Systematic Review and Meta-Analysis

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Efficacy and safety of PD-1/PD-L1 inhibitors combined with CTLA-4 inhibitor versus chemotherapy for advanced lung cancer

A meta-analysis

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Abstract

Background: This meta-analysis was performed to compare efficacy and tolerability between antiprogrammed cell death (PD-1)/programmed cell death-ligand-1 (PD-L1) + anticytotoxic T-lymphocyte-associated protein-4 (CTLA-4) treatment and chemotherapy in advanced lung cancer.

Methods: Cochrane Library, Embase, and PubMed databases were searched for potential articles. The fixed-effect model or random-effect model was adopted for pooled analysis based on the I^2 and *P*-value.

Results: Six articles with 1338 patients were identified and subjected to meta-analysis. Compared with chemotherapy, anti-PD-1/PD-L1 + anti-CTLA-4 treatment could significantly improve the overall survival (hazard ratio [HR] = 0.78, 95%confidence interval [CI]: 0.71–0.84, *P* = .21) and progression-free survival (HR = 0.77, 95%CI: 0.71–0.83, *P* = .30) of advanced lung cancer patients. Moreover, there was no obvious difference in the incidence of 3 to 4 adverse events (AEs) serious adverse reactions (HR = 1.35, 95% CI: 0.66–2.74, *P* < .00001) between the 2 treatment groups, but the incidence rates of AEs leading to discontinuation (HR = 2.56, 95%CI: 1.53–4.30, *P* < .00001) and AEs leading to death (HR = 2.10, 95%CI: 1.21–3.63, *P* = .20) were higher. Furthermore, no remarkable differences in objective response rate (HR = 1.31, 95%CI: 0.97–1.77, *P* = .02) were observed between the 2 groups.

Conclusion: Our meta-analysis revealed that PD-1/PD-L1 inhibitors plus CTLA-4 inhibitor could markedly improve the endpoint outcomes of patients compared with chemotherapy alone, and did not significantly increase the serious adverse reactions. Thus, it can serve as a new treatment strategy for advanced lung cancer.

Abbreviations: AEs = adverse events, CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte-associated protein-4, ES-SCLC = extensive stage-small cell lung cancer, HR = hazard ratio, ICIs = immune checkpoint inhibitors, NSCLC = nonsmall cell lung cancer, OR = odds ratio, ORR = objective response rate, OS = overall survival, PD-1 = programmed cell death-1, PD-L1 = programmed cell death-ligand-1, PFS = progression-free survival, RCTs = randomized controlled trials, SCLC = small-cell lung cancer.

Keywords: advanced lung cancer, chemotherapy, cytotoxic T-lymphocyte-associated protein-4, programmed cell death/programmed cell death-ligand-1

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All data generated or analyzed during this study are included in this published article.

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1. Introduction

Lung cancer is one of the main causes of cancer mortality worldwide.[1] Nonsmall cell lung cancer (NSCLC) represents about 85% of all lung cancers, while small-cell lung cancer (SCLC) represents 10% to 15% of all lung cancers.[2] SCLC remains a difficult disease to manage, and there are no significant advancements in the systemic treatment of this disease.[3] Although systemic cytotoxic chemotherapy and targeted therapy have been the mainstay of treatment for advanced stage NSCLC, progress remains limited.[4] Thus, new lung cancer therapies are urgently required to improve the disease prognosis. A recent study has suggested that immunotherapies are effective against lung cancer, and can serve as a new treatment option with minimal toxicities.[5]

Immunotherapy strategies are designed to reverse tumor immune suppression and activate antitumor responses.[6] There are 2 most extensively studied immune-checkpoint pathways: cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) pathway and programmed cell death-1 (PD-1).[7] Through the inhibition of PD-1 and CTLA-4 binding with their ligands, T cells can be activated and proliferated, thus leading to T cell-mediated tumor infiltration, and ultimately tumor suppression.[8] Over the past few decades, immune checkpoint inhibitors (ICIs) have made substantial breakthroughs in lung cancer treatment.[9] Nevertheless, the clinical efficacy of ICI monotherapy is limited and remains unsatisfactory.[10,11] Recently, some researches demonstrated that combination therapy could produce a higher tumor response rate in patients with NSCLC and SCLC.[12–15] In the tumor microenvironment, PD-1 modulates the functions of T cell effector; while in lymph nodes, CTLA-4 suppresses the early activation and differentiation of T cells.[16] Therefore, anti-PD-1/PD-L1 combined with anti-CTLA-4 is considered a complementary treatment to trigger the inhibition of immune checkpoints.[11] Numerous clinical trials have been conducted to investigate the effectiveness of PD-1/PD-L1 combined with CTLA-4 blockade in lung cancer patients. A Phase III trial (ARCTIC) demonstrated that durvalumab plus tremelimumab did not remarkably improve overall survival (OS) or progression-free survival (PFS) versus standard of care in advanced NSCLC patients.[17] However, another Phase III trial (Checkmate227) indicated that nivolumab plus ipilimumab resulted in a longer duration of OS versus chemotherapy in NSCLC patients.[18]

These clinical trials have shown opposite results. Hence, we performed a meta-analysis to investigate whether anti-PD-1/PD-L1 + anti-CTLA-4 can improve the OS, PFS and objective response rate (ORR) of advanced lung cancer patients compared to chemotherapy alone. In addition, the tolerability of multi-ICIs combination therapy was also compared with that of chemotherapy alone.

2. Methods

2.1. Article searching

Relevant clinical trials, which were published from January 2018 to December 2020, were searched through online databases (Cochrane Library, Embase, and PubMed). Search terms included: "anti-PD-1", "anti-PD-L1", "anti-CTLA-4", "immune checkpoint inhibitors", "lung cancer", "SCLC", and "NSCLC". The search was restricted to the articles published in English language. In cases of duplicate publications, more comprehensive studies were chosen for subsequent meta-analysis. All information was extracted by 2 authors independently, and any consensus was resolved through negotiation.

2.2. Inclusion criteria

We included all randomized controlled Phase III trials to compare the clinical efficacy of anti-PD-1/PD-L1 combined with anti-CTLA-4 treatment versus chemotherapy in advanced lung cancer patients. The endpoint outcomes included at least 1 or more OS, PFS, ORR, and adverse events (AEs).

2.3. Exclusion criteria

The exclusion criteria included: review articles, nonclinical experimental research, repeated clinical research, incomplete data, and unable to extract the relevant data.

2.4. Data extraction

All information was independently extracted by 2 researchers through a standardized data extraction form. Discrepancies were resolved through discussion with the 3rd researcher. The extracted data included the first author, study design, patient characteristics, treatment and measurement results of experimental group and control group.

2.5. Quality evaluation

Two researchers examined the methodological quality of trials that met the eligibility criteria for evaluation. Risk of bias was assessed in compliance with the Cochrane handbook for systematic reviews of interventions.[19]

2.6. Statistical analysis

Cochrane RevMan 5.3 software (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) was employed for the meta-analyses. Hazard ratio (HR) was used to compare dichotomous variables, and odds ratio (OR) was used to count variables. All results were given 95% confidence interval (CI). The I^2 statistic was applied to determine the effects of statistical heterogeneity on meta-analysis findings. Based on the Cochrane evaluation criteria, the random-effect model was selected when $I^2 > 50\%$ and $P < .1$ (severe heterogeneity); otherwise, the fixed-effect model was chosen when $I^2 \leq 50\%$ and $P > .1$. Subgroup analysis was performed to address obvious clinical heterogeneity. All tests were double-sided.

2.7. Ethics

The data we used are based on previously published researches, and these researches have been ethically approved. Therefore, ethical approval is not required.

3. Results

3.1. Article selection and study characteristics

There were 1338 documents searched from the databases. After reading the title and abstract of each article, 41 articles were screened out. The full texts of these articles were then assessed comprehensively. After excluding duplicate studies, nonrandomized control, and I or II phase trials, 6 articles[18,20–24] that meet

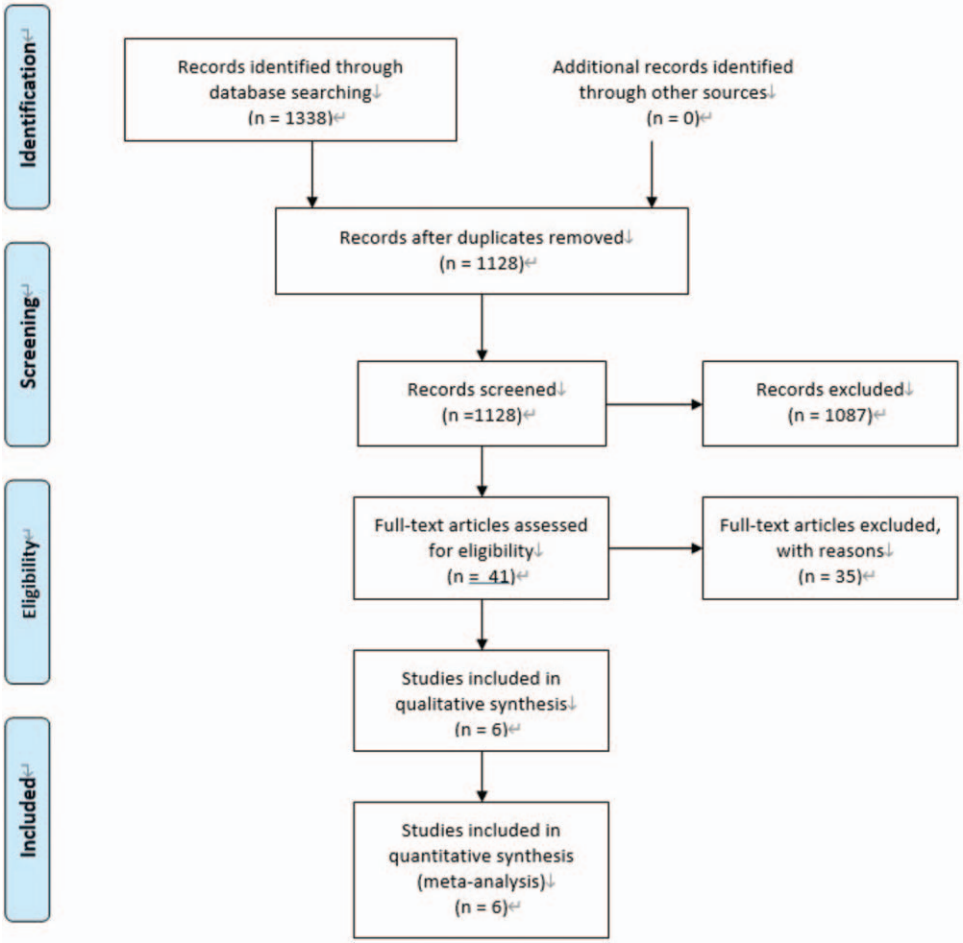

Figure 1. Flowchart of literature screening process.

the criteria were selected with a total of 3962 patients. At last, the 6 randomized controlled trials (RCTs) were subjected to the meta-analysis. Figure 1 summarizes the detailed information about article selection. The 6 included studies were eligible for PFS, OS and adverse reaction data analysis, and of those, 5 were eligible for ORR data analysis. Based on a histological perspective, 4 of the included RCTs were NSCLC and the remaining 2 were SCLC. Table 1 lists the characteristics of the 6 RCTs. Table 2 displays the endpoint outcomes of the selected studies.

3.2. Meta-analysis findings

3.2.1. Overall survival. The 6 RCTs were included to determine the OS of patients treated with anti-PD-1/PD-L1 + anti-CTLA-4 ± chemotherapy or chemotherapy only. As shown in Figure 2, the fixed-effect model meta-analysis indicated that the pooled HR of OS was 0.78 (95%CI: 0.71–0.84, $I^2 = 30\%$, $P = .21$). The result showed that, compared to chemotherapy alone, the combination of anti-PD-1/PD-L1 and anti-CTLA-4 with or without chemotherapy exhibited higher OS rate in advanced lung cancer patients. Subgroup analysis was stratified according to the histological type of this disease. The pooled HR values were 0.73 (95%CI: 0.66–0.81, $I^2 = 0\%$, $P = .39$) and 0.87 (95%CI: 0.75–1.00, $I^2 = 0\%$, $P = .43$) in advance NSCLC[18,21,23,24] and extensive stage-small cell lung cancer (ES-SCLC)[20,22] patients, respectively (Fig. 3). Compared to the chemotherapy group, anti-PD-1/PD-L1 + anti-CTLA-4 ± chemotherapy could exert superior OS in both advanced NSCLC and SCLC patients. The differences of all analyses were statistically significant.

3.2.2. Progression-free survival. All 6 RCTs reported PFS, and the pooled HR of PFS was 0.77 (95%CI: 0.71–0.83, $I^2 = 17\%$, $P = .30$; Fig. 4). HR of PFS was determined by the fixed-effect model. The result demonstrated that, compared to chemotherapy alone, anti-PD-1/PD-L1 + anti-CTLA-4 ± chemotherapy could enhance the PFS of advanced lung cancer patients. Subgroup analysis revealed that combination therapy had a higher PFS than chemotherapy alone in both advance NSCLC (HR = 0.77, 95% CI: 0.70–0.84, $I^2 = 35\%$, $P = .20$) and ES-SCLC (HR = 0.78, 95% CI: 0.68–0.88, $I^2 = 27\%$, $P = .24$) patients (Fig. 5). The differences of all analyses was statistically significant.

3.2.3. Objective response rate. Five[18,20,21,23,24] of the 6 RCTs were included to assess the ORR of advanced lung cancer patients, and the pooled HR of ORR was 1.31 (95%CI: 0.97–1.77, $I^2 = 67\%$, $P = .02$; Fig. 6). The result indicated that no obvious difference in ORR was found between anti-PD-1/PD-L1 + anti-CTLA-4 ± chemotherapy and chemotherapy only treatment groups. A random-effect model was used for the analysis of ORR.

Table 1

Characteristics of the studies included in the meta-analysis.

Study	Phase	Masking	Histology	Therapy line	Number of patients (experimental/ chemotherapy)	Experimental arm	Chemotherapy arm
D. Planchard 2020	III	Open-label	NSCLC	3+	173/110	Durvalumab + tremelimumab (12 wk durvalumab 20 mg/kg + tremelimumab 1 mg/kg q4w then 34 wk durvalumab 10 mg/kg q2w)	standard of chemotherapy q3w
Hellmann 2019	III	Open-label	NSCLC	1	583/583	Nivolumab (at a dose of 3 mg/kg of body weight every 2 wk) plus ipilimumab (at a dose of 1 mg/kg every 6 wk)	Platinumdoublet chemotherapy q3w
Martin Reck 2020	III	Open-label	NSCLC	1	361/358	Nivolumab 360 mg q3w + ipilimumab 1 mg/kg q6w + platinum-doublet chemotherapy (2 cycles)	Platinum-doublet chemotherapy q3w
Naiyer A. Rizvi 2020	III	Open-label	NSCLC	1	372/372	Durvalumab (20 mg/kg every 4 wk) + tremelimumab (1 mg/kg every 4 weeks, up to 4 doses)	Platinum-based doublet chemotherapy q3w
Luis G. Paz-Ares 2020	III	Open-label	ES-SCLC	1	268/269	Durvalumab1500 mg + tremelimumab75 mg + EP q3w	EP q3w
Owonikoko 2019	III	Open-label	ED-SCLC	Maintenance therapy after 1L	279/275	Nivolumab 1 mg/kg + ipilimumab 3 mg/ kg q3w	Platinum-based doublet chemotherapy q3w

ES-SCLC = extensive stage-small cell lung cancer, NSCLC = nonsmall cell lung cancer.

3.2.4. Adverse events. Grade 3 to 4 AEs were reported in all 6 studies. Our meta-analyses revealed that the pooled HR of grade 3 to 4 AEs was 1.35 [95%CI:0.66–2.74, $I^2 = 96\%$, $P < .00001$; Fig. 7], the pooled HR of AEs leading to discontinuation was 2.56 [95%CI: 1.53–4.30, $I^2 = 85\%$, $P < .00001$; Fig. 8], and the pooled HR of AEs leading to death was 2.10 [95%CI: 1.21–3.63, $I^2 = 33\%$, $P = .20$; Fig. 9]. These findings implied that, compared to chemotherapy alone, anti-PD-1/PD-L1 + anti-CTLA-4 ± chemotherapy did not significantly increase the incidence rates of grade 3 to 4 AEs, but could increase the incidence rates of AEs leading to discontinuation and AEs leading to death. The differences of all analyses were statistically significant.

3.3. Publication bias

As demonstrated in Figure 10, no significant publication bias existed in the present meta-analysis.

4. Discussion

Chemotherapy, cytotoxic drugs, and molecular targeted drugs have been commonly prescribed to treat advanced lung cancer, but their efficacy has reached a therapeutic plateau.[3,25] A number of studies have confirmed that immunotherapy as a new treatment strategy has achieved encouraging results in lung cancer.[7,26] Growing evidence has shown that anti-PD-1/PD-L1 combined with anti-CTLA-4 therapies may exhibit superior inhibitory activity in multiple tumors compared to anti-PD-1 or anti-CTLA-4 monotherapy.[27] However, the efficacy and safety of anti-PD-1/PD-L1 + anti-CTLA-4 compared with chemotherapy in the treatment of advanced lung cancer remain largely unconfirmed. Six randomized clinical trials have publicly addressed the corresponding results of these drugs.[18,20–24] Hence, we conducted a meta-analysis to provide valid and reliable conclusions.

Our study demonstrated that the combination of anti-PD-1/PD-L1 and anti-CTLA-4 exerted a survival benefit (OS and PFS) in advanced lung cancer patients when compared to chemotherapy alone. This survival benefit had also been observed when meta-analysis was stratified for advanced NSCLC and ES-SCLC. However, we found that there was no obvious difference in ORR between PD-1/PD-L1 + CTLA-4 ICIs-treated and chemotherapy-treated patients. These findings showed that anti-PD-1/PD-L1 + anti-CTLA-4 therapy might not have obvious advantages in

Table 2

The methodological quality of included trials.

Study	PD-L1 expression level	ORR (experimental vs chemotherapy)	Median OS HR (95%CI)	Median PFS HR (95%CI)	Treatment-related grade 3/4 AEs (experimental vs chemotherapy)	AEs leading to discontinuation (experimental vs chemotherapy)	AEs leading to death (experimental vs chemotherapy)
D. Planchard 2020	<25%	14.9% vs 6.8%	0.8 (0.61–1.05)	0.77 (0.59–1.01)	22% vs 36.4%	18.5% vs 17.3%	0% vs 0%
Hellmann 2019	≧0%	33.1% vs 27.8%	0.73 (0.64–0.84)	0.79 (0.69–0.91)	32.8% vs 36%	18.1% vs 9.1%	1.4% vs 1.1%
Martin Reck 2020	≧0%	38% vs 25%	0.66 (0.55–0.8)	0.68 (0.57–0.82)	47% vs 38%	19% vs 7%	2% vs 2%
Naiyer A. Rizvi 2020	≧25%	34.4% vs 37.7%	0.85 (0.61–1.17)	1.05 (0.72–1.53)	22.9% vs 33.8%	13.2% vs 9.4%	1.6% vs 0.9%
Luis G. Paz-Ares 2020	≧0%	58.4% vs 58%	0.82 (0.68–1.0)	0.84 (0.7–1.01)	70.3% vs 62.8%	21.4% vs 9.4%	10.2% vs 5.6%
Owonikoko 2019	≧0%	-	0.92 (0.75–1.12)	0.72 (0.6–0.87)	52% vs 8%	31% vs 4%	2.5% vs <1%

AEs = adverse events, HR = hazard ratio, ORR = objective response rate, OS = overall survival, PD-1 = programmed cell death-1, PFS = progression-free survival.

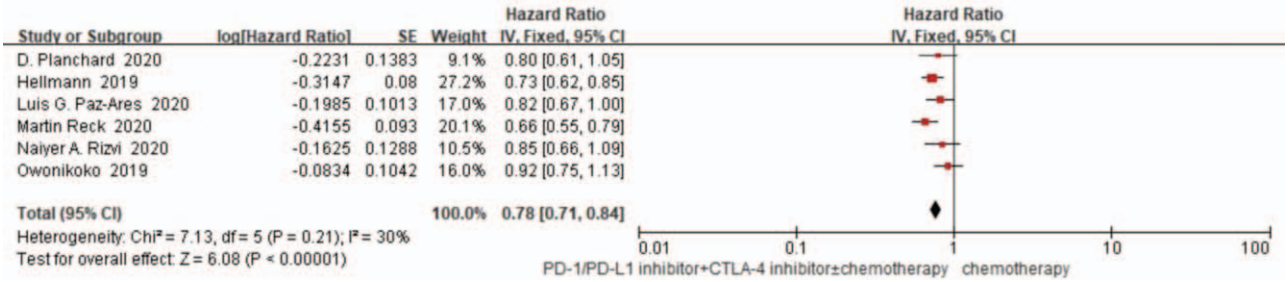

Figure 2. Forest plot of HRs for overall survival in anti-PD-1/PD-L1 + anti-CTLA-4±chemotherapy versus chemotherapy groups. CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte-associated protein-4, PD-1 = programmed cell death-1, PD-L1 = programmed cell death-ligand-1.

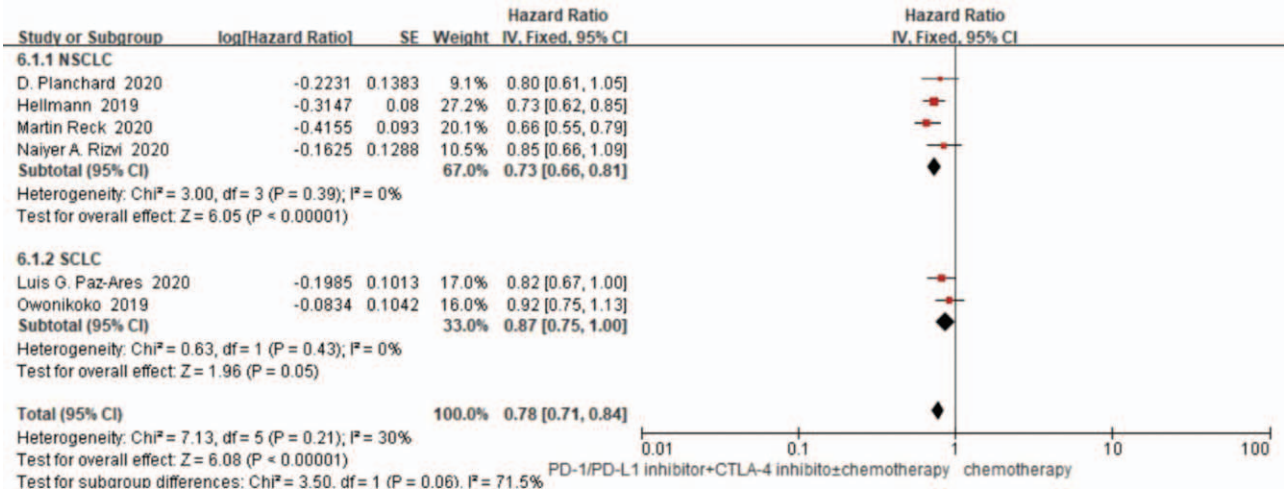

Figure 3. Subgroup analyses on overall survival according to histology. CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte-associated protein-4, NSCLC = nonsmall cell lung cancer, PD-1 = programmed cell death-1, PD-L1 = programmed cell death-ligand-1, SCLC = small-cell lung cancer.

antitumor activity, but it could prolong the survival of advanced lung cancer patients. Besides, it has been reported that ipilimumab combined with nivolumab can improve the ORR of melanoma patients,[28] and such combination exhibits a high investigator-evaluated ORR in colorectal cancer patients.[29] However, in this study, ORR did not match with OS and PFS, which might be due to the small sample sizes of the included RCTs or a lack of original data, and we were unable to perform a hierarchical analysis of PD-L1 expression. Moreover, some randomized controlled studies about the efficacy of anti-PD-1/PD-L1 combined with anti-CTLA-4 therapy are still ongoing, such as CheckMate 032,[30] kEYNOTE-598,[31] and EMPOWER-lung 4.[32] Therefore, more studies with larger sample are still warranted.

At the same time, we found that compared to chemotherapy only, the PD-1/PD-L1 and CTLA-4 ICIs therapy did not result in an increased risk of grade 3 to 4 AEs, but caused higher risks of AEs leading to discontinuation and AEs leading to death. It is well

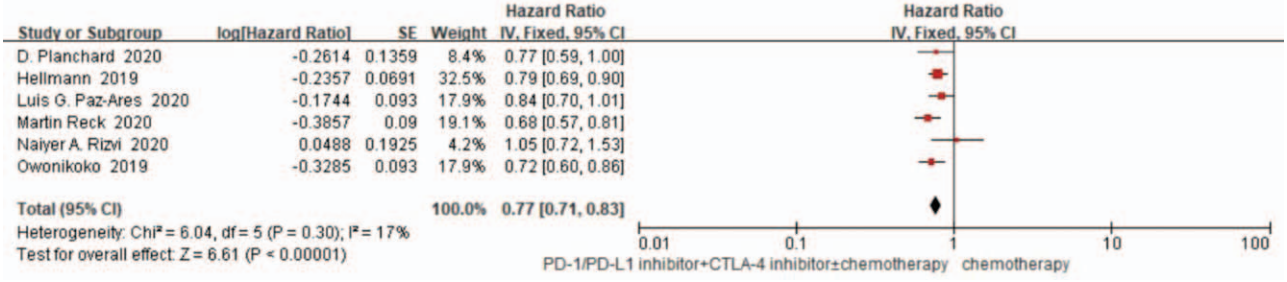

Figure 4. Forest plot of HRs for progression-free survival in anti-PD-1/PD-L1 + anti-CTLA-4±chemotherapy versus chemotherapy groups. CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte-associated protein-4, HR = hazard ratio, PD-1 = programmed cell death-1, PD-L1 = programmed cell death-ligand-1.

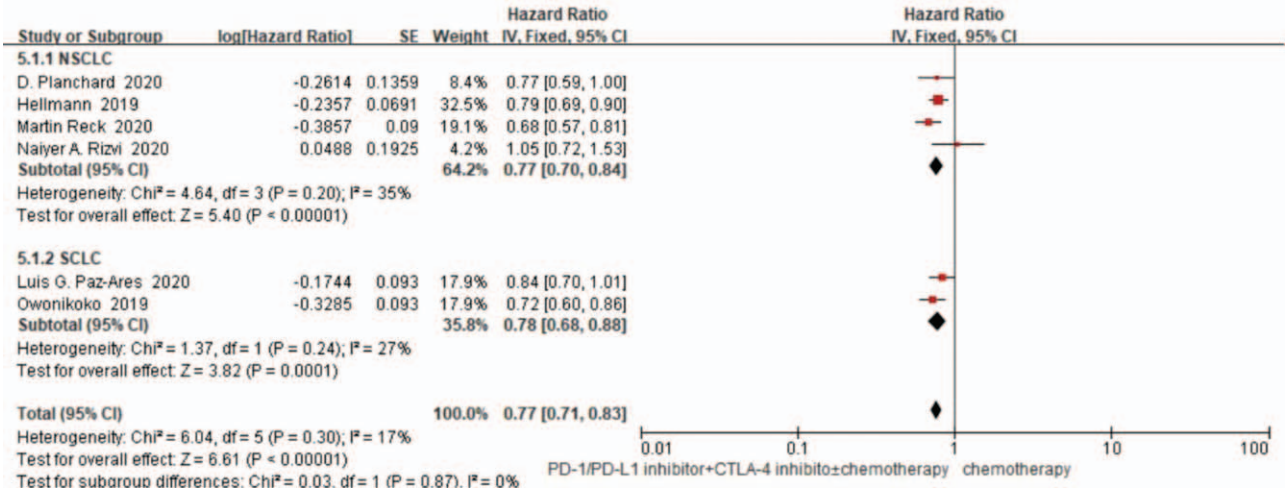

Figure 5. Subgroup analyses on progression-free survival according to histology. CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte-associated protein-4, NSCLC = nonsmall cell lung cancer, PD-1 = programmed cell death-1, PD-L1 = programmed cell death-ligand-1, SCLC = small-cell lung cancer.

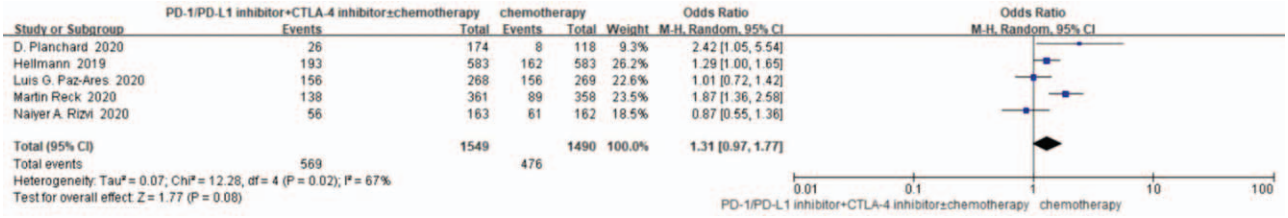

Figure 6. Forest plot of HRs for objective response rate in anti-PD-1/PD-L1 + anti-CTLA-4±chemotherapy versus chemotherapy groups. CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte-associated protein-4, HR = hazard ratio, PD-1 = programmed cell death-1, PD-L1 = programmed cell death-ligand-1.

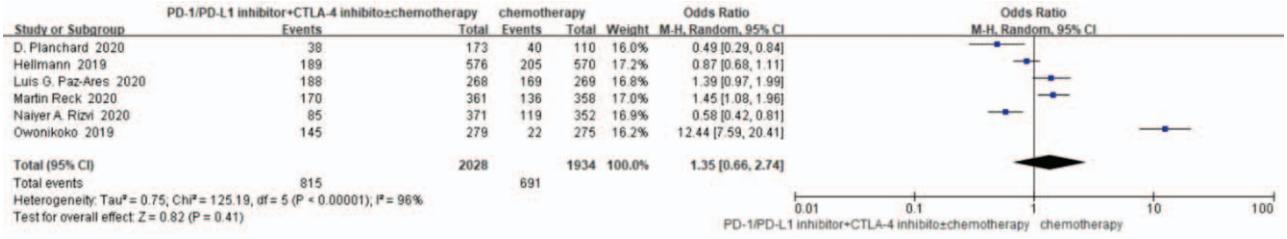

Figure 7. Comparison of 3 to 4 treatment-related adverse effects (AEs) between anti-PD-1/PD-L1 + anti-CTLA-4 ± chemotherapy and chemotherapy only groups. CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte-associated protein-4, PD-1 = programmed cell death-1, PD-L1 = programmed cell death-ligand-1.

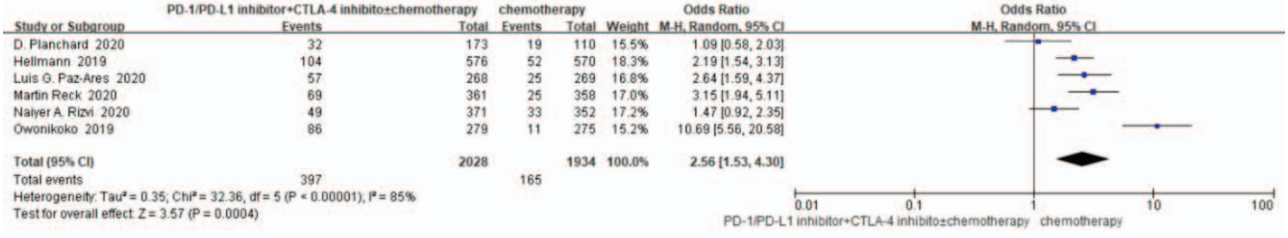

Figure 8. Comparison of AEs leading to discontinuation between anti-PD-1/PD-L1 + anti-CTLA-4 ± chemotherapy and chemotherapy only groups. AEs = adverse effects, CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte-associated protein-4, PD-1 = programmed cell death-1, PD-L1 = programmed cell death-ligand-1.

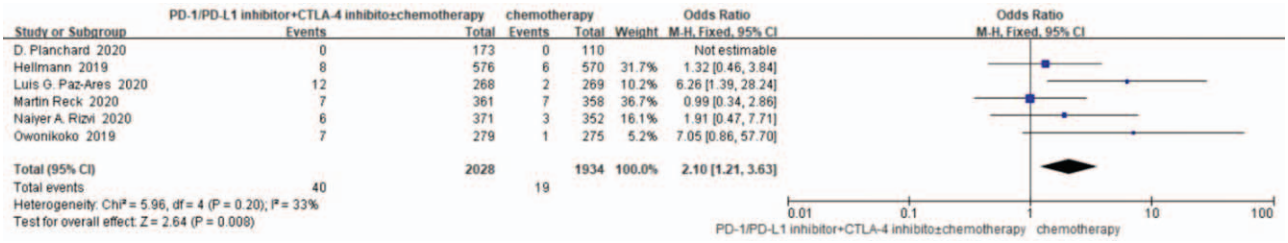

Figure 9. Comparison of AEs leading to death between anti-PD-1/PD-L1 + anti-CTLA-4 ± chemotherapy and chemotherapy only groups. AEs = adverse effects, CI = confidence interval, CTLA-4 = cytotoxic T-lymphocyte-associated protein-4, PD-1 = programmed cell death-1, PD-L1 = programmed cell death-ligand-1.

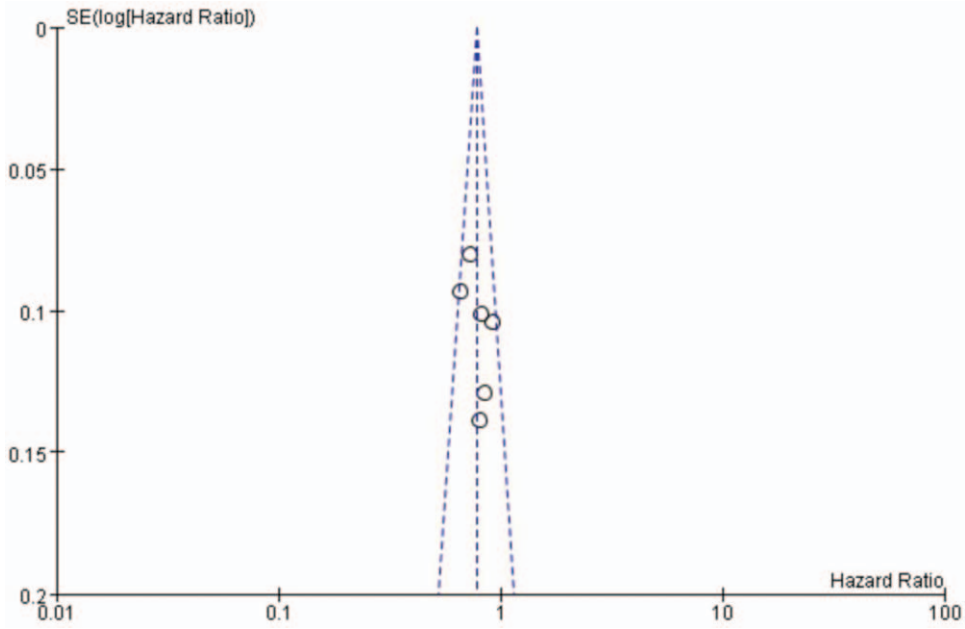

Figure 10. Evaluation for the published segregation of funnel figure.

known that immune-related AEs can be triggered by ICIs, such as ICI-related hypophysitis, thyroid dysfunction, bullous pemphigoid, diarrhoea, hepatitis, pneumonia, and so on. When PD-1/PD-L1 inhibitors were combined with CTLA-4 inhibitors, these toxic effects were considerably more common.[10] However, only a few studies had proven that no additional immune-related AE was induced by the combination of PD-1/PD-L1 + CTLA-4 ICIs therapy.[33] Thus, we believed that these findings might explain the tolerability of anti-PD-1/PD-L1 combined with anti-CTLA-4 therapy. Nevertheless, there were also some limitations in this study, for example, all grade AEs had not been analyzed, and different types of AEs were not analyzed separately due to the lack of relevant data. Therefore, further meta-analysis is urgently needed to improve the results by including more RCTs with larger sample sizes.

In conclusion, PD-1/PD-L1 + CTLA-4 ICI therapies remarkably prolong OS and PFS, and have similar risk of 3-4 AEs compared to chemotherapy. Our work confirms that anti-PD-1/PD-L1 combined with anti-CTLA-4 therapy can be a novel treatment strategy for advanced lung cancer. It is worth noting that PD-1/PD-L1 + CTLA-4 ICI therapies can increase the risks of AEs leading to discontinuation and AEs leading to death. This finding may provide key information for clinicians regarding the selection of appropriate combination therapy and the health status of advanced lung cancer patients who are planned to be treated with anti-PD-1/PD-L1 and/or anti-CTLA-4 treatment.

Author contributions

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Project administration: Juan Wang.
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Supervision: Li Zhang.
Validation: Li Zhang, Chun Cheng.
Visualization: Juan Wang.
Writing – original draft: Pei-Pei Zhang.
Writing – review & editing: Chun Cheng, Da-Ke Chen.

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