



Programmed Cell Death Protein-1 Inhibitors Versus Programmed Death-Ligand 1 Inhibitors in Addition to Chemotherapy for the First-Line Treatment of Advanced NSCLC: A Systematic Review and Meta-Analysis

Alessandro Di Federico, MD,^{a,b} Andrea De Giglio, MD,^{a,b,*} Claudia Parisi, MD,^{a,b} Francesco Gelsomino, MD,^{a,b} Luca Boni, MD,^c Andrea Ardizzoni, Prof^{a,b}

^aDepartment of Specialized, Experimental and Diagnostic Medicine, University of Bologna, Bologna, Italy

^bDivision of Medical Oncology, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Azienda Ospedaliero–Universitaria di Bologna, Bologna, Italy

^cEpidemiologia Clinica, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Ospedale Policlinico San Martino–IST Nord CBA, Genova, Italy

Received 11 March 2021; revised 1 July 2021; accepted 18 July 2021
Available online - 2 August 2021

ABSTRACT

Introduction: The addition of programmed cell death protein-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitors to first-line chemotherapy (CT) improved the outcomes of advanced NSCLC. Nonetheless, no direct comparison exists between these combination treatments.

Methods: We performed a meta-analysis of randomized clinical trials to evaluate and compare the efficacy and safety of PD-(L)1 inhibitors in combination with first-line CT for advanced NSCLC.

Results: A total of eight randomized clinical trials were included. The addition of a PD-(L)1 inhibitor to CT improved progression-free survival, overall survival, and objective response rate compared with CT alone. The risk of grade greater than or equal to 3 treatment-related adverse events was slightly higher with the addition of a PD-(L)1 inhibitor to CT as compared with CT alone. A subgroup analysis according to the targeted receptor (PD-1 versus PD-L1) revealed that the addition of a PD-1 inhibitor to CT led to better objective response rate ($p = 0.0001$), progression-free survival ($p = 0.006$), and overall survival ($p = 0.002$) compared with that of a PD-L1 inhibitor. The risk of grade greater than or equal to 3 treatment-related adverse events was significantly increased with the addition of a PD-L1 inhibitor to CT, but not with the addition of a PD-1 inhibitor. A direct comparison using the meta-regression analysis confirmed the statistical significance of all previous findings.

Conclusions: On the basis of this meta-analysis, the addition of a PD-1 inhibitor to first-line CT revealed statistically significant better outcomes and less additional toxicity

compared with that of a PD-L1 inhibitor, as compared with CT alone, in advanced NSCLC, regardless of PD-L1 status.

© 2021 The Authors. Published by Elsevier Inc. on behalf of the International Association for the Study of Lung Cancer. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords: Non-small cell lung cancer; PD-1; PD-L1; Immunotherapy; Chemotherapy; Meta-analysis

*Corresponding author.

Disclosure: Dr. Ardizzoni reports receiving grants and personal fees from Bristol-Myers Squibb, Merck Sharp & Dohme, Eli Lilly, Boehringer Ingelheim, and Pfizer; grants from Celgene; and grants and personal fees from Roche, outside of the submitted work. The remaining authors declare no conflict of interest.

Address for correspondence: Andrea De Giglio, MD, Department of Specialized, Experimental and Diagnostic Medicine, University of Bologna, Via Giuseppe Massarenti, 9, 40138 Bologna, Italy. E-mail: dr.degiglio@gmail.com

Cite this article as: Di Federico A, De Giglio A, Parisi C, et al. Programmed cell death protein-1 inhibitors versus programmed death-ligand 1 inhibitors in addition to chemotherapy for the first-line treatment of advanced NSCLC: a systematic review and meta-analysis. *JTO Clin Res Rep.* 2021;2:100214.

© 2021 The Authors. Published by Elsevier Inc. on behalf of the International Association for the Study of Lung Cancer. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

ISSN: 2666-3643

<https://doi.org/10.1016/j.jtocrr.2021.100214>

Introduction

Lung cancer represents the first cause of cancer-related death worldwide.¹ NSCLC accounts for at least 85% of histologic diagnosis and mainly occurs at an advanced stage, leading to poor 5-year survival expectancy.^{2,3} With the advent of immune checkpoint inhibitors (ICIs) targeting the programmed cell death protein-1 (PD-1)-programmed death-ligand 1 (PD-L1) axis, the outcomes of patients with nononcogene-addicted advanced NSCLC have drastically changed. Pembrolizumab demonstrated its superiority to standard platinum-based chemotherapy (CT) as upfront treatment for patients with NSCLC with PD-L1 expression greater than or equal to 50%.^{4,5} In addition, cohort G of the phase 1/2 KEYNOTE 021 study opened the way to the combination of pembrolizumab and carboplatin-pemetrexed regimen as first-line treatment for nonsquamous NSCLC, revealing the improvement of both objective response rate (ORR) and progression-free survival (PFS) regardless of PD-L1 expression.^{6,7} Thereafter, several phase 3 trials confirmed these results for both squamous and nonsquamous NSCLCs treated with CT plus a PD-1 inhibitor, also highlighting a revolutionary benefit in terms of overall survival (OS).^{8–12} Similarly, the addition of atezolizumab, a PD-L1 inhibitor, to CT with or without the antiangiogenic drug bevacizumab outperformed standard CT doublets for nonsquamous NSCLCs.^{13–16} Nevertheless, the absence of a head-to-head comparison between PD-(L)1 inhibitors as single-agent therapy and their combination with chemotherapeutic regimens, or between different ICI-CT combinations, does not allow evidence-based treatment decisions.¹⁷

Herein, we performed a meta-analysis to weigh the efficacy and safety of randomized clinical trials (RCTs) comparing standard platinum-based regimens in combination with an anti-PD-(L)1 inhibitor or placebo and to explore whether the combination of a PD-1 inhibitor to CT outperforms that of a PD-L1 inhibitor to CT.

Materials and Methods

Search Strategies

RCTs reporting OS, PFS, ORR, and safety data published before February 1, 2021, were searched through the online databases MEDLINE (PubMed), EMBASE, and Cochrane Database of Systematic Reviews and Central Register of Controlled Trials (Wiley). Keywords used for the research were the following: “immunotherapy”, “pembrolizumab”, “atezolizumab”, “sintilimab”, “durvalumab”, “avelumab”, “nivolumab”, “chemotherapy”, “platinum based”, “cisplatin”, “carboplatin”, “pemetrexed”, “paclitaxel”, “nab-paclitaxel”, “non-small cell lung cancer”, “NSCLC”, “first-line”, “upfront”, “untreated”,

“metastatic”, “stage IV”, and “advanced.” Inclusion criteria for study selection were as follows: (1) patients with previously untreated advanced NSCLC; (2) treatment with the combination of either a PD-1 or PD-L1 inhibitor and first-line CT-based treatment, with at least one control arm; and (3) availability of OS and PFS data regardless of PD-L1 expression. Exclusion criteria were as follows: (1) nonrandomized controlled trials; (2) absence of hazard ratio (HR) for efficacy outcomes (OS or PFS) independently from PD-L1 expression; and (3) evaluation of immunotherapy doublets (e.g., PD-1 or PD-L1 inhibitor plus anti-CTLA-4 agent).

Only articles published in peer-reviewed journals and written in the English language were considered. Data from additional resources, such as relevant abstract derived from proceedings of main international oncological meetings, were also included in the research. Studies were retrieved and reviewed by three different authors (A.D.F., A.D.G., and C.P.).

Records underwent a first screening for title and abstract. Relevant articles were subsequently screened for full text and analyzed to identify those meeting the inclusion criteria. The bibliography of each relevant article was finally searched.

The Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines were adopted to conduct this meta-analysis.

Risk of Bias

The risk of bias of the included studies was independently evaluated by three authors (A.D.F., A.D.G., and C.P.), using the tools of the Cochrane Collaboration for assessing risk of bias (selection, performance, detection, attrition, and reporting bias). The results of this meta-analysis were interpreted according to the risk of bias, and any disagreement was resolved by discussion to reach consensus. A summary of the risk of bias evaluation is reported in [Table 1](#). The presence of publication bias was evaluated through funnel plots ([Fig. 1A–D](#)).

Outcome Measures

Efficacy outcomes (OS and PFS, expressed as HR, and ORR, expressed as risk ratio [RR]) were extracted from the selected studies. OS was defined as the time from the date of treatment assignment to the date of death from any cause; PFS was defined as the time from treatment assignment to disease progression or death from any cause; ORR was defined as the proportion of patients who achieved a partial or complete response to therapy according to the Response Evaluation Criteria in Solid Tumors version 1.1. Grade greater than or equal to 3 treatment-related adverse events (TRAEs), classified according

Table 1. Summary of Authors' Judgment on the Risk of Bias for Each Selected Randomized Controlled Clinical Trial According to the Cochrane Collaboration for Assessing Risk of Bias

Category	KEYNOTE021	KEYNOTE189	KEYNOTE407	Impower130	Impower131	Impower132	Impower150	ORIENT-11
Random sequence generation	Low	Low	Low	Low	Low	Low	Low	Low
Allocation concealment	Low	Low	Low	Low	Low	Low	Low	Low
Selective reporting	Low	Low	Low	Low	Low	Low	Low	Low
Blinding participants and personnel	High	Low	Low	High	High	High	High	High
Blinding outcome assessment	Low	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Incomplete outcome data	Low	Low	Low	Low	Low	Low	Low	Low
Other	Unclear	Unclear	Short follow-up duration	Unclear	Unclear	Low	Low	Unclear

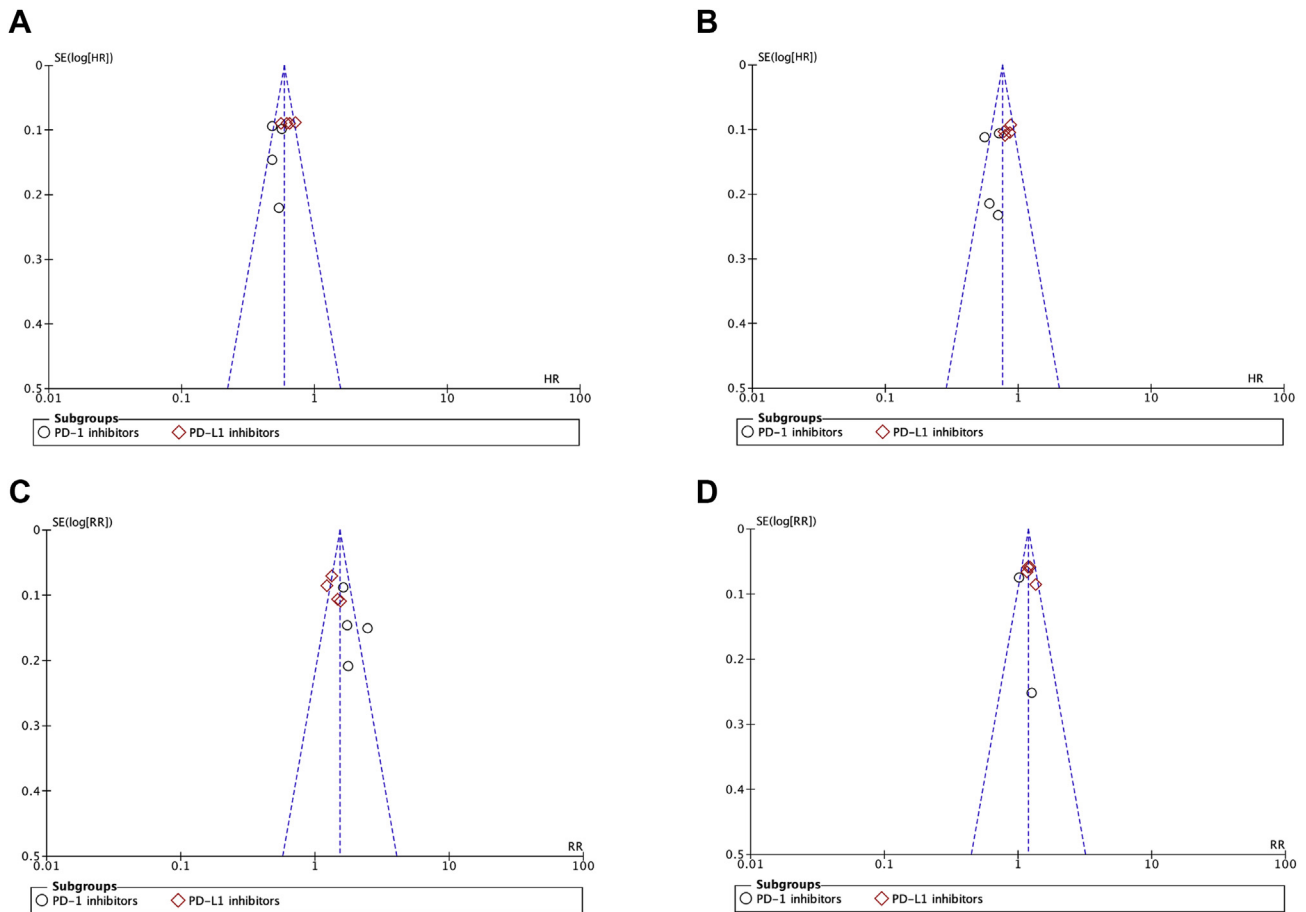


Figure 1. Funnel plots of (A) PFS, (B) OS, (C) ORR, and (D) grade greater than or equal to 3 TRAEs revealing basic symmetry, suggesting the absence of publication biases. ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RR, risk ratio; TRAEs, treatment-related adverse events.

to WHO or National Cancer Institute Common Toxicity Criteria, were also collected for the analysis, and their incidence was expressed as RR.

Data Extraction and Analysis

This meta-analysis was performed using a dedicated software (Review Manager Version 5.4; The Cochrane Collaboration). Summary measures were HR with 95% confidence interval (CI) for OS and PFS and RR with 95% CI for ORR and grade greater than or equal to 3 TRAEs. For the time-to-event variables, including OS and PFS, HRs with 95% CIs were evaluated for each study. The inverse variance technique was adopted for the meta-analysis of the HR. RRs with 95% CIs were calculated for each study for the analysis of ORR and grade greater than or equal to 3 TRAEs. The Mantel–Haenszel method was used to combine the RRs of the analyzed trials. Finally, a meta-regression analysis was used to directly compare PD-1 inhibitors and PD-L1 inhibitors in terms of OS (HR), PFS (HR), grade greater than or equal to 3 TRAEs (RR), and ORR (RR). The meta-regression analysis was performed using a dedicated software (Comprehensive Meta-Analysis Version 3; Biostat Inc.). Statistical heterogeneity between studies was evaluated using the chi-square test and the I^2 statistic. Considering the number of the included studies and their poor heterogeneity, the fixed-effect model was used for this meta-analysis. Nevertheless, all the analyses were repeated using the random-effect model to verify their consistency.

For KEYNOTE 021, KEYNOTE 189, and KEYNOTE 407, data from updated analyses were used for this meta-analysis.

Results

The initial database search yielded a total of 426 records eligible for inclusion (one identified through conference abstract research). On the basis of duplicate records and review of titles or abstracts, two articles were excluded, resulting in 424 potentially eligible studies. Through reviewing titles and abstracts of all articles, 402 articles were excluded in accordance with the exclusion criteria. Full texts of the 22 remaining articles were further reviewed in detail, and, finally, eight prospective RCTs (four RCTs testing atezolizumab plus CT versus CT alone, three RCTs testing pembrolizumab plus CT versus CT alone, and one RCT testing sintilimab plus CT versus CT alone), published from 2016 to 2021 and including a total of 4466 patients, matched the inclusion criteria and were selected for this meta-analysis. The included trials have almost superimposable inclusion and exclusion criteria. In particular, key eligibility criteria were the following: unresectable NSCLC; absence of previous treatment with CT or ICI; at least one measurable lesion per Response Evaluation

Criteria in Solid Tumors 1.1; baseline Eastern Cooperative Oncology Group performance status score of 0 or 1; absence of untreated or symptomatic brain metastasis; absence of active immunosuppressive treatment. Three trials testing the PD-L1 inhibitor atezolizumab allowed the inclusion of patients with sensitizing EGFR mutations or ALK rearrangements if they have had disease progression (during or after treatment) or intolerance to treatment with at least one tyrosine kinase inhibitor, although their presence represented an exclusion criterion for the other trials. The search process is summarized in the flow diagram of the Preferred Reporting Items for Systematic Review and Meta-Analyses (Fig. 2). A brief summary of the included studies is reported in Table 2.

Funnel plots of PFS, OS, ORR, and grade greater than or equal to 3 TRAEs revealed basic symmetry, suggesting no publication bias (Fig. 1).

In the safety analysis, only trials reporting TRAEs were included (six of eight). KEYNOTE 189 and ORIENT-11, owing to a different method of safety recording, were excluded (Table 2).

PD-(L)1 Inhibitor Plus CT Versus CT Alone

Both PD-1 and PD-L1 inhibitors were found to improve the outcomes of patients with advanced NSCLC compared with CT alone, regardless of PD-L1 expression. The addition of a PD-(L)1 inhibitor to CT improved both PFS (HR = 0.59, 95% CI: 0.55–0.63) (Fig. 3A) and OS (HR = 0.76, 95% CI: 0.70–0.82) (Fig. 3B). ORR was also improved by the combination of an ICI to CT as compared with CT alone (RR = 1.52, 95% CI: 1.41–1.63) (Fig. 3C). The risk of grade greater than or equal to 3 TRAEs was slightly higher with the addition of a PD-(L)1 inhibitor to CT (RR = 1.19, 95% CI: 1.12–1.26) (Fig. 3D) than with CT alone.

PD-1 Inhibitor Plus CT Versus PD-L1 Inhibitor Plus CT

A subgroup analysis was performed according to the targeted receptor (PD-1 versus PD-L1) to evaluate if the addition of a PD-1 inhibitor or a PD-L1 inhibitor to histology-driven CT could lead to different outcomes in terms of efficacy and safety. We observed that the addition of a PD-1 inhibitor to CT had a greater impact on PFS (HR = 0.52, 95% CI: 0.46–0.58) than that of a PD-L1 inhibitor (HR = 0.63, 95% CI: 0.58–0.69) (Fig. 3A) as compared with CT alone (p for subgroup differences = 0.006, I^2 = 86.6%). Similar results were observed in terms of OS ([HR for PD-1 inhibitors = 0.64, 95% CI: 0.56–0.73] versus [HR for PD-L1 inhibitors = 0.83, 95% CI: 0.75–0.92], p for subgroup differences = 0.002; I^2 = 89.1%) (Fig. 3B) and ORR ([RR for PD-1 inhibitors = 1.86, 95% CI: 1.63–2.11] versus [RR for PD-L1

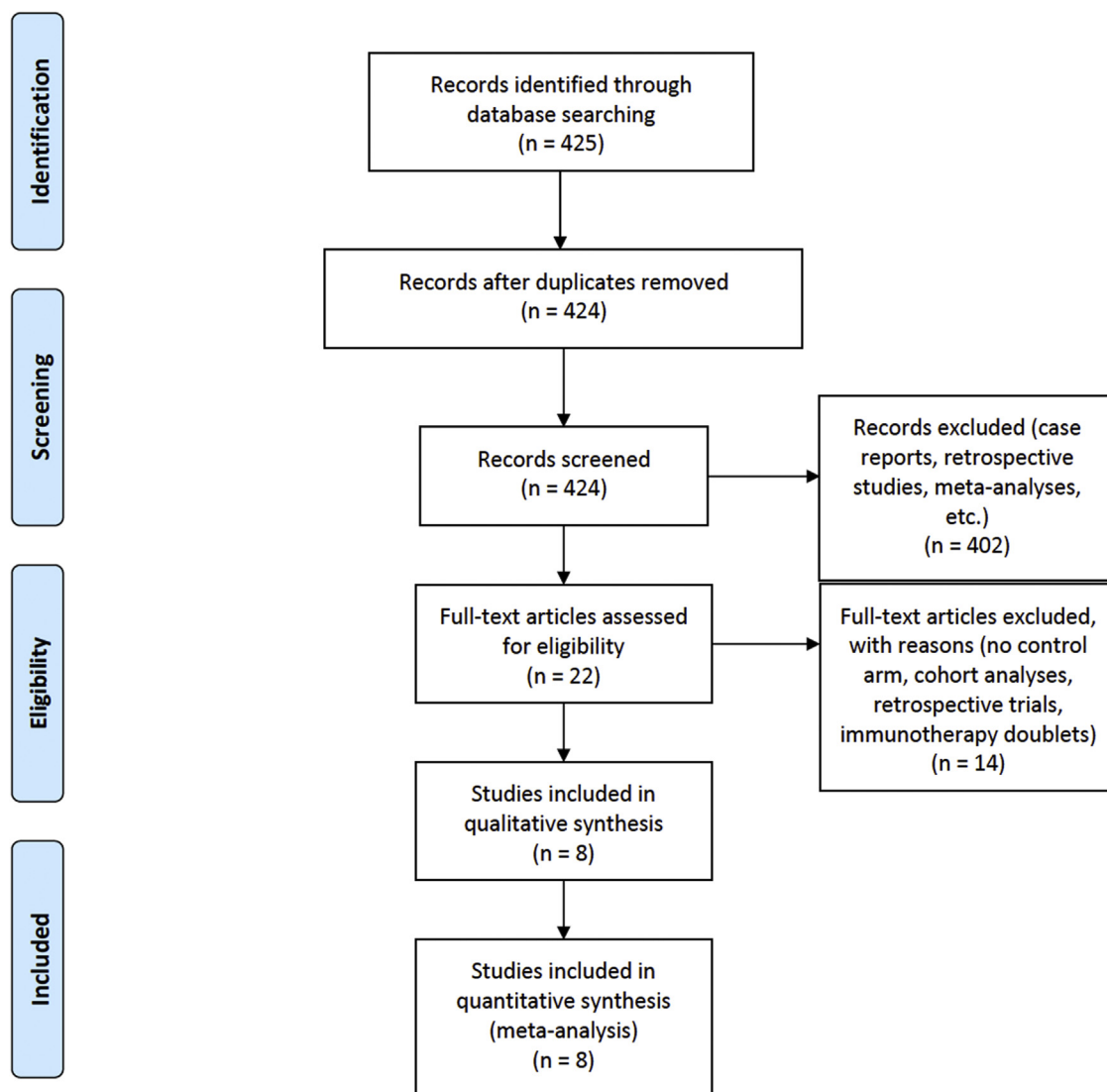


Figure 2. PRISMA study flow diagram. PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses.

inhibitors = 1.36, 95% CI: 1.25–1.48], p for subgroup differences = 0.001, $I^2 = 93.5\%$) (Fig. 3C). Moreover, the risk of grade greater than or equal to 3 TRAEs was significantly increased (p for subgroup differences = 0.04, $I^2 = 75.6\%$) with the addition of a PD-L1 inhibitor to CT (RR = 1.22, 95% CI: 1.15–1.30), but not with the addition of a PD-1 inhibitor to CT (RR = 1.04, 95% CI: 0.90–1.20) (Fig. 3D).

A direct comparison of the two types of inhibitors using a meta-regression analysis confirmed that the addition of a PD-1 inhibitor to CT, as compared with that of a PD-L1 inhibitor to CT, was associated with improved PFS (HR = 0.82, 95% CI: 0.71–0.95, $p = 0.007$), OS (0.77, 95% CI: 0.65–0.91, $p = 0.002$), and ORR (RR = 1.33, 95% CI: 1.08–1.56, $p = 0.0002$).

A further comparison in the subgroup of patients with PD-L1 greater than or equal to 50% in terms of PFS and OS was performed using a meta-regression analysis.

Trials excluded owing to lack of data for this population were KEYNOTE 021 in the PFS analysis and KEYNOTE 021, ORIENT-11, and IMpower150 in the OS analysis. No difference either in terms of PFS (HR = 0.79, 95% CI: 0.57–1.10, $p = 0.166$) or OS (HR = 1.04, 95% CI: 0.65–1.67; $p = 0.865$) was documented between the two groups.

Moreover, the addition of a PD-1 inhibitor to CT seemed to be associated with lower risk of grade greater than or equal to 3 TRAEs than that of a PD-L1 inhibitor (RR = 0.84, 95% CI: 0.73–0.98, $p = 0.027$).

Discussion

An increasing number of studies evaluated the addition of a PD-(L)1 inhibitor to CT as upfront treatment for noncogene-addicted advanced NSCLC. As, to date, pembrolizumab, atezolizumab, and sintilimab have all been found to improve clinical outcomes obtained with

Table 2. Main Characteristics of the Randomized Clinical Trials Selected for the Meta-Analysis

Trial	Phase	Histology	No. of Intervention/ Control	Arms of Treatment	Primary Outcome	TRAEs Reported
KEYNOTE 021 ^{6,7}	II	Nonsquamous	60/63	Pembrolizumab + carboplatin + pemetrexed vs. carboplatin + pemetrexed	ORR	Yes
KEYNOTE 189 ^{10,11}	III	Nonsquamous	410/206	Pembrolizumab + cisplatin or carboplatin + pemetrexed vs. cisplatin or carboplatin + pemetrexed	PFS, OS	No
KEYNOTE 407 ^{8,9}	III	Squamous	278/281	Pembrolizumab + carboplatin + nab-paclitaxel or paclitaxel vs. carboplatin + nab-paclitaxel or paclitaxel	PFS, OS	Yes
ORIENT-11 ¹²	III	Nonsquamous	266/131	Sintilimab + pemetrexed + cisplatin or carboplatin vs. pemetrexed + cisplatin or carboplatin	PFS, OS	No
IMpower130 ¹⁵	III	Nonsquamous	483/240	Atezolizumab + carboplatin + nab-paclitaxel vs. carboplatin + nab-paclitaxel	PFS, OS	Yes
IMpower131 ¹³	III	Squamous	343/340	Atezolizumab + carboplatin + nab-paclitaxel vs. carboplatin + nab-paclitaxel	PFS, OS	Yes
IMpower132 ¹⁶	III	Nonsquamous	292/286	Atezolizumab + cisplatin or carboplatin + pemetrexed vs. cisplatin or carboplatin + pemetrexed	PFS, OS	Yes
IMpower150 ¹⁴	III	Nonsquamous	400/400	Atezolizumab + bevacizumab + carboplatin + paclitaxel vs. bevacizumab + carboplatin + paclitaxel	PFS, OS	Yes

ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TRAE, treatment-related adverse event.

CT alone, we believed that a meta-analysis to explore if there were differences depending on the targeted receptor would have been worthwhile. On the basis of our study, the addition of an ICI, either PD-1 or PD-L1 inhibitor, to CT significantly improved the outcomes of patients with NSCLC and only modestly increased the risk of developing severe adverse events. Despite the superiority of the overall effect of the combination strategy over CT, it should be highlighted that two studies in the PD-L1 inhibitor plus CT group did not meet one of their coprimary end points. In fact, both IMpower131 and IMpower132, which tested histology-driven CT plus atezolizumab versus CT alone in squamous and nonsquamous NSCLCs, respectively, failed to reveal an OS benefit with the combination strategy, despite reaching a significant PFS improvement.^{13,16} Therefore, the results of these two trials are those

largely responsible for the poorer outcomes obtained by the PD-L1 inhibitor plus CT subgroup compared with PD-1 plus CT subgroup, at least in terms of OS. Nevertheless, definitive conclusions cannot be easily drawn. In fact, despite the difficulty in indirectly comparing different trials, it is worth of consideration that, excluding the only phase 2 trial,^{6,7} control arms of phase 3 studies testing the PD-L1 inhibitor atezolizumab had numerically better outcomes in terms of median OS than those testing PD-1 inhibitors.^{8-10,13-15} Conversely, ORR and median PFS of the control arms were numerically similar in the two groups. Moreover, the IMpower132 experimental regimen has a survival benefit in the Asian population of the study, leading to its approval in Japan.¹⁶

A recent cross-sectional meta-analysis conducted on 11,379 patients with cancer enrolled in 19 RCTs

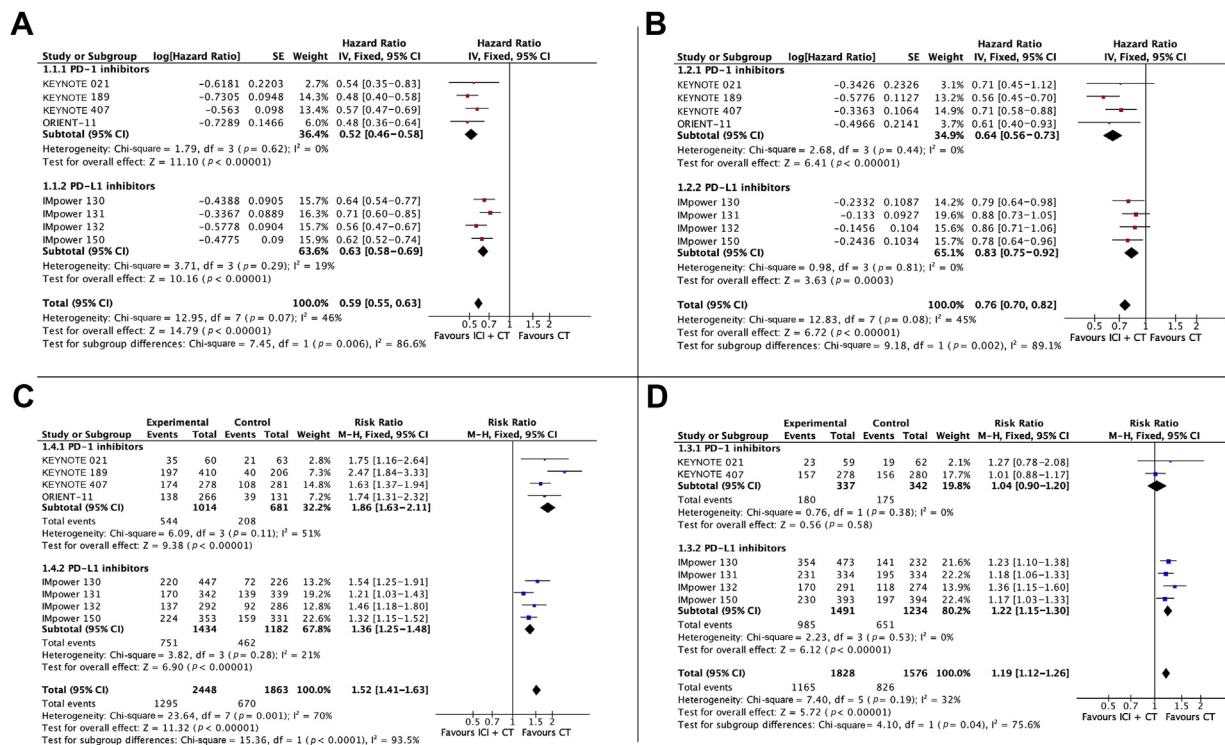


Figure 3. Hazard ratios of (A) PFS and (B) OS and (C) risk ratios of ORR and (D) grade greater than or equal to 3 TRAEs of the addition of a PD-(L)1 inhibitor to first-line chemotherapy-based treatment. The subgroup analysis revealed favorable survival, improved response rate, and less toxicity with the addition of a PD-1 inhibitor to CT as compared with the addition of a PD-L1 inhibitor to CT. CI, confidence interval; CT, chemotherapy; ICI, immune checkpoint inhibitor; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TRAE, treatment-related adverse event.

revealed favorable outcomes with PD-1 inhibitors compared with PD-L1 inhibitors in terms of both PFS (HR = 0.73, 95% CI: 0.56-0.96, $p = 0.02$) and OS (HR = 0.75, 95% CI: 0.65-0.86, $p < 0.001$), with no significant difference in their safety profile.¹⁸ In advanced NSCLC, a meta-analysis comparing PD-(L)1 inhibitors as monotherapy for previously treated patients revealed that PD-1 inhibitors were associated with a similar risk of any grade greater than or equal to 3 adverse events (except for the risk of pneumonitis, which was higher with PD-1 inhibitors) but better OS (HR = 0.67, 95% CI: 0.60-0.74) and PFS (HR = 0.81, 95% CI: 0.72-0.91) trends than PD-L1 inhibitors (HR for OS = 0.80, 95% CI: 0.71-0.90; HR for PFS = 1.02, 95% CI: 0.89-1.17).¹⁹ In agreement with preexistent data, our meta-analysis confirmed that both PD-1 and PD-L1 inhibitors improved the outcomes of patients with advanced NSCLC when added to first-line, histology driven, platinum-based CT.^{20,21} Nevertheless, the addition of a PD-1 inhibitor to CT seemed to be safer in terms of TRAEs of grade greater than or equal to 3 and to provide higher benefit in terms of PFS, OS, and ORR when compared with that of a PD-L1 inhibitor added to CT. We hypothesize three orders of reasons that could explain these findings, which are as follows: clinical, pharmacologic, and biological ones.

First, we analyzed and compared the characteristics of patients enrolled in studies evaluating the two ICIs. Inclusion and exclusion criteria of all studies were almost superimposable, and patients enrolled had similar baseline characteristics. Three of four trials testing the addition of a PD-1 inhibitor to CT (KEYNOTE 021, KEYNOTE 189, and ORIENT-11) and three of four trials testing atezolizumab (IMpower130, IMpower132, and IMpower150) enrolled patients with nonsquamous NSCLC, whereas the remaining two (KEYNOTE 407 and IMpower131) enrolled patients with squamous NSCLC.⁶⁻¹⁶ It is unlikely that the difference between the outcomes obtained by the addition of PD-1 or PD-L1 inhibitor could be attributed to dissimilar NSCLC histologies, as trials that tested each agent in both histologies (squamous and non-squamous) have been included in this meta-analysis. Moreover, the subgroups (PD-1 versus PD-L1) were balanced as they included the same number of trials per histology (Table 2). It is worth considering that of the two included trials conducted on squamous NSCLC,^{8,9,13} only the one testing the addition of a PD-1 inhibitor to CT (KEYNOTE 407) demonstrated a survival benefit over CT alone. Nevertheless, as previously mentioned, also one trial testing the combination of

the PD-L1 inhibitor atezolizumab plus CT versus CT alone in nonsquamous histology failed to reach a survival improvement (IMpower132), making difficult to attribute the better outcomes obtained by the anti-PD-1 subgroup to a poor performance of anti-PD-L1 in squamous histology. Moreover, atezolizumab recently was found to perform well as a single-agent therapy in either squamous or nonsquamous NSCLC with PD-L1 greater than or equal to 50%.²² The proportion of patients with PD-L1-positive NSCLC was slightly higher in studies testing PD-1 inhibitors ($\approx 63.5\%$) than in those testing PD-L1 inhibitors ($\approx 50\%$), but this little gap is unlikely to be responsible for statistically significant different outcomes. Consistently, the comparison performed in the subgroup of patients with PD-L1 greater than or equal to 50% revealed no PFS or OS differences. Differently from all the trials evaluating the addition of a PD-L1 inhibitor to CT, IMpower130, IMpower131, and IMpower150 trials also included a minority of patients with known EGFR gene mutation or ALK gene rearrangements, which are considered negative predictive factors of response to immunotherapy.²³ Nevertheless, interestingly, the subgroup analysis of patients with EGFR-mutated NSCLC enrolled in the IMpower150 trial reported improved outcomes with the combination treatment as compared with CT alone.²⁴

The different pharmacokinetic and pharmacodynamic profiles of these agents may provide an additional reason for the observed results. Pembrolizumab and sintilimab retain higher binding affinity for its ligand ($K_d = 0.029$ nM and 0.074 nM, respectively) than atezolizumab ($K_d = 1.75$ nM).^{25,26} Pembrolizumab and sintilimab are immunoglobulin G4, that represents the preferred class of immunoglobulin for immunotherapy. In fact, its low affinity for C1q and Fc receptors minimizes the risk to trigger host effector functions, such as activation of the complement system and antibody-dependent cytotoxicity.²⁷ Conversely, the immunoglobulin G1 class, such as that of atezolizumab, harbors a higher potential of antibody-dependent cytotoxicity activation; to reduce this risk, atezolizumab was engineered with a modification in the Fc domain.²⁸ Anyhow, the main diversity between these ICIs might stand in their different targeted receptors. In fact, although disrupting the interaction between PD-1 and its primary ligand, PD-L1, the inhibition of these targets prevents their bind with further side ligands, such as PD-L2 in the case of pembrolizumab and sintilimab or B7.1 in the case of atezolizumab. PD-L2 has lower level and range of expression compared with PD-L1, but its presence has been recently reported in a large number of tumor types.^{29,30} Similar to PD-L1, the interaction with PD-1 seems to dampen and regulate T-cell immune response

during the induction and effector phases, thus having similar effects with PD-L1 and playing a role in cancer immune evasion.³¹⁻³³ Nevertheless, although a wide number of studies documented the association between PD-L1 expression and impaired survival, the same correlation with PD-L2 is still debated.³⁴⁻³⁹

Finally, the limitations of this meta-analysis should be acknowledged. Included studies had slightly different CT backbones. Nevertheless, all of them were platinum-based regimens that represent the standard chemotherapeutic options for patients with advanced NSCLC, with known superimposable outcomes. Moreover, HRs reported only indicate the incremental treatment effect added by the combination of an ICI and CT as compared with the same CT regimen without ICI. For these reasons, we do not see it as a relevant bias of the analysis. Consistently, for the one study (IMpower150) that included bevacizumab, the antiangiogenic agent was comprised in the CT backbone; thus, the difference between the two treatment arms of the study was only represented by the addition of atezolizumab in one. Again, as we only evaluated the incremental effect of the ICI as compared with the same treatment without ICI, we do not see it as a relevant bias. A further limitation consisted in the exclusion of two of eight trials selected in the safety analysis. In fact, KEYNOTE 189 and ORIENT-11, which both belonged to the PD-1 inhibitor group, did not report TRAEs as safety recording.^{10,12} Finally, methodology of response assessment was different among the trials analyzed. In fact, some studies adopted a blinded independent assessment,⁶⁻¹¹ whereas response evaluation was investigator assessed in others.¹²⁻¹⁶ This aspect could represent a limit to data interpretation and cross-trial comparison.

In conclusion, our meta-analysis revealed that the addition of a PD-1 inhibitor to CT seems to be more effective and safer than that of a PD-L1 inhibitor. These findings need validation in prospective trials of direct comparison among different ICIs in combination with platinum-based CT.

CRediT Authorship Contribution Statement

Alessandro Di Federico: Conceptualization, Formal analysis, Writing—original draft.

Andrea De Giglio: Conceptualization, Data curation, Writing—original draft.

Claudia Parisi: Writing—review and editing.

Francesco Gelsomino: Supervision, Writing—review and editing.

Luca Boni: Formal analysis.

Andrea Ardizzoni: Methodology, Supervision, Project administration.

Acknowledgments

This study was partially funded by the Associazione Italiana per la Ricerca sul Cancro (AIRC) (Investigator Grant—IG 2016, code 19026 to Dr. Ardizzoni).

References

1. Global Cancer Observatory. <https://gco.iarc.fr/>. Accessed October 2, 2020
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
3. Dela Cruz CS, Tanoue LT, Matthay RA. Lung cancer: epidemiology, etiology, and prevention. *Clin Chest Med*. 2011;32:605-644.
4. 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.
5. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393:1819-1830.
6. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol*. 2016;17:1497-1508.
7. Awad MM, Gadgeel SM, Borghaei H, et al. Long-term overall survival from KEYNOTE-021 cohort G: pemetrexed and carboplatin with or without pembrolizumab as first-line therapy for advanced nonsquamous NSCLC. *J Thorac Oncol*. 2021;16:162-168.
8. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379:2040-2051.
9. Paz-Ares L, Vicente D, Tafreshi A, et al. A randomized, placebo-controlled trial of pembrolizumab plus chemotherapy in patients with metastatic squamous NSCLC: protocol-specified final analysis of KEYNOTE-407. *J Thorac Oncol*. 2020;15:1657-1669.
10. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078-2092.
11. Gadgeel S, Rodríguez-Abreu D, Speranza G, et al. Updated analysis from KEYNOTE-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2020;38:1505-1517.
12. 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 non-squamous NSCLC: a randomized, double-blind, phase 3 study (Oncology pRogram by InnovENT anti-PD-1-11). *J Thorac Oncol*. 2020;15:1636-1646.
13. 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.
14. 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.
15. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20:924-937.
16. Nishio M, Barlesi F, West H, et al. Atezolizumab plus chemotherapy for first-line treatment of non-squamous non-small cell lung cancer: results from the randomized phase III IMpower132 trial. *J Thorac Oncol*. 2021;16:653-664.
17. Di Federico A, De Giglio A, Parisi C, Gelsomino F, Ardizzoni A. PD-1/PD-L1 inhibitor monotherapy or in combination with chemotherapy as upfront treatment for advanced NSCLC with PD-L1 expression \geq 50%: selecting the best strategy. *Crit Rev Oncol Hematol*. 2021;160:103302.
18. Duan J, Cui L, Zhao X, et al. 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. *JAMA Oncol*. 2020;6:375-384.
19. Tartarone A, Roviello G, Lerose R, Roudi R, Aieta M, Zoppoli P. Anti-PD-1 versus anti-PD-L1 therapy in patients with pretreated advanced non-small-cell lung cancer: a meta-analysis. *Future Oncol*. 2019;15:2423-2433.
20. Wang C, Qiao W, Jiang Y, et al. The landscape of immune checkpoint inhibitor plus chemotherapy versus immunotherapy for advanced non-small-cell lung cancer: a systematic review and meta-analysis. *J Cell Physiol*. 2020;235:4913-4927.
21. Zhou Y, Chen C, Zhang X, et al. Immune-checkpoint inhibitor plus chemotherapy versus conventional chemotherapy for first-line treatment in advanced non-small cell lung carcinoma: a systematic review and meta-analysis. *J Immunother Cancer*. 2018;6:155.
22. Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. *N Engl J Med*. 2020;383:1328-1339.
23. Blons H, Garinet S, Laurent-Puig P, Oudart JB. Molecular markers and prediction of response to immunotherapy in non-small cell lung cancer, an update. *J Thorac Dis*. 2019;11(suppl 1):S25-S36.
24. Reck M, Mok TSK, Nishio M, et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. *Lancet Respir Med*. 2019;7:387-401.
25. Rocco D, Malapelle U, Del Re M, et al. Pharmacodynamics of current and emerging PD-1 and PD-L1 inhibitors for the treatment of non-small cell lung cancer. *Expert Opin Drug Metab Toxicol*. 2020;16:87-96.
26. Wang J, Fei K, Jing H, et al. Durable blockade of PD-1 signaling links preclinical efficacy of sintilimab to its clinical benefit. *MAbs*. 2019;11:1443-1451.

27. Scapin G, Yang X, Prorise WW, et al. Structure of full-length human anti-PD1 therapeutic IgG4 antibody pembrolizumab. *Nat Struct Mol Biol.* 2015;22:953-958.
28. Lee HT, Lee SH, Heo YS. Molecular interactions of antibody drugs targeting PD-1, PD-L1, and CTLA-4 in immuno-oncology. *Molecules.* 2019;24:1190.
29. Ahmad SM, Martinenaite E, Holmström M, et al. The inhibitory checkpoint, PD-L2, is a target for effector T cells: novel possibilities for immune therapy. *Oncoimmunology.* 2017;7:e1390641.
30. Panjwani PK, Charu V, DeLisser M, Molina-Kirsch H, Natkunam Y, Zhao S. Programmed death-1 ligands PD-L1 and PD-L2 show distinctive and restricted patterns of expression in lymphoma subtypes. *Hum Pathol.* 2018;71:91-99.
31. Latchman Y, Wood CR, Chernova T, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. *Nat Immunol.* 2001;2:261-268.
32. Zhang Y, Chung Y, Bishop C, et al. Regulation of T cell activation and tolerance by PDL2. *Proc Natl Acad Sci U S A.* 2006;103:11695-11700.
33. Akbari O, Stock P, Singh AK, et al. PD-L1 and PD-L2 modulate airway inflammation and iNKT-cell-dependent airway hyperreactivity in opposing directions. *Mucosal Immunol.* 2010;3:81-91.
34. Rozali EN, Hato SV, Robinson BW, Lake RA, Lesterhuis WJ. Programmed death ligand 2 in cancer-induced immune suppression. *Clin Dev Immunol.* 2012;2012:656340.
35. Ohigashi Y, Sho M, Yamada Y, et al. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. *Clin Cancer Res.* 2005;11:2947-2953.
36. Hamanishi J, Mandai M, Iwasaki M, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. *Proc Natl Acad Sci US A.* 2007;104:3360-3365.
37. Gao Q, Wang XY, Qiu SJ, et al. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. *Clin Cancer Res.* 2009;15:971-979.
38. Jung HI, Jeong D, Ji S, et al. Overexpression of PD-L1 and PD-L2 is associated with poor prognosis in patients with hepatocellular carcinoma. *Cancer Res Treat.* 2017;49:246-254.
39. Yang H, Zhou X, Sun L, Mao Y. Correlation between PD-L2 expression and clinical outcome in solid cancer patients: a meta-analysis. *Front Oncol.* 2019;9:47.