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Use of Immunotherapy With Programmed Cell Death 1 vs Programmed Cell Death Ligand 1 Inhibitors in Patients With Cancer
A Systematic Review and Meta-analysis

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IMPORTANCE Immune checkpoint inhibitors of programmed cell death 1 (PD-1) and its ligand (PD-L1) have led to a paradigm shift in cancer treatment. Understanding the clinical efficacy and safety profile of these drugs is necessary for treatment strategy in clinical practice.

OBJECTIVE To assess the differences between anti–PD-1 and anti–PD-L1 regarding efficacy and safety shown in randomized clinical trials across various tumor types.

DATA SOURCES Systematic searches of PubMed, Cochrane CENTRAL, and Embase were conducted from January 1, 2000, to March 1, 2019. In addition, abstracts and presentations from all major conference proceedings were reviewed.

STUDY SELECTION All randomized clinical trials that compared anti–PD-1 and anti–PD-L1 with standard treatment in patients with cancer were selected as candidates. Retrospective studies, single-arm phase 1/2 studies, and trials comparing anti–PD-1 and anti–PD-L1 with other immunotherapies were excluded. Studies of anti–PD-1 and anti–PD-L1 therapy were screened and paired by the matching of clinical characteristics as mirror groups.

DATA EXTRACTION AND SYNTHESIS Three investigators independently extracted data from each study following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guideline. Trial names, first author, year of publication, study design, National Clinical Trial identifier number, blinding status, study phase, pathologic characteristics, number of patients, patients' age and sex distribution, Eastern Cooperative Oncology Group Performance Status, lines of treatment, study drugs, biomarker status, follow-up time, incidence of adverse events, and hazard ratios (HRs) with 95% CIs for overall survival and progression-free survival were extracted. A random-effects model was applied for data analysis.

MAIN OUTCOMES AND MEASURES Differences in OS between anti–PD-1 and anti–PD-L1 across different cancer types were assessed. An effect size was derived from each mirror group and then pooled across all groups using a random-effects model.

RESULTS Nineteen randomized clinical trials involving 11 379 patients were included in the meta-analysis. Overall, anti–PD-1 exhibited superior overall survival (HR, 0.75; 95% CI, 0.65-0.86; $P < .001$) and progression-free survival (HR, 0.73; 95% CI, 0.56-0.96; $P = .02$) compared with anti–PD-L1. No significant difference was observed in their safety profiles. Sensitivity analysis presented consistency in the overall estimates across these analyses. Consistent results were observed through frequentist and bayesian approaches with the same studies.

CONCLUSIONS AND RELEVANCE Comprehensive analysis suggests that anti–PD-1 exhibited favorable survival outcomes and a safety profile comparable to that of anti–PD-L1, which may provide a useful guide for clinicians.

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Supplemental content

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Immunotherapy is one of the most important breakthroughs in cancer treatment, especially immune checkpoint inhibitors targeting programmed cell death 1 (PD-1) and PD ligand 1 (PD-L1), which significantly prolonged overall survival (OS) and possessed superior safety profile in patients with cancer compared with standard therapies across a wide range of tumor types.[1,2] With the increasing studies in immunotherapy, differences between the clinical performance of anti-PD-1 and anti-PD-L1 started to be reported. For example, recent findings from the KEYNOTE-426 study demonstrated significant OS improvement with the combination of anti-PD-1 (pembrolizumab) plus axitinib vs sunitinib in previously untreated patients with advanced renal cell carcinoma (RCC)[3]; however, anti-PD-L1 (avelumab) plus axitinib failed to demonstrate OS superiority over sunitinib in the same settings.[4] In addition, anti-PD-1 (pembrolizumab) plus carboplatin and nab-paclitaxel has been approved by the US Food and Drug Administration for first-line treatment of metastatic, squamous non–small cell lung cancer (NSCLC) based on the positive results from KEYNOTE-407,[5] while anti-PD-L1 (atezolizumab) plus carboplatin and nab-paclitaxel failed to show an OS benefit compared with chemotherapy in squamous NSCLC in IMpower131.[6,7] Such disparities have attracted widespread attention by clinicians, and there is a need to better understand the similarities and differences between anti-PD-1 and anti-PD-L1 for the ultimate benefit of patients with cancer.

With the lack of head-to-head comparisons available, some systematic reviews and meta-analyses have been conducted regarding the clinical performance of different immune checkpoint inhibitors through indirect comparisons.[8-14] However, whether anti-PD-1 and anti-PD-L1 deliver different clinical outcomes remained controversial. One meta-analysis from the American Society of Clinical Oncology 2018 annual meeting suggested no significant differences regarding the efficacy and safety of anti-PD-1 vs anti-PD-L1 across different tumor types.[15] Similar results were reported in another study focusing on the second-line monotherapy with nivolumab, pembrolizumab, or atezolizumab in NSCLC.[11] However, other studies published in the same period suggested that anti-PD-1 exhibited superior efficacy compared with anti-PD-L1 either as monotherapy in patients with metastatic and previously treated NSCLC[13] or in combination with chemotherapy as the first-line treatment of advanced squamous NSCLC.[14]

One main reason for the discrepancies from previous studies may be the insufficient comparability of the included studies and the lack of appropriate approach for indirect comparisons. As known, the validity of adjusted indirect comparisons depends on the internal validity and similarity of the trials involved.[16] Considering the variations and inconsistencies regarding study designs and patient characteristics across different trials, a risk of bias will be introduced if comparisons of anti-PD-1 vs anti-PD-L1 were conducted between the pooled results from all related studies on each side, leaving the important issue of systematic bias or confounding unaddressed.

In this study, we aimed to assess the differences between anti-PD-1 and anti-PD-L1 in a systematic review and meta-analysis through adjusted indirect comparisons based on a well-designed mirror principle to minimize the potential bias. In brief, studies of anti-PD-1 and anti-PD-L1 were screened and paired with mirrored trial characteristics, including tumor types, treatment lines, intervention regimens, control groups, and biomarker status, into individual mirror groups for further comparisons.

Key Points

Question Do anti–programmed cell death 1 and anti–programmed cell death ligand 1 deliver different clinical outcomes?

Findings In this systematic review and meta-analysis of 19 randomized clinical trials involving 11 379 patients, anti–programmed cell death 1 appears to exhibit significantly greater overall survival compared with anti–programmed cell death ligand 1 with a comparable safety profile in patients with solid tumors.

Meaning Anti–programmed cell death 1 appears to exhibit favorable survival outcomes and a comparable safety profile with anti–programmed cell death ligand 1 in cancer therapy, which may provide valuable insight for future treatment strategy.

Methods

Search Strategy and Selection Criteria

We searched PubMed, Cochrane CENTRAL, and Embase from January 1, 2000, to March 1, 2019, for randomized clinical trials of immune checkpoint inhibitors (anti-PD-1, anti-PD-L1) that compared anti-PD-1 and anti-PD-L1 with standard treatment in solid tumors. We also reviewed abstracts and presentations from all major conference proceedings, including the American Society of Clinical Oncology and the European Society for Medical Oncology, until March 1, 2019. Key words for the literature search included *randomized*, *PD-1*, *PD-L1*, *nivolumab*, *pembrolizumab*, *atezolizumab*, *durvalumab*, *cemiplimab-rwlc*, *avelumab*, and *programmed death receptor 1* (eTable 1 in the Supplement).

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline and the PRISMA extension statement. A prospective protocol was created in advance and uploaded to the PROSPERO online platform.

All randomized clinical trials that had compared the efficacy of anti-PD-1 or anti-PD-L1 as monotherapy or in combination with standard treatment in patients with solid tumors were selected. We excluded retrospective studies, single-arm phase 1 or 2 clinical studies, and randomized trials that compared anti-PD-1 and anti-PD-L1 treatment with other immunotherapies. When duplicate publications for the same study were identified, we included only the most recent and complete reports or the ones supporting the approval by the US Food and Drug Administration.

Eligible studies with either anti-PD-1 or anti-PD-L1 were selected and paired based on comparable characteristics and used as one mirror group. More specifically, the mirrored studies referred to the paired trials with anti-PD-1 and anti-

PD-L1 with accurate matching of clinical designs and patient characteristics, including pathologic types, treatment lines, intervention types (immune checkpoint inhibitor monotherapy or combination therapy), design of control groups (standard therapies), and biomarker status (PD-L1 expression level) (**Figure 1**). Only successful paired clinical studies were included for further analysis. Owing to the lack of standard therapy for third-line or later treatment in gastric or gastroesophageal junction cancer (GC), the ATTRACTION-2[17] with anti-PD-1 vs placebo and JAVELIN Gastric 300[18] trials with anti-PD-L1 vs physician's choice of chemotherapy or best supportive care were also eligible for this study. Two of us (L.C. and X.Z.) independently searched and reviewed the results to determine whether the trials met the inclusion criteria.

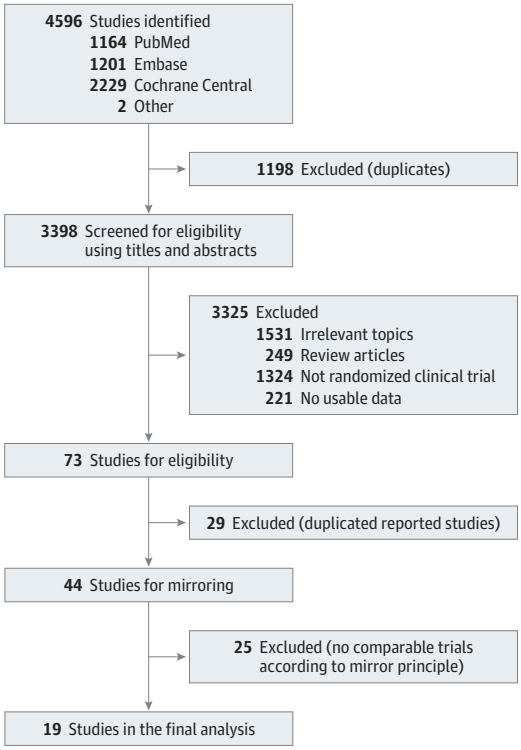
The primary outcome was the difference in efficacy between anti-PD-1 and anti-PD-L1, measured in terms of the OS difference. The secondary outcome was the differences in progression-free survival (PFS) and adverse events (AEs). For each study, 3 of us (J.D., L.C., and Z.W.) independently extracted data from the studies. The study name, first author, year of publication, study design, National Clinical Trials identification number, blinding status, study phase, pathologic characteristics, number of patients, patients' age and sex distribution, Eastern Cooperative Oncology Group performance status, lines of treatment, study drugs, follow-up time, biomarker status, incidence of AEs, and hazard ratios (HRs) with 95% CIs for OS and PFS were extracted.

The methodologic quality for each study was evaluated using the tool recommended by the Cochrane Collaboration handbook[19] based on the original study or its update and the supplementary materials. The adequacy of the following aspects was assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each aspect was evaluated, with an assessment index associated with the risk of bias classified as low, high, or unknown. All disagreements in study selection, data extraction, and quality assessment were resolved by discussion to achieve consensus among all investigators.

Statistical Analysis

Hazard ratio was used as the effect size for OS or PFS, and risk ratio (RR) was used as the effect size of AEs. Hazard ratios or RRs were pooled using the inverse variance method.[19,20] Effects from the interventions with 2 different doses in KEYNOTE-010 were combined with Review Manager, version 5.3 (RevMan; Cochrane Collaboration) according to the Cochrane Collaboration handbook recommendation to form a single effect.[19] Frequentist and bayesian approaches are well-known and commonly used in indirect comparisons. A frequentist *P* value is an expectation of a long-run frequency, whereas a bayesian posterior is an expression of a degree of belief. Previous methodologic studies have demonstrated that results derived from these 2 approaches usually agree with each other and rarely differ in the direction or treatment rankings.[19,21] In our study, to avoid the potential discrepancies from the statistical models, we applied both frequentist and bayesian approaches in the indirect comparisons.

Figure 1. Study Selection

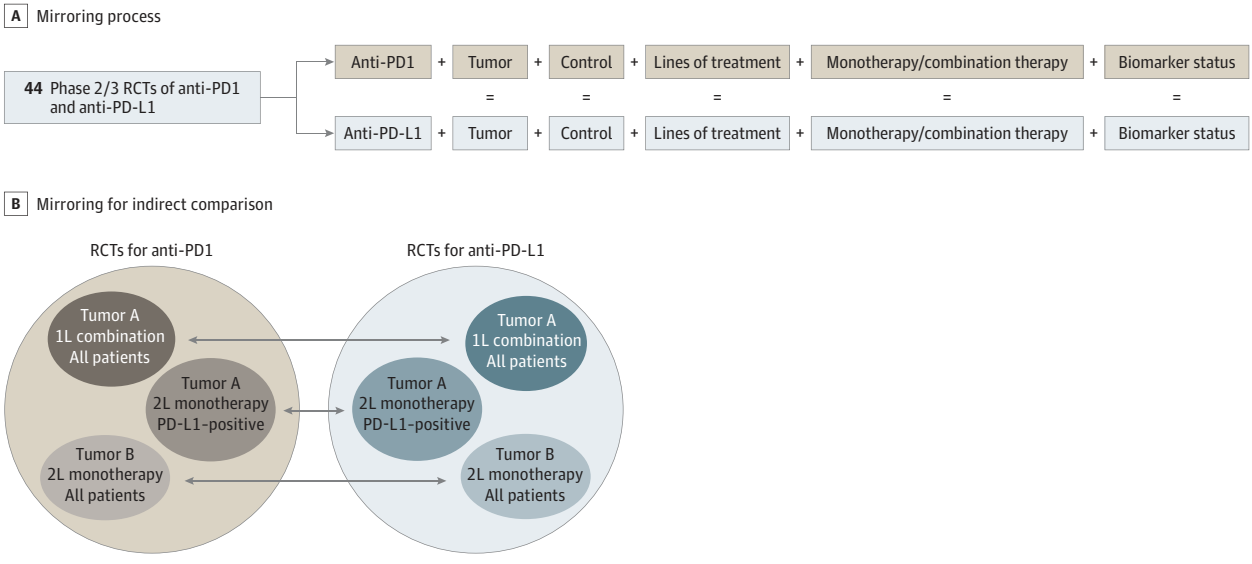


Studies selected based on the mirror principle.

As the main results, indirect comparison of immune checkpoint inhibitors was carried out with a frequentist approach using the R package netmeta, version 1.0-1 (R Foundation for Statistical Computing), for each mirror group based on the generic inverse variance method using a random-effects model.[22,23] When multiple studies were present for one intervention within the group, effect sizes of these studies were first combined through the same approach. The effect sizes derived from each group were then pooled across different mirror groups using Review Manager with a random-effects model.[24] During this step, a fixed-effects model was applied as a sensitivity test. Statistical heterogeneity was evaluated using the *Q* test and inconsistency index (I^2). To assess the stability of results, preplanned subgroup analyses, by tumor types or intervention types, and sensitivity analyses, by exclusion of each type of tumor, were performed for OS and PFS outcomes. All reported *P* values are 2-sided, with findings at $P < .05$ considered significant. Both types of effect sizes are reported with 95% CIs.

In addition, the consistency of OS and PFS outcomes was assessed with a bayesian framework approach with the same trials screened using the mirror principle. Hazard ratios and 95% credible intervals (CrIs) were computed with a hierarchical model by Markov chain Monte Carlo (MCMC) methods with JAGS software, version 4.3.0, and R, version 3.5.3 package gemtc, version 0.8-2, for each mirror group.[21,25,26] The effect

Figure 2. Illustration of Selection Based on the Mirror Principle



Illustrations of study mirroring (A) and mirroring for indirect comparison (B). 1L indicates first-line treatment; 2L, second-line treatment; PD-1, programmed cell death 1; PD-L1, PD-ligand 1; and RCTs, randomized clinical trials.

sizes were then pooled through the same approach. The deviance information criterion was used to choose the effects model, and the model with the lowest deviance information criterion was considered to provide the best data fit.[21,27]

The Begg and Egger tests were used to assess publication bias.[28,29] A *P* value <.10 indicates significant asymmetry and publication bias. A meta-regression analysis was applied following the instruction in the Cochrane Collaboration handbook (Stata, version 15; StataCorp) to examine the heterogeneity between studies and the influence of potential confounders on effect sizes.

Results

Systematic Review and Characteristics

A total of 4596 publications were retrieved through the initial literature search, and 3398 studies remained after duplications were excluded. With title and abstract review, 3325 publications were excluded because the topics were irrelevant, the articles were reviews, the studies were nonrandomized controlled trials, or no usable data were reported. Seventy-three potentially relevant articles were identified for detailed review. After a full-text review, 29 duplicate studies were removed, and 25 of 44 studies were excluded owing to a lack of comparability based on the mirror principle. Following this process, 19 randomized clinical trials[3-5,7,17,18,30-42] involving 11 379 patients were identified as eligible to be included in the meta-analysis (Figure 1). These studies were divided into 7 mirror groups with matched tumor types, treatment lines, biomarker status, and intervention types for adjusted indirect comparison. Illustration of the mirror principle is shown in **Figure 2**.

The selected studies covered 10 trials with anti-PD-1 (including 3 with nivolumab and 3 with pembrolizumab in monotherapy settings, and 4 with pembrolizumab in combination with standard therapy) and 9 trials with anti-PD-L1 (including 2 with avelumab and 3 with atezolizumab in monotherapy settings, and 1 with avelumab and 3 with atezolizumab in combination with standard therapy) compared with control groups receiving standard therapies. Thirteen trials were done in patients with NSCLC, 2 trials in patients with GC, 2 trials in patients with urothelial cancer (UC), and 2 trials in patients with RCC (**Figure 3**; eTable 2 in the Supplement). All included trials were well-designed with well-defined main outcomes. Data from 3 trials (IMpower130,[39] IMpower131,[6,7] and IMpower132[40]) were retrieved from conference presentations. The assessment of risk of bias of each included study is provided in eTable 3 in the Supplement. The Begg test and Egger test were carried out for the evaluation of publication bias,[28,29] and *P* values of .58 and .48 were obtained, respectively, indicating that no bias exists for the selected studies (eFigure 1 in the Supplement).

A similarity of clinical characteristics was observed between the anti-PD-1 and anti-PD-L1 trials within each mirror group (eTable 2 in the Supplement), which supported the possible comparability of the trials involved with a minimal risk of bias and apparent transitivity of effect size across different groups, further supporting the validity of adjusted indirect comparisons.[16,43]

OS Comparison: Frequentist Approach

The primary outcome of the analysis was the difference in OS between studies with anti-PD-1 and anti-PD-L1. The pooled results across all mirror groups suggested that, overall, patients obtained greater OS benefit from treatments containing anti-

Figure 3. Trial Characteristics and Mirror Design

Intervention	Control: Standard Therapy	Tumor Type	Lines of Treatment	PD-L1 Status	Clinical Trial	HR for OS	Pooled Indirect HR
Mirror 1							
Anti-PD1							
Nivolumab	Docetaxel	NSCLC	2	Nonselective	CheckMate 017[30], CheckMate 057[31], CheckMate 078[42]	PD-1 1	-1
Anti-PD-L1							
Atezolizumab	Docetaxel	NSCLC	2	Nonselective	POPLAR[38], OAK[37]	PD-L1 1	
Mirror 2							
Anti-PD1							
Pembrolizumab	Docetaxel	NSCLC	2	≥1%	KEYNOTE-010[33]	PD-1 2	-2
Anti-PD-L1							
Avelumab	Docetaxel	NSCLC	2	≥1%	JAVELIN Lung 200[41]	PD-L1 2	
Mirror 3							
Anti-PD1							
Nivolumab	Placebo	GC	3	Nonselective	ATTRACTION-2[17]	PD-1 3	-3
Anti-PD-L1							
Avelumab	Paclitaxel, irinotecan, or BSC	GC	3	Nonselective	JAVELIN Gastric 300[18]	PD-L1 3	
Mirror 4							
Anti-PD1							
Pembrolizumab	Vinflunine, paclitaxel, or docetaxel	UC	≤3	Nonselective	KEYNOTE-045[35]	PD-1 4	-4
Anti-PD-L1							
Atezolizumab	Vinflunine, paclitaxel, or docetaxel	UC	≤3	Nonselective	IMvigor211[32]	PD-L1 4	
Mirror 5							
Anti-PD1 combination							
Pembrolizumab + pemetrexed-carboplatin	Pemetrexed-carboplatin	Nonsquamous NSCLC	1	Nonselective	KEYNOTE-021[34], KEYNOTE-189[36]	PD-1 5	-5
Anti-PD-L1 combination							
Atezolizumab + (pemetrexed + cisplatin/carboplatin)/carboplatin + nab-paclitaxel	(Pemetrexed + cisplatin/carboplatin)/carboplatin + nab-paclitaxel	Nonsquamous NSCLC	1	Nonselective	IMpower130[39], Impower132[40]	PD-L1 5	
Mirror 6							
Anti-PD1 combination							
Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel	Carboplatin + paclitaxel/nab-paclitaxel	Squamous NSCLC	1	Nonselective	KEYNOTE-407[5]	PD-1 6	-6
Anti-PD-L1 combination							
Atezolizumab + carboplatin + nab-paclitaxel	Carboplatin + nab-paclitaxel	Squamous NSCLC	1	Nonselective	IMpower131[6,7]	PD-L1 6	
Mirror 7							
Anti-PD1 combination							
Pembrolizumab + axitinib	Sunitinib	RCC	1	Nonselective	KEYNOTE-426[3]	PD-1 7	-7
Anti-PD-L1 combination							
Avelumab + axitinib	Sunitinib	RCC	1	Nonselective	JAVELIN Renal 101[4]	PD-L1 7	

BSC indicates best supportive care; GC, gastric or gastroesophageal junction cancer; HR, hazard ratio; NSCLC, non–small cell lung cancer; PD-1, programmed cell death 1; PD-L1, PD-ligand 1; RCC, renal cell carcinoma; and UC, urothelial carcinoma.

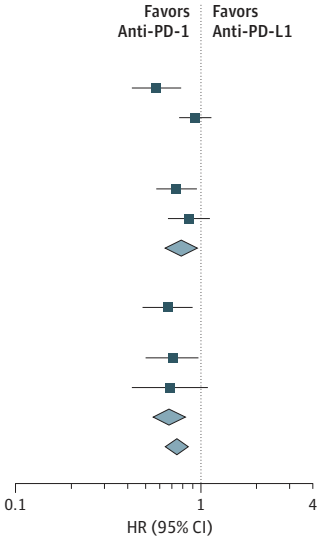
PD-1 compared with anti–PD-L1 with either a random-effects model (HR, 0.75; 95% CI, 0.65-0.86; $P < .001$) (**Figure 4**A) for heterogeneity ($I^2 = 37\%$; $P = .15$) or a fixed-effects model (HR, 0.77; 95% CI, 0.69-0.85; $P < .001$) (eFigure 2 in the Supplement).

Preplanned subgroup analysis was performed to examine the potential source of heterogeneities. When stratified by intervention types, anti–PD-1 appeared to show better OS than anti–PD-L1 as monotherapy (HR, 0.78; 95% CI, 0.63-0.95; $P = .01$) and combination therapy (HR, 0.68; 95% CI, 0.55-0.83; $P < .001$) (Figure 4A). Interstudy heterogeneity was observed among studies with immune checkpoint inhibitors as monotherapy ($I^2 = 61\%$; $P = .05$), but not as combination therapy ($I^2 = 0\%$; $P = .97$). For tumor types, the OS values were significantly prolonged for patients treated with anti–PD-1 compared with anti–PD-L1 with a random-effects model in NSCLC (HR, 0.77; 95% CI, 0.65-0.92; $P < .001$; for heterogeneity, $I^2 = 38\%$; $P = .18$) and GC (HR, 0.57; 95% CI, 0.42-0.78; $P < .001$), but not in UC (HR, 0.86; 95% CI, 0.66-1.12; $P = .26$) or RCC (HR, 0.68; 95% CI, 0.42-1.09; $P = .11$) (Figure 4B). Sen-

Figure 4. Overall Survival Outcomes in Patients Who Received Therapies Based on Anti–Programmed Cell Death 1 (PD-1) vs Anti–PD-Ligand 1 (PD-L1)

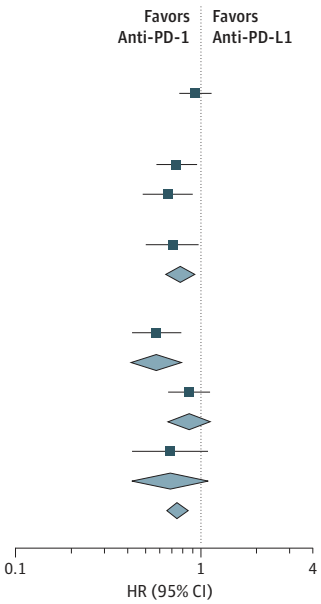
A Type of therapy

Tumor	Lines of Treatment	Studies of Anti-PD-1	Studies of Anti-PD-L1	Patients, No.	HR (95% CI)
Monotherapy					
Gastric carcinoma	≥3	ATTRACTION-2[17]	JAVELIN Gastric 300[18]	864	0.57 (0.42-0.78)
NSCLC	≥2	CheckMate 017[30], CheckMate 057[31], CheckMate 078[42]	POPLAR[38], OAK[37]	2495	0.93 (0.76-1.14)
NSCLC (PD-positive)	≥2	KEYNOTE-010[33]	JAVELIN Lung 200[41]	1562	0.73 (0.57-0.95)
Urothelial carcinoma	≥3	KEYNOTE-045[35]	IMvigor211[32]	1473	0.86 (0.66-1.12)
Pooled HR (subgroup)					0.78 (0.63-0.95)
Combination therapy					
Nonsquamous NSCLC	1	KEYNOTE-021[34], KEYNOTE-189[36]	IMpower130[39], Impower132[40]	1996	0.66 (0.48-0.90)
Squamous NSCLC	1	KEYNOTE-407[5]	IMpower131[6,7]	1242	0.70 (0.50-0.97)
Renal cell carcinoma	1	KEYNOTE-426[3]	JAVELIN Renal 101[4]	1747	0.68 (0.42-1.09)
Pooled HR (subgroup)					0.68 (0.55-0.83)
Pooled HR					0.75 (0.65-0.86)



B Type of tumor

Tumor	Lines of Treatment	Studies of Anti-PD-1	Studies of Anti-PD-L1	Patients, No.	HR (95% CI)
NSCLC					
NSCLC	≥2	CheckMate 017[30], CheckMate 057[31], CheckMate 078[42]	POPLAR[38], OAK[37]	7295	0.93 (0.76-1.14)
NSCLC (PD-positive)	≥2	KEYNOTE-010[33]	JAVELIN Lung 200[41]		0.73 (0.57-0.95)
Nonsquamous NSCLC	1	KEYNOTE-021[34], KEYNOTE-189[36]	IMpower130[39], Impower132[40]		0.66 (0.48-0.90)
Squamous NSCLC	1	KEYNOTE-407[5]	IMpower131[6,7]		0.70 (0.50-0.97)
Pooled HR (subgroup)					0.77 (0.65-0.92)
Carcinoma					
Gastric	≥3	ATTRACTION-2[17]	JAVELIN Gastric 300[18]	864	0.57 (0.42-0.78)
Pooled HR (subgroup)					0.57 (0.42-0.78)
Urothelial	≥3	KEYNOTE-045[35]	IMvigor211[32]	1473	0.86 (0.66-1.12)
Pooled HR (subgroup)					0.86 (0.66-1.12)
Renal cell	1	KEYNOTE-426[3]	JAVELIN Renal 101[4]	1747	0.68 (0.42-1.09)
Pooled HR (subgroup)					0.68 (0.42-1.09)
Pooled HR					0.75 (0.65-0.86)



A, Survival outcomes by type of therapy. Squares represent adjusted indirect effect size (hazard ratio [HR]). Horizontal lines indicate 95% CIs. Diamonds indicate the meta-analytic pooled HRs, calculated separately by monotherapy and combination therapy subgroups, and the overall pooled HRs (95% CIs) in patients with cancer. B, Survival outcomes by tumor type. Squares represent subgroup-specific pooled HRs. Horizontal lines indicate 95% CIs. Diamonds indicate the meta-analytic pooled HRs, calculated separately by tumor types, and the overall pooled HRs (95% CIs) in patients with cancer. NSCLC indicates non-small cell lung cancer.

sitivity analysis with a fixed-effects model in NSCLC noted consistently favorable outcome in OS for anti-PD-1 vs anti-PD-L1 (HR, 0.79; 95% CI, 0.69-0.90; $P < .001$) (eFigure 3 in the Supplement). Data were available from only 2 studies for comparison of GC, UC, or RCC, providing insufficient power to draw reliable conclusions within these tumor types.

To assess the stability of our results, another sensitivity analysis was conducted by repeating the analyses and omitting 1 tumor type each time. The overall estimates remained consistent across these analyses (eTable 4 in the Supplement). In addition, meta-regression analysis revealed no significant effect of PS or age on OS effect sizes (eTable 5 in the Supplement).

PFS Comparison: Frequentist Approach

Analyses of PFS between anti-PD-1 and anti-PD-L1 were conducted using the frequentist approach. Six groups of indirect comparison covering 17 studies with available PFS data were

included in the analysis. Consistent with the results for OS, patients receiving anti-PD-1 appeared to exhibit better PFS than those receiving anti-PD-L1 (HR, 0.73; 95% CI, 0.56-0.96; $P = .02$) (eFigure 4 in the Supplement). For subgroup analysis, anti-PD-1 seemed to lead to borderline significantly superior PFS than anti-PD-L1 as monotherapy (HR, 0.62; 95% CI, 0.37-1.05; $P = .08$) and significant superior PFS as combination therapy (HR 0.86; 95% CI, 0.74-0.99; $P = .04$) (eFigure 4 in the Supplement). Substantial heterogeneity was observed for overall PFS ($I^2 = 83\%$; $P < .001$) and in studies with immune checkpoint inhibitors as monotherapy ($I^2 = 91\%$; $P < .001$), but not in studies with immune checkpoint inhibitors as combination therapy ($I^2 = 0\%$; $P = .37$). Results of sensitivity analysis repeated with 1 tumor type omitted at each evaluation are shown in eTable 6 in the Supplement.

Indirect Comparisons of OS and PFS With the Bayesian Approach

Consistent results were observed when the bayesian framework was used with the model fit assessed with deviance information criterion scores (eTable 7 and eTable 8 in the Supplement). The data suggested that anti-PD-1 exhibited significant or borderline significant OS and PFS superiority compared with anti-PD-L1 across different tumor types in either overall population (OS: HR, 0.79; 95% CrI, 0.71-0.88; PFS: HR, 0.80; 95% CrI, 0.69-0.93), as monotherapy (OS: HR, 0.85; 95% CrI, 0.74-0.97; PFS: HR, 0.77; 95% CrI, 0.58-1.02), or combined with standard treatment (OS: HR, 0.67; 95% CrI, 0.55-0.82; PFS: HR, 0.82; 95% CrI, 0.69-0.97) (eFigure 5 and eFigure 6 in the Supplement). Sensitivity analyses by omitting 1 tumor type each time are reported in eTable 9 and eTable 10 in the Supplement.

Safety Analysis

The overall safety profiles of anti-PD-1 and anti-PD-L1 were comparable for both any AE (grades 3-5: RR, 1.04; 95% CI, 0.78-1.39; $P = .78$) and immune-related AEs (grades 3-5: RR, 0.88; 95% CI, 0.46-1.68; $P = .69$) (**Table**). The risk of AEs leading to death or discontinuation was also comparable between anti-PD-1 and anti-PD-L1 (any AE leading to death: RR, 1.01; 95% CI, 0.53-1.93; $P = .98$; any AE leading to discontinuation: RR, 1.20; 95% CI, 0.95-1.52; $P = .13$; immune-related AEs leading to death: RR, 1.38; 95% CI, 0.11-16.89; $P = .80$) (Table). Significant heterogeneity across the studies was observed in any AE of grades 3 to 5 ($I^2 = 90\%$; $P < .001$), but not in any AE leading to discontinuation ($I^2 = 0\%$; $P = .81$) or death ($I^2 = 0\%$; $P = .68$), or in any immune-related AE of grades 3 to 5 ($I^2 = 0\%$; $P = .80$) or leading to death ($I^2 = 0\%$, $P = .59$).

Discussion

To our knowledge, this is the first systematic review and meta-analysis that compared treatment outcomes and safety profiles between anti-PD-1 and anti-PD-L1 in patients with solid tumors. The results suggest that anti-PD-1 is associated with statistically significant improved survival outcomes and comparable AEs with anti-PD-L1.

As a strength of this work, data were obtained from 19 randomized clinical trials, which were selected based on the mirror principle to ensure the comparability of the included studies and avoid the risk of bias in this meta-analysis. One previous meta-analysis suggested that the treatment efficacy was similar between anti-PD-1 and anti-PD-L1 in patients with cancer.[44] However, the reliability of this study remains inconclusive owing to the lack of comparability of the included trials. For example, for UC, head and neck carcinoma, and melanoma, only trials with anti-PD-1 were included, which will lead to a great risk of bias in the comparison. The mirror principle used in our present study may provide a valuable tool for the indirect comparative analysis with a minimal risk of bias across multiple interventions.[16,43]

The magnitude of possible survival benefit of anti-PD-1 compared with anti-PD-L1 is clinically relevant, which may provide important clues for treatment selection for clinicians in clinical practice. Agents used in both UC and RCC showed better outcomes with anti-PD-1, even without reaching statistical significance owing to the insufficient statistical power, with only 1 mirror group available for each indication. The results were robust according to the subsequent analysis, suggesting that both frequentist and bayesian approaches supported the superior OS outcomes with anti-PD-1 compared with anti-PD-L1. Two previous, large phase 1 studies testing the Bristol-Myers Squibb PD-1 antibody and PD-L1 antibody have provided similar evidence, with a higher overall response rate for anti-PD-1 (20%-25%) than anti-PD-L1 (6%-17%) being observed in NSCLC, RCC, and melanoma.[45,46]

One reason for the possibly improved efficacy of anti-PD-1 compared with anti-PD-L1 is the inherent differences between anti-PD-1 and anti-PD-L1. PD-1 antibodies can bind to PD-1 and further block the binding of PD-1 to its ligands (PD-L1 and PD-L2) at the same time. However, although PD-L1 antibodies would also inhibit the binding of PD-1 to PD-L1, the interaction of PD-1 and PD-L2 remains intact, which may inhibit activation of T cells. Therefore, the tumor might escape antitumor immune response through the PD-1/PD-L2 axis when being treated with anti-PD-L1.[47] The PD-L2 expression status was also identified as a significant predictor of survival benefit to immune checkpoint inhibitor treatment independent of PD-L1 expression status.[48,49] It was reported that patients with NSCLC and GC demonstrated moderate to high PD-L2 expression,[48] supporting our observation of the superior clinical efficacy of anti-PD-1 compared with anti-PD-L1 in NSCLC and GC. Inhibition of PD-L1 also plays an important role in blocking the interaction between PD-L1 and CD80, which is a negative regulator of T-lymphocyte activation.[50] Such blockage would be achieved with an anti-PD-L1 antibody but not an anti-PD-1 antibody, which increases the complexity of their performance in cancer treatment.

The possible survival superiority seems even stronger when anti-PD-1 was used in combination with standard therapies, which lowered the risk of death by 32% compared with anti-PD-L1 plus standard therapies as evidenced in the results of NSCLC and RCC trials. Previous studies showed that chemotherapy may enhance the expression of PD-L1,[51,52] leading to the synergistic effect of immune checkpoint inhibitors with chemotherapy. As a result, T-cell activation might be inhibited

Table. Adjusted Risk Ratios Comparing Treatment-Related AEs in Patients Who Received Anti–PD- vs Anti–PD-L1–Based Therapies

Tumor	Lines of Treatment, No.	Studies		Any AEs				Immune-Related AEs		
				Grade		Outcome		Grade		Outcome
		With Anti–PD-1	With Anti–PD-L1	Any	3-5	Death	Discontinuation	Any	3-5	Death
Monotherapy										
Gastric carcinoma	≥3	ATTRACTION-2[17]	JAVELIN Gastric 300[18]	2.42 (1.74-3.38)	7.28 (3.09-17.11)	3.81 (0.09-155.32)	1.47 (0.32-6.71)	NA	NA	NA
NSCLC	≥2	CheckMate 017,[30] CheckMate 057,[31] CheckMate 078[42]	POPLAR,[38] OAK[37]	1.00 (0.91-1.09)	0.56 (0.42-0.74)	0.88 (0.06-12.62)	1.03 (0.62-1.71)	NA	NA	NA
NSCLC (PD-L1–positive)	≥2	KEYNOTE-010[33]	JAVELIN Lung 200[41]	1.08 (0.96-1.21)	2.05 (1.38-3.04)	2.00 (0.40-9.92)	0.92 (0.48-1.76)	NA	NA	NA
Urothelial carcinoma	≤3	KEYNOTE-045[35]	IMvigor211[32]	0.87 (0.77-0.98)	0.65 (0.45-0.96)	2.23 (0.36-13.73)	2.04 (0.90-4.62)	1.66 (0.95-2.88)	1.13 (0.32-4.02)	9.00 (0.09-906.39)
Pooled subgroup RR				1.15 (0.92-1.44)	1.42 (0.59-3.40)	1.92 (0.67-5.50)	1.15 (0.81-1.63)	1.66 (0.95-2.88)	1.13 (0.32-4.02)	9.00 (0.09-906.39)
Combination therapy										
Nonsquamous NSCLC	1	KEYNOTE-021,[34] KEYNOTE-189[36,a]	IMpower130,[39] IMpower132[40]	0.97 (0.93-1.01)	0.84 (0.71-0.98)	0.73 (0.26-2.04)	1.13 (0.69-1.86)	0.80 (0.48-1.31)	0.98 (0.32-2.95)	1.16 (0.02-75.55)
Squamous NSCLC	1	KEYNOTE-407[5,a]	IMpower131[6,7]	0.96 (0.91-1.01)	0.85 (0.73-0.99)	0.97 (0.19-4.83)	1.24 (0.67-2.28)	1.47 (0.91-2.39)	0.67 (0.24-1.90)	0.34 (0.00-23.69)
Renal cell carcinoma	1	KEYNOTE-426[3]	JAVELIN Renal 101[4]	1.00 (0.96-1.04)	1.06 (0.90-1.24)	0.19 (0.01-2.43)	1.42 (0.79-2.54)	NA	NA	NA
Pooled subgroup RR				0.98 (0.96-1.00)	0.91 (0.79-1.05)	0.68 (0.30-1.55)	1.24 (0.90-1.71)	1.09 (0.60-1.98)	0.80 (0.38-1.71)	0.63 (0.03-12.45)
Pooled results				1.01 (0.95-1.08)	1.04 (0.78-1.39)	1.01 (0.53-1.93)	1.20 (0.95-1.52)	1.24 (0.79-1.93)	0.88 (0.46-1.68)	1.38 (0.11-16.89)

Abbreviations: AEs, adverse events; NA, not available; NSCLC, non–small cell lung cancer; PD-1, programmed cell death 1; PD-L1, PD ligand 1; RR, risk ratio.

[a] Data provided were all-cause AEs, without attribution to any treatment.

by PD-L1 antibody overconsumption owing to extra PD-L1 expression, which needs to be explored in future studies.

Limitations

There are several limitations of this study. First, the clinical settings were not identical among all comparison groups. For instance, the proportion of patients with *EGFR* mutation and *ALK* rearrangement was higher in CheckMate 017[30] and CheckMate 057[31] than that in POPLAR[38] and OAK,[37] and NSCLC with such mutation was reported to be less sensitive to immune checkpoint inhibitors than wild-type NSCLCs.[53-55] Nevertheless, these patients accounted for only about 10% of the population in these studies; thus, the risk of such bias is limited. Second data from IMpower130 (mature data),[39] IMpower131 (second interim analysis),[6,7] and IMpower132 (interim analysis)[40] were available only from conference presentations. These data may be associated with limited peer review and immature data, which may lead to potential bias. However, considering that all of these studies were randomized clinical trials with a high level of evidence, their follow-up times were comparable with those of the other completed trials (eTable 2 in the Supplement), and the methodology and outcomes were reported in detail, we expect that these data will not differ much from the final analysis. The final results of IMpower130 were published[56] after the cutoff date of our data collection, and the results were identical to those retrieved from the conference presentations as used in this analysis. In addition, because all 3 of the IMpower studies were based on combination treatment with immune checkpoint inhibitors plus chemotherapy, the reliability of the results in the monotherapy subgroup will not be affected.

Conclusions

Our meta-analysis suggests that anti–PD-1 exhibited better survival outcomes than anti–PD-L1 in patients with solid tumors in either overall, monotherapy, or combination therapy settings, with comparable safety profiles. Owing to the lack of direct evidence from randomized clinical trials, adjusted indirect comparison was adopted in the present study as a surrogate. To minimize the potential risk of bias, a mirror principle was applied to ensure the internal similarity of the included studies. Future head-to-head studies are warranted for direct comparison across alternative interventions.

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