 0.92; OS, p = 0.63) (Fig. 3*A*–*D*).

Subgroup Analysis by PD-L1 Expression Level

In the PD-L1 less than 1% subgroup, pooled HR for PFS in domestic PD-1/PD-L1+Chemo was 0.58 (95% CI: 0.50–0.66, I^2 = 0%), whereas in imported PD-1/PD-L1+Chemo was 0.42 (95% CI: 0.22–0.79) (Fig. 4*A*); pooled HR for OS in domestic PD-1/PD-L1+Chemo was 0.69 (95% CI: 0.58–0.82, I^2 = 0%), whereas in imported PD-1/PD-L1+Chemo was 0.50 (95% CI: 0.25–1.00) (Fig. 4*B*).

In the PD-L1 1% to 49% subgroup, pooled HR for PFS in domestic PD-1/PD-L1+Chemo was 0.52 (95% CI: 0.45–0.62, I^2 = 20%), whereas in imported PD-1/PD-L1+Chemo was 0.38 (95% CI: 0.17–0.85) (Fig. 4*C*); pooled HR for OS in domestic PD-1/PD-L1+Chemo was 0.67 (95% CI: 0.55–0.81, I^2 = 0%), whereas in imported PD-1/PD-L1+Chemo was 0.36 (95% CI: 0.15–0.87) (Fig. 4*D*).

In the PD-L1 greater than or equal to 50% subgroup, pooled HR for PFS in domestic PD-1/PD-L1+Chemo was 0.39 (95% CI: 0.32–0.46, I^2 = 0%), whereas in imported PD-1/PD-L1+Chemo was 0.29 (95% CI: 0.14–0.61) (Fig. 4*E*); pooled HR for OS in domestic PD-1/PD-L1+Chemo was 0.50 (95% CI: 0.38–0.66, I^2 = 0.0%), whereas in imported PD-1/PD-L1+Chemo was 0.44 (95% CI: 0.17–1.14) (Fig. 4*F*).

No significant difference was observed between domestic and imported immunochemotherapies in all subgroups (Fig. 4*A*–*F*).

Subgroup Analyses by Methodological Factors

There was no significant difference between domestic and imported immunochemotherapies for other

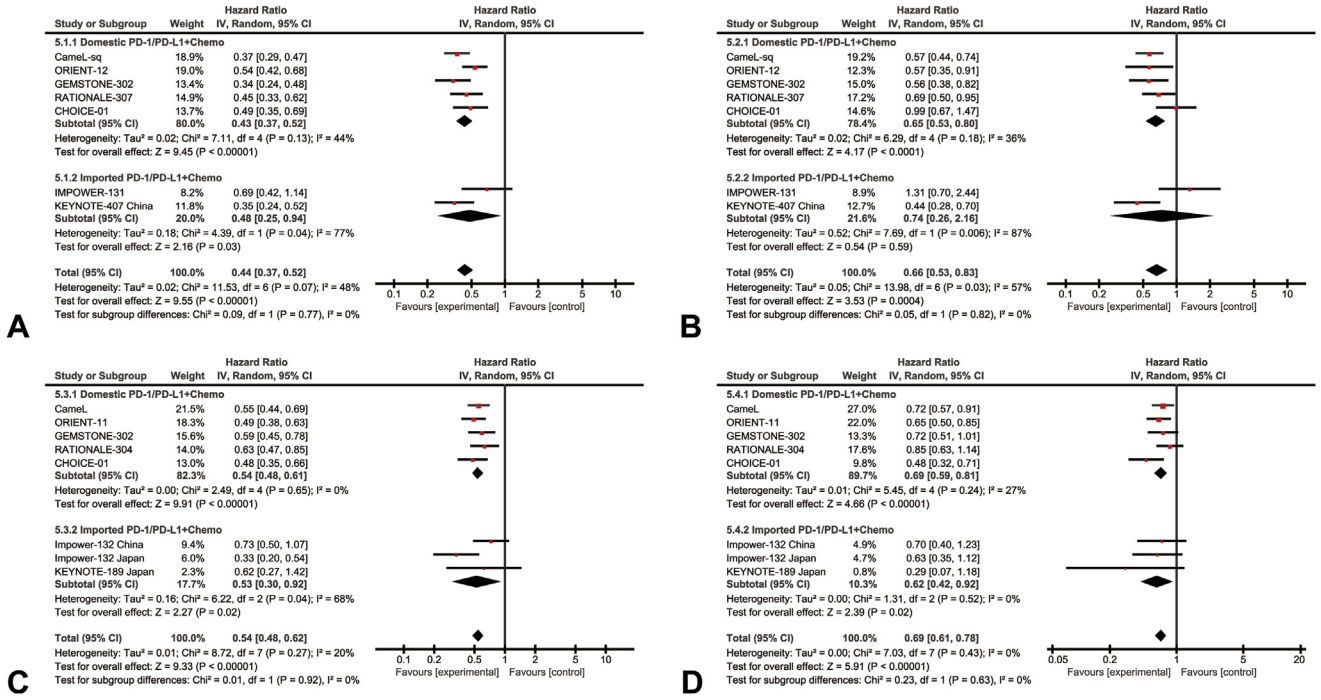

Figure 3. Pooled analysis of efficacy in different histology types. (*A*) Pooled HR for PFS in squamous NSCLC cohort. (*B*) Pooled HR for OS and in squamous NSCLC cohort. (*C*) Pooled HR for PFS in nonsquamous NSCLC cohort. (*D*) Pooled HR for OS in nonsquamous NSCLC cohort. CI, confidence interval; HR, hazard ratio; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

subgroups, including the target of immune checkpoints, blinding of participants and personnel, and median follow-up duration. The detailed results of additional analyses are found in Supplementary Table 4.

Publication Bias and Sensitivity Analysis

The funnel plots provided in Supplementary Figure 4 and the *p* value from Egger's test suggested that no obvious publication bias existed. Sensitivity analysis revealed that the results of PFS, OS, ORR, and incidence rate of grade greater than or equal to three trAEs were stable (Supplementary Fig. 5*A*–*D*).

Discussion

Despite the fact that pembrolizumab, nivolumab, atezolizumab, and durvalumab were found to have potent antitumor effects in conclusive clinical trials, it is important to note that China's large population of patients affected by cancer has different economic backgrounds from those in developed western countries. The overall cost of cancer therapy is an important, sometimes decisive, factor in patients' choice of the appropriate treatments. Currently, the NMPA has included camrelizumab, tislelizumab, and sintilimab into the National Directory of Medical Insurance, and the overall costs of domestic PD-1/PD-L1 antibodies are generally lower than those of the other four drugs mentioned previously[34,35] (e.g., $441.69 per 100 mg for sintilimab versus $2783.78 per 100 mg for pembrolizumab[35]). Thus, these domestic drugs might substantially improve the situation of cancer therapy and provide more acceptable choices for Chinese patients.

In this study, we included studies comparing imported or domestic anti–PD-1/PD-L1 antibodies plus chemotherapy versus chemotherapy for the first-line treatment of Asian patients with non–oncogene-addicted NSCLC. According to the results from meta-analysis, we found that both imported and domestic anti–PD-1/PD-L1 combination treatment regimens were associated with superior clinical benefits over chemotherapy alone. Notably, there was no significant difference between domestic and imported PD-1/PD-L1 combination therapies, with the exception of the ORR. There are several possible factors that might contribute to the improvement in ORR in the imported group compared with the domestic group. First, the sample size in the imported group was relatively small, which may introduce selection bias and influence the estimation of ORR. Second, three open-label studies, IMpower-132, Japan cohort in IMpower-132, and Chinese cohort in IMpower-132, only reported investigator-assessed ORR, suggesting that there was potential detection bias. Third, differences in the prevalence of some baseline characteristics were

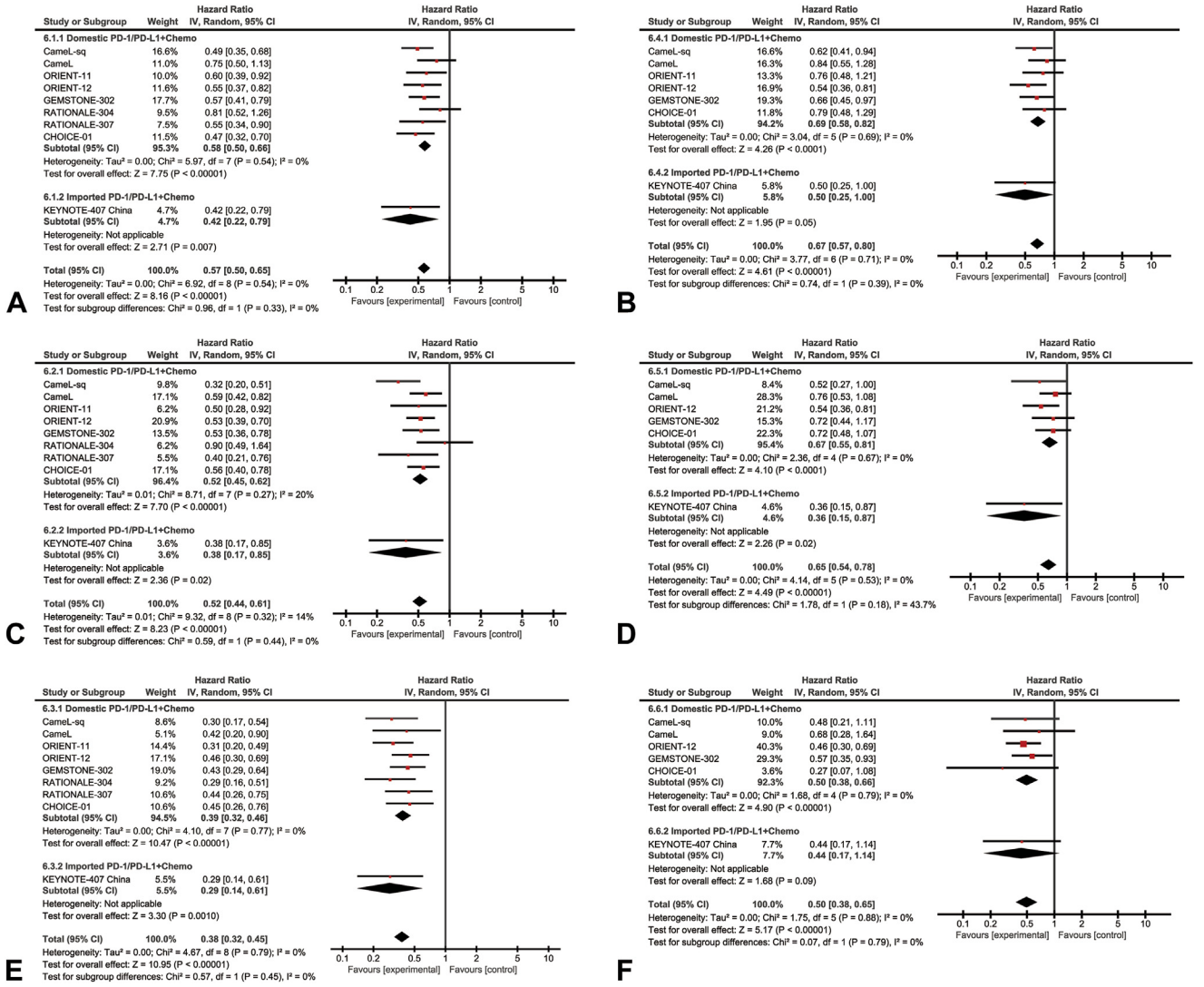

Figure 4. Pooled analysis of efficacy in different PD-L1 expression levels. (*A*) Pooled HR for PFS in the PD-L1 less than 1% cohort. (*B*) Pooled HR for OS and in the PD-L1 less than 1% cohort. (*C*) Pooled HR for PFS in the PD-L1 1% to 49% cohort. (*D*) Pooled HR for OS in the PD-L1 1% to 49% cohort. (*E*) Pooled HR for PFS in the PD-L1 greater than or equal to 50% cohort. (*F*) Pooled HR for OS in the PD-L1 greater than or equal to 50% cohort. CI, confidence interval; HR, hazard ratio; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

observed between the Chinese studies and the global studies. Patients in the Chinese studies had a higher prevalence of ECOG PS of 1 than in the global studies (Table 2), which may suggest that patients in the imported group had a lesser disease burden. Besides, there are unbalanced baseline characteristics between treatment groups in global studies. In the Japanese cohort of IMpower-132, the proportion of patients with high PD-L1 expression (TC3 or IC3) was higher in the combination therapy arm than in the monotherapy arm (14.6% versus 1.9%). In the Chinese cohort of KEYNOTE-407, the proportion of patients with an ECOG PS of 1 was higher in the monotherapy arm than in the combination treatment arm (81.7% versus 69.2%). Considering these potential biases, future studies with a large sample size are needed to investigate the ORRs of domestic and imported anti–PD-1/PD-L1 antibodies.

As for subgroup analysis, the domestic PD-1/PD-L1 combination regimens not only provided significant PFS and OS benefits for patients with positive PD-L1 (PD-L1 $\geq$ 1%) but also for patients with PD-L1 of less than 1%, a population deemed to have limited benefit from PD-1/PD-L1 antibodies previously.[36,37] When grouped by histologic type, domestic PD-1/PD-L1 combination regimens provided PFS and OS benefits in patients with squamous and nonsquamous NSCLC. Of note, the pooled OS of the imported combination regimens in the squamous NSCLC cohort revealed great heterogeneity and failed to reach statistical significance. Besides, the patient number was relatively small in the PD-L1 greater

than or equal to 50% cohort in KEYNOTE-407, and the CI of OS was wide, precluding more definitive conclusions in the imported combination group. On the basis of the comprehensive results of this study, domestic anti–PD-1/PD-L1 antibodies plus chemotherapy are recommended for the first-line treatment of non–oncogene-addicted NSCLC in China.

The value of this topic is obvious. First, previous studies have not analyzed the comparative efficacy of domestic anti–PD-1/PD-L1 antibodies on Chinese populations. There has been an acknowledgment of China's low participation rate in international clinical trials. Among the clinical trials involving 954 new anticancer drugs led by the top 20 pharmaceutical companies globally from 2011 to 2021, only 8.8% of drugs have not been tested in the USA, whereas up to 79.4% of drugs have never been tested in China.[9] The disparity has led to obvious drug lag, defined as the time between a new drug being approved by the U.S. FDA and approved in China.[38] Although having been reduced tremendously in the past 10 years,[38] drug lag has lowered the availability of global anticancer drugs for Chinese patients. Therefore, our study focused on drugs approved by the NMPA, which are available to Chinese patients. Second, we retrieved the latest survival data from updated outcome results, which had not been included in previously published meta-analyses.

Studies have reported that Asians may have different tumor mutation profiles and thereby experience different clinical responses from non-Asians when receiving immunotherapy.[39–42] Because of China's low participation rate in early phase trials and in synchronous trials compared with the USA,[9] we included only five international clinical trials that reported clinical outcomes of the Asian cohort for this study in an effort to minimize heterogeneity. Li et al.[43] have evaluated PD-1 inhibitors versus platinum-based chemotherapy as first-line treatment for advanced NSCLC. They found that the combination of chemotherapy with PD-1/PD-L1 inhibitors enhanced survival benefits at the cost of an increase in adverse events, which was consistent with our results. Nevertheless, this study only evaluated imported anti–PD-1/PD-L1 antibodies. Zhao et al.[44] conducted a network meta-analysis to compare the efficacy and safety of first-line immunochemotherapy for advanced NSCLC in China. Nevertheless, this study only focused on squamous NSCLC and incorporated results from global patients without considering ethnic differences. Liu et al.[45] also explored the comparative efficacy and safety of ICI-based treatments, but the latest research, such as Camel-sq, GEMSTONE-302, and CHOICE-01, was not included.

Other domestic anti–PD-1/PD-L1 antibody-based combination treatment strategies, such as combinations of anti–PD-1/PD-L1 antibody and anti-VEGFR antibody, and combinations of domestic anti–PD-1/PD-L1 antibody and anti-TIGIT antibody, have not been included in our analysis due to their early stages and immature results.

Several international studies have been conducted combining anti–PD-1/PD-L1 antibodies with anti-VEGFR antibodies, including anti–CTLA-4 antibodies. In CheckMate-227, nivolumab plus ipilimumab, a CTLA-4 inhibitor, resulted in a longer OS duration compared with chemotherapy in patients with NSCLC.[46] The results of IMpower-150 revealed that the addition of atezolizumab to bevacizumab plus chemotherapy significantly improved PFS and OS among patients with metastatic nonsquamous NSCLC.[47] In light of these results, such combination regimens are highly promising, and the efficacy of domestic anti–PD-1/PD-L1 antibody-based combination treatments is yet to be determined.

Studies have reported that Asian patients exhibit significantly different tumor mutation profiles than White patients. Specifically, upward of 47.9% of Asians harbor the EGFR mutation, whereas approximately 15% of White patients do.[48] Whether this population can benefit from the PD-1/PD-L1 antibodies is a concern of great importance. Researchers found that nivolumab plus chemotherapy would not provide a better PFS than chemotherapy for EGFR-mutated metastatic NSCLC previously treated with EGFR tyrosine kinase inhibitors in a global phase III trial, CheckMate-722.[49] Besides, the KEYNOTE-789 trial reported that pembrolizumab plus chemotherapy did not significantly improve PFS and OS versus chemotherapy in patients with tyrosine kinase inhibitor-resistant, EGFR-mutated metastatic nonsquamous NSCLC.[50] Nevertheless, an interim result suggested that sintilimab plus bevacizumab biosimilar IBI305 and chemotherapy prolonged PFS for patients with EGFR-mutated nonsquamous NSCLC.[51] Longer follow-up is necessary to confirm the efficacy of this triplet combination treatment. Apart from this, domestic clinical trials are also actively investigating the combination of ICIs and radiotherapy/chemoradiotherapy for the treatment of NSCLC. The combination of these therapies and immunotherapy is also an important part of this topic and will be studied separately in our future work.

This study has the following limitations. First, in terms of indirect comparison between domestic and imported immunochemotherapies, this study estimated the relative treatment effects based on the constant hazard ratio. Nevertheless, ICI trials often observed with long tails and crossovers in the survival curves may cause time-varying risks, leading to misinterpretation of

clinical significance.[52] To reduce this bias, we conducted a subgroup analysis based on follow-up duration to find no significant difference between domestic and imported immunochemotherapies in short-term and long-term periods. Considering that the follow-up time of different RCTs is not the same, future investigations may compare the relative treatment effects of these interventions based on the unified research time frame and survival curves. Second, studies on imported anti–PD-1/PD-L1 antibodies provided limited stratified outcomes based on clinicopathologic characteristics, such as age, smoking status, and metastasis status, which made it difficult to analyze heterogeneity adequately. Third, only five international clinical trials that reported clinical outcomes from the Asian cohort were eligible for this analysis. Phase III clinical trials IMpower-130,[20] IMpower-150,[47] and CheckMate-227,[46] which enrolled 17 (2.3%), 102 (12.8%), and 347 (20.0%) Asian patients, respectively, were not included in this meta-analysis because they did not report Asian patient nor Chinese patient data specifically. Studies such as IMPOWER-131 and IMPOWER-132 are limited in sample size and have a high crossover rate after treatment, which can lead to heterogeneity and negative results. Advantages might be observed when expanding the sample size. To overcome these limitations, large-scale studies with more comparable baseline information or even head-to-head trials are necessary to verify these findings.

In conclusion, based on the present limited data, the current meta-analysis suggested that domestic PD-1/PD-L1 antibodies plus chemotherapy were promising therapies compared with chemotherapy alone for the first-line treatment of Chinese patients with advanced NSCLC. More importantly, domestic PD-1/PD-L1 antibodies are not second to imported ones in clinical efficacy and safety. Our results inform clinical decision-making regarding the first-line use of domestic anti–PD-1/PD-L1 antibodies plus chemotherapy for patients with advanced NSCLC in China.

CRediT Authorship Contribution Statement

Qi-An Chen: Methodology, Validation, Formal analysis, Data Curation, Writing—Original Draft.

Kai Ma: Methodology, Validation, Data Curation, Writing—Original Draft.

Lin Zhang: Validation, Data Curation, Writing—Original Draft.

Wei-Hao Lin: Methodology, Data Curation, Visualization.

Xian-Xian Wu: Data Curation, Visualization.

Yi-Bo Gao: Conceptualization, Writing—Review and Editing, Supervision, Funding acquisition.

Disclosure

The authors declare that they have no competing interests.

Acknowledgments

This work was supported by the National Key R&D Program of China (2020AAA0109500), the National Natural Science Foundation of China (82122053), the R&D Program of Beijing Municipal Education Commission (KJZD20191002302), CAMS Initiative for Innovative Medicine (2021-1-I2M-012), Key-Area Research and Development Program of Guangdong Province (2021B0101420005), Shenzhen Science and Technology Program (RCJC20221008092811025, ZDSYS20220606101604009), Shenzhen High-level Hospital Construction Fund (CFA202201001), Sanming Project of Medicine in Shenzhen (SZSM202211011), Aiyou Foundation (KY201701), Cancer Research Program of National Cancer Center (NCC201919B02), and National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen (SZ2020ZD001, E010221007, SZ2020ZD010).

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100678.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209-249.
2. Zheng R, Zhang S, Zeng H, et al. Cancer incidence and mortality in China, 2016. *J N Atl Cancer Cent*. 2022;2:1-9.
3. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. *Mayo Clin Proc*. 2008;83:584-594.
4. Garon EB, Hellmann MD, Rizvi NA, et al. Five-year overall survival for patients with advanced non–small-cell lung cancer treated with pembrolizumab: results from the Phase I KEYNOTE-001 study. *J Clin Oncol*. 2019;37:2518-2527.
5. Dafni U, Tsourti Z, Vervita K, Peters S. Immune checkpoint inhibitors, alone or in combination with chemotherapy, as first-line treatment for advanced non-small cell lung cancer. A systematic review and network meta-analysis. *Lung Cancer*. 2019;134:127-140.
6. Yan T, Yu L, Shangguan D, et al. Advances in pharmacokinetics and pharmacodynamics of PD-1/PD-L1 inhibitors. *Int Immunopharmacol*. 2023;115:109638.

7. Guo L, Wei R, Lin Y, Kwok HF. Clinical and recent patents applications of PD-1/PD-L1 targeting immunotherapy in cancer treatment-current progress, strategy, and future perspective. *Front Immunol*. 2020;11:1508.
8. World Health Organization. Cancer. Cancer causes. http://gco.iarc.fr. Accessed October 13, 2022.
9. Huang H, Wu D, Miao H, et al. Accelerating the integration of China into the global development of innovative anticancer drugs. *Lancet Oncol*. 2022;23:e515-e520.
10. Wu D, Huang H, Zhang M, et al. The global landscape of neoadjuvant and adjuvant anti-PD-1/PD-L1 clinical trials. *J Hematol Oncol*. 2022;15:16.
11. Robine N, Varmus H. New York's Polyethnic-1000: a regional initiative to understand how diverse ancestries influence the risk, progression, and treatment of cancers. *Trends Cancer*. 2022;8:269-272.
12. Li G, Qin Y, Xie C, Wu YL, Chen X. Trends in oncology drug innovation in China. *Nat Rev Drug Discov*. 2021;20:15-16.
13. Keam SJ. Toripalimab: first global approval. *Drugs*. 2019;79:573-578.
14. Lu S, Wang J, Yu Y, et al. Tislelizumab plus chemotherapy as first-line treatment for locally advanced or metastatic nonsquamous NSCLC (RATIONALE 304): a randomized Phase 3 trial. *J Thorac Oncol*. 2021;16:1512-1522.
15. Ren S, Chen J, Xu X, et al. Camrelizumab plus carboplatin and paclitaxel as first-line treatment for advanced squamous NSCLC (CameL-Sq): a Phase 3 trial. *J Thorac Oncol*. 2022;17:544-557.
16. Zhou C, Chen G, Huang Y, et al. Camrelizumab plus carboplatin and pemetrexed versus chemotherapy alone in chemotherapy-naive patients with advanced non-squamous non-small-cell lung cancer (CameL): a randomised, open-label, multicentre, phase 3 trial. *Lancet Respir Med*. 2021;9:305-314.
17. Zhou C, Chen G, Huang Y, et al. Camrelizumab plus carboplatin and pemetrexed as first-line treatment for advanced nonsquamous NSCLC: extended follow-up of CameL Phase 3 trial. *J Thorac Oncol*. 2023;18:628-639.
18. Zhou C, Wu L, Fan Y, et al. Sintilimab plus platinum and gemcitabine as first-line treatment for advanced or metastatic squamous NSCLC: results from a randomized, double-blind, Phase 3 trial (ORIENT-12). *J Thorac Oncol*. 2021;16:1501-1511.
19. Yang Y, Wang Z, Fang J, et al. Efficacy and safety of sintilimab plus pemetrexed and platinum as first-line treatment for locally advanced or metastatic nonsquamous NSCLC: a randomized, double-blind, Phase 3 study (oncology pRogram by InnovENT anti-PD-1-11). *J Thorac Oncol*. 2020;15:1636-1646.
20. Zhou C, Cheng Y, Chen J, et al. 3MO First-line camrelizumab plus carboplatin and paclitaxel for advanced squamous non-small cell lung cancer: updated overall survival results from the phase III CameL-sq trial. *Ann Oncol*. 2022;33(suppl):28.
21. Zhou C, Wang Z, Sun Y, et al. Sugemalimab versus placebo, in combination with platinum-based chemotherapy, as first-line treatment of metastatic non-small-cell lung cancer (GEMSTONE-302): interim and final analyses of a double-blind, randomised, phase 3 clinical trial. *Lancet Oncol*. 2022;23:220-233.
22. Zhou C, Wang Z, Sun M, et al. Interim survival analysis of the randomized phase III GEMSTONE-302 trial: sugemalimab or placebo plus chemotherapy as first-line treatment for metastatic NSCLC [published correction appears in *Nat Cancer*. 2024;5:209]. *Nat Cancer*. 2023;4:860-871.
23. Wang J, Lu S, Yu X, et al. Tislelizumab plus chemotherapy vs chemotherapy alone as first-line treatment for advanced squamous non-small-cell lung cancer: a Phase 3 randomized clinical trial. *JAMA Oncol*. 2021;7:709-717.
24. Lu S, Wang J, Yu Y, et al. 138P Randomized phase III study of tislelizumab plus chemotherapy versus chemotherapy alone as first-line treatment for advanced non-squamous non-small cell lung cancer (nsq-NSCLC): RATIONALE-304 updated analysis. *Immuno-Oncol Technol*. 2022;16:100250.
25. Wang J, Lu S, Yu X, et al. 132P Randomized phase III study of tislelizumab plus chemotherapy versus chemotherapy alone as first-line treatment for advanced squamous non-small cell lung cancer (sq-NSCLC): RATIONALE-307 updated analysis. *Immuno-Oncol Technol*. 2022/12/01/ 2022;16:100244. https://doi.org/10.1016/j.iotech.2022.100244. Accessed 13 October 2023.
26. Wang Z, Wu L, Li B, et al. Toripalimab plus chemotherapy for patients with treatment-naive advanced non-small-cell lung cancer: a multicenter randomized Phase III trial (CHOICE-01). *J Clin Oncol*. 2023;41:651-663.
27. Jotte R, Cappuzzo F, Vynnychenko I, et al. Atezolizumab in combination with carboplatin and nab-paclitaxel in advanced squamous NSCLC (IMpower131): results from a randomized Phase III trial. *J Thorac Oncol*. 2020;15:1351-1360.
28. Nishio M, Saito H, Goto K, et al. IMpower132: atezolizumab plus platinum-based chemotherapy vs chemotherapy for advanced NSCLC in Japanese patients. *Cancer Sci*. 2021;112:1534-1544.
29. Lu S, Fang J, Wang Z, et al. Results from the IMpower132 China cohort: atezolizumab plus platinum-based chemotherapy in advanced non-small cell lung cancer. *Cancer Med*. 2023;12:2666-2676.
30. Horinouchi H, Nogami N, Saka H, et al. Pembrolizumab plus pemetrexed-platinum for metastatic nonsquamous non-small-cell lung cancer: KEYNOTE-189 Japan Study. *Cancer Sci*. 2021;112:3255-3265.
31. Cheng Y, Zhang L, Hu J, et al. Pembrolizumab plus chemotherapy for Chinese patients with metastatic squamous NSCLC in KEYNOTE-407. *JTO Clin Res Rep*. 2021;2:100225.
32. Johnson ML, Cho BC, Luft A, et al. Durvalumab with or without tremelimumab in combination with chemotherapy as first-line therapy for metastatic non-small-cell lung cancer: the Phase III POSEIDON study. *J Clin Oncol*. 2023;41:1213-1227.
33. Baxi S, Yang A, Gennarelli RL, et al. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. *BMJ*. 2018;360:k793.
34. Zhang L, Geng Z, Hao B, Tislelizumab, et al. A modified anti-tumor programmed death receptor 1 antibody. *Cancer Control*. 2022;29. https://doi.org/10.1177/10732748221111296.

35. Qiao L, Zhou Z, Zeng X, et al. Cost-effectiveness of domestic PD-1 inhibitor camrelizumab combined with chemotherapy in the first-line treatment of advanced nonsquamous non-small-cell lung cancer in China. *Front Pharmacol*. 2021;12:728440.
36. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med*. 2016;375:1823–1833.
37. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372:2018–2028.
38. Li G, Liu Y, Xie C, Zhou Q, Chen X. Characteristics of expedited programmes for cancer drug approval in China. *Nat Rev Drug Discov*. 2021;20:416.
39. Chang E, Gong Y, Vallejo JJ, et al. FDA analysis of outcomes in Asian patients (pts) with metastatic non-small cell lung cancer (mNSCLC) receiving immune checkpoint inhibitors (ICI). *J Clin Oncol*. 2019;37:e20690.
40. Peng L, Wu YL. Immunotherapy in the Asiatic population: any differences from Caucasian population? *J Thorac Dis*. 2018;10:S1482–S1493.
41. Peng L, Qin BD, Xiao K, et al. A meta-analysis comparing responses of Asian versus non-Asian cancer patients to PD-1 and PD-L1 inhibitor-based therapy. *Oncoimmunology*. 2020;9:1781333.
42. Qian J, Nie W, Lu J, et al. Racial differences in characteristics and prognoses between Asian and white patients with nonsmall cell lung cancer receiving atezolizumab: an ancillary analysis of the Poplar and OAK studies. *Int J Cancer*. 2020;146:3124–3133.
43. Li ZQ, Yan HC, Gu JJ, Yang YL, Zhang MK, Fang XJ. Comparative efficacy and safety of PD-1/PD-L1 Inhibitors versus platinum-based chemotherapy for the first-line treatment of advanced non-small cell lung cancer: a meta analysis of randomized controlled trials. *Pharmacol Res*. 2020;160:105194.
44. Zhao M, Shao T, Ren Y, Zhou C, Tang W. Identifying optimal PD-1/PD-L1 inhibitors in first-line treatment of patients with advanced squamous non-small cell lung cancer in China: updated systematic review and network meta-analysis. *Front Pharmacol*. 2022;13:910656.
45. Liu L, Bai H, Wang C, et al. Efficacy and safety of first-line immunotherapy combinations for advanced NSCLC: a systematic review and network meta-analysis. *J Thorac Oncol*. 2021;16:1099–1117.
46. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med*. 2019;381:2020–2031.
47. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378:2288–2301.
48. Dearden S, Stevens J, Wu YL, Blowers D. Mutation incidence and coincidence in non small-cell lung cancer: meta-analyses by ethnicity and histology (mutMap). *Ann Oncol*. 2013;24:2371–2376.
49. Mok T, Nakagawa K, Park K, et al. Nivolumab plus chemotherapy in epidermal growth factor receptor-mutated metastatic non-small-cell lung cancer after disease progression on epidermal growth factor receptor tyrosine kinase inhibitors: final results of CheckMate 722. *J Clin Oncol*. 2024;42:1252–1264.
50. Yang JC-H, Lee DH, Lee JS, et al. Pemetrexed and platinum with or without pembrolizumab for tyrosine kinase inhibitor (TKI)-resistant, EGFR-mutant, metastatic nonsquamous NSCLC: Phase 3 KEYNOTE-789 study. *J Clin Oncol*. 2023;41. https://doi.org/10.1200/JCO.2023.41.17_suppl.LBA9000.
51. Lu S, Wu L, Jian H, et al. Sintilimab plus bevacizumab biosimilar IBI305 and chemotherapy for patients with EGFR-mutated non-squamous non-small-cell lung cancer who progressed on EGFR tyrosine-kinase inhibitor therapy (ORIENT-31): first interim results from a randomised, double-blind, multicentre, phase 3 trial [published correction appears in *Lancet Oncol*. 2022;23:e404]. *Lancet Oncol*. 2022;23:1167–1179.
52. Hsu CY, Lin EP, Shyr Y. Development and evaluation of a method to correct misinterpretation of clinical trial results with long-term survival. *JAMA Oncol*. 2021;7:1041–1044.