The efficacy and safety of anti-PD-1/PD-L1 antibodies combined with chemotherapy or CTLA4 antibody as a first-line treatment for advanced lung cancer

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Abstract

Checkpoint inhibitors show promising efficacy in advanced lung cancer, especially in non-small cell lung cancer. This meta-analysis was conducted to explore the therapeutic efficacy and safety of anti-PD-1/PD-L1 antibodies combined with chemotherapy or CTLA4 antibody as first-line treatments for patients with advanced lung cancer. A systematic search was performed in databases for this system review and quantitative meta-analysis. Twelve trials were finally enrolled in the meta-analysis. Our analyses revealed that the combined overall response rate (ORR) and disease control rate (DCR) for immune checkpoint inhibitors combined with chemotherapy for the treatment of non-small cell lung cancer (NSCLC) were 47.0% (95% CI: 34.2% - 60.2%) and 80.9% (95% CI: 69.4% - 88.7%), respectively. The combined ORR and DCR for CTLA4 antibody combined with chemotherapy for the treatment of small-cell lung cancer (SCLC) were 65.4% (61.1%-69.5%) and 87.6% (84.5%-90.2%), respectively. The combined six-month progression-free survival rates (PFSRs6m) for NSCLC and SCLC were 50.2% (95% CI: 21.9% - 78.4%) and 30.7% (21.2%-40.3%), respectively, and the OSRs1y were 56.4% (39.1%-73.7%) and 36.9% (33.3%-40.5%), respectively. In addition, the combined ORR and DCR for the checkpoint inhibitors plus CTLA4 antibody treatment group in NSCLC were 29.6% (95% CI: 11.4%-57.8%) and 48.7% (16.8%-81.7%), respectively. In subgroup analyses, a significant improvement in PFS was observed in NSCLC and SCLC, with a combined hazard ratio and...
95% confidence interval of 0.841 (0.737-0.961) and 0.856 (0.756-0.968), respectively. In summary, synergistic activity and an acceptable safety profile were observed with checkpoint inhibitor plus chemotherapy combination treatment in lung cancer.

Keywords: anti-PD-1/PD-L1 antibodies, anti-CTLA4 antibodies, lung cancer, chemotherapy.

**Novelty and impact statements**

1. Synergistic activity and an acceptable safety profile were observed with checkpoint inhibitor plus chemotherapy combination treatment in lung cancer. There was a significant improvement in PFS but not in OS.
2. Modest activity with tolerable adverse effects was observed for lung cancer patients who received anti-PD-1/PD-L1 antibodies plus CTLA4 antibody therapy.
Introduction

Lung cancer remains the most common cancer worldwide and the primary cause of death caused by cancer in China. The latest release of cancer statistics in China reported 733,000 newly diagnosed lung cancer cases and 60 million lung cancer deaths in 2015. Non-small cell lung cancer (NSCLC) was the primary subtype for approximately 80% of cases. Approximately 2/3 of NSCLC patients cannot receive radical treatment, such as surgery, because they were diagnosed at a late stage. Therefore, platinum-based traditional chemotherapy is the primary treatment for advanced NSCLC. However, because of the limited efficacy and remarkably toxic side effects of chemotherapy, the survival of patients with advanced NSCLC is unsatisfactory. Great improvements in gene-driven targeted therapy have produced numerous targeted drugs that have achieved good curative effects by targeting disease-driving genes, including epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and ROS proto-oncogene 1, receptor tyrosine kinase (ROS1), in clinical trials for lung cancer patients. The response rate for patients with gene-driven mutations ranged from 62-85%, which was significantly better than that for chemotherapy. However, there is no particularly effective treatment for NSCLC patients without oncogenic-driver alterations. Notably, SCLC is an aggressive, poorly differentiated neuroendocrine tumor, and its prognosis is extremely poor because of its high growth fraction and easily widespread metastases.

Immune checkpoint inhibitors were an inspiring breakthrough in lung cancer management in the past decades. Programmed cell death protein 1 (PD-1) is primarily expressed on activated T cells, Treg cells, B cells and NK cells. The PD-1 ligand PD-L1 is expressed on stromal cells and tumor cells. The primary function of the PD-1/PD-L1 pathway is to induce tumor cells to evade immune attack. The most typical immune checkpoint inhibitors are PD-1 (nivolumab or pembrolizumab) and PD-L1 (atezolizumab) antibodies. PD-1 and PD-L1 antibodies are an effective approach with a significant overall survival (OS) benefit compared with single-agent docetaxel as a second-line treatment in advanced NSCLC patients. Cytotoxic T-lymphocyte-associated protein 4 (CTLA4) inhibits the activation of cytotoxic T-cells via binding to its ligand, CD28. Ipilimumab is a monoclonal antibody (IgG1) that blocks CTLA4 and enhances the T cell response. Pembrolizumab was approved by the US Food and Drug Administration (FDA) as a first-line therapy for PD-L1-positive and EGFR-, ALK-, and ROS1-negative patients following the results of the Keynote-024 study. Therefore, immune checkpoint inhibitors are primary management therapies for advanced lung cancer patients. An intense interest in the identification of the optimal strategy for the use of drugs in advanced lung cancer was recently generated. One highlight of this interest is the development of combination treatment regimens based on immune checkpoint inhibitors (PD-1 and PD-L1 antibodies) and additional incorporation of CTLA4 monoclonal antibody or chemotherapy.

Preclinical data demonstrated that chemotherapy induced PD-L1 expression on tumor cells and modulated the immune effect against tumor cells. A significantly higher rate of adverse side effects was observed, but the combination anti-CTLA4 and anti-PD1 therapy improved the response rates and progression-free survival compared with those in patients who received nivolumab monotherapy. The anti-CTLA4 and anti-PD1 antibody combination has been approved as a treatment regimen for...
advanced BRAF wild-type melanoma patients.²¹

Few studies²²-²⁴ have investigated the efficacy of combination anti-PD1/PD-L1 and anti-CTLA4 antibodies or chemotherapy in lung cancer, and controversy regarding the optimal use of PD1/PD-L1 and CTLA4 immune checkpoint inhibitors and chemotherapy remains. Therefore, our meta-analysis provides sufficient evidence of the efficacy and safety of the combination of anti-PD1/PD-L1 with anti-CTLA4 antibodies or chemotherapy in advanced lung cancer patients.

**Patients and Methods**

**Search strategy and study selection**

We used free-text words and MeSH terms to increase sensitivity. The following search strategy was used: (pembrolizumab OR lambrolizumab OR Keytruda OR MK-3475 OR PEMBRO OR Nivolumab OR MEDI-4736 OR darvalumab OR MPDL-3280A OR atezolizumab OR Tecentriq OR MSB0010718C OR avelumab OR ipilimumab OR Yervoy OR CP-675206 OR tremelimumab) OR chemotherapy AND lung cancer. Studies with the most complete data were used in cases of duplicate publications.

Two investigators (Fan Yun and Xu Xiaoling) independently searched PubMed, SpringerLink, Embase, Web of Science, Medline and the Cochrane Library. The last search was performed on September 4, 2017. A computerized search of the online proceedings of the ASCO Annual Meetings, the European Society for Medical Oncology (ESMO), European Lung Cancer Conference (ELCC) and the World Conference of Lung cancer (WCLC) was also performed. Study selection was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.²⁵

The following inclusion criteria were used: (1) the study reported anti-CTLA4, anti-PD-1 or anti-PD-L1 antibodies in lung cancer patients; (2) the study investigated any of the following measurements: response rate (RR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS); and (3) the study was a clinical trial published in English.

The following exclusion criteria were used: (1) studies without related data; (2) editorials, letters, case reports, expert opinions or reviews; and (3) duplicate publications.

**Data extraction and quality assessment**

Two authors (Xu Xiaoling and Fan Yun) independently performed the data extraction. Any discrepancies were resolved by discussion. The following information was extracted from each study: first author, publication year, number of patients, randomization, trial phase, treatment, pathological type, follow-up information, events of complete response, partial response, stable disease or progressive disease, six-month PFS rate (PFSR₆m) or one-year OS rate (OSR₁y).

The heterogeneity between studies was evaluated by Cochrane’s Q and the I² statistic. A p-value less
than 0.05 was considered significant heterogeneity for the Q statistic. An $I^2 > 50\%$ implied significant heterogeneity. A random effect model by DerSimonian and the Laird method were used, or a fixed effect model by Mantel-Haenszel, was used if heterogeneity was observed. Subgroup analysis was performed to reduce heterogeneity between studies. Funnel plots were used to detect possible publication bias. Sensitivity analysis was performed to assess the stability of combined results by excluding studies one by one. Most analyses were performed using MetaAnalyst (version Beta 3.13; Tufts Evidence-based Practice Center, the USA).

In subgroup analyses, for the five randomized studies, hazard ratio (HR) and its 95% confidence interval (CI) of PFS and OS was extracted. The related analyses were conducted with STATA version 11.0 (Stata Corporation, College Station, TX). For all analyses, $p < 0.05$ was considered statistically significant.

Quality Control

The Newcastle Ottawa Scale (NOS) was used to evaluate the quality of enrolled single-arm or non-controlled studies. Studies were divided into three grades: poor, modest, and high quality, according to scores ranging from 0–3, 4–6, and 7–9, respectively.

Results

Literature search

Figure 1 shows a flow diagram for study inclusion. The preliminary literature search identified 296 abstracts and 242 papers from databases and 54 conference abstracts that fulfilled our inclusion criteria. Seventeen papers were excluded due to duplication. Titles and abstracts were reviewed, and 165 potential full-text articles were evaluated for eligibility. All relevant references were reviewed. Twelve clinical trials were finally identified for inclusion in our study, including 7 non-randomized trials and 5 randomized trials. Nine of these 12 studies reported the efficacy of anti-PD-1/PD-L1 or anti-CTLA4 antibodies plus chemotherapy in the treatment of advanced lung cancer, whereas three investigated the efficacy of anti-PD-1/PD-L1 antibodies plus CTLA4 antibody.

Study characteristics

Three of the studies were two-armed, and two studies were triple-armed. Most of the studies were multi-armed but without a control group. Most trials were phase 1/2 studies. In total, 1514 patients were enrolled in this meta-analysis. Most studies were from the USA; two studies were from Germany, and two studies were from Japan. Most of the studied patients had a PS of 0 to 1. The median follow-up ranged from 4.2 to 19.0 months.

Nine articles investigated NSCLC patients, and one study specifically studied non-squamous NSCLC patients. Seven studies investigated the efficacy of checkpoint inhibitors plus chemotherapy in NSCLC patients. The other two studies examined the efficacy of anti-PD-1/PD-L1 antibodies plus CTLA4
antibody in SCLC patients. Another three studies used extensive or recurrent SCLC patients. All research provided data to extract the overall response rate (ORR) and the DCR. However, only nine studies were available to extract the PFSR_{6m}, and eight studies were available to determine the OSR_{1y}. In addition, only five studies provided an HR value and its 95% CI. Details of the study characteristics are summarized in Table 1.

Main analysis

NSCLC

A total of nine studies including 878 patients assessed the efficacy of combination regimens, including immune checkpoint inhibitors, in NSCLC patients (Figure 2). The combined ORR and DCR were 42.7% (95% CI: 30.9%-55.4%) and 75.7% (59.9%-86.7%), respectively. The combined PFSR_{6m} and OSR_{1y} values were 51.1% (29.4%-72.8%) and 57.0% (41.8%-72.2%), respectively. The random-effect model was used for all four analyses because significant heterogeneity was detected.

SCLC

Three studies evaluated the potential benefit of an immune checkpoint inhibitor combined with chemotherapy in SCLC patients (Figure 3). The random-effects model was used because of modestly significant heterogeneity (I^2 = 0.492 for the ORR, and I^2 = 0.495 for the DCR). The analysis demonstrated that the combined ORR and DCR were 38.4% (95% CI: 14.8%-69.0%) and 73.6% (95% CI: 32.8%-94.1%), respectively. The combined PFSR_{6m} and OSR_{1y} were 26.1% (95% CI: 16.4%-35.8%) and 34.9% (95% CI: 29.6%-40.3%), respectively. Modestly significant heterogeneities were also detected in both analyses.

Subgroup analyses

To investigate possible reasons for the heterogeneity, we performed subgroup analyses according to whether the trial was randomized, the different combination strategies for NSCLC treatment and the chemotherapy regimens (gemcitabine and pemetrexed). All the results are presented in Table 2.

Five studies were randomized studies and provided HR values for PFS and OS (Table 2). The combined HR and its 95% CI for PFS of the three studies that investigated the efficacy of checkpoint inhibitors combined with chemotherapy in NSCLC was 0.841 (0.737-0.961), with statistical significance (z = 2.55, p = 0.011). A similar result was observed in SCLC, the combined HR and its 95% CI for PFS of the two related studies was 0.856 (0.756-0.968). This finding indicates that checkpoint inhibitors combined with chemotherapy led to a significant improvement in PFS compared with chemotherapy alone in SCLC. Unfortunately, there was no statistical significance for OS in the five studies that investigated the efficacy of checkpoint inhibitors combined with chemotherapy for either NSCLC or SCLC. The combined HR and its 95% CI were 0.894 (95% CI: 0.773-1.035; p = 0.135) and 0.941 (95% CI: 0.816-1.084; p = 0.400), respectively. A forest plot is shown in Figure 4. No evidence of publication bias was detected by Begg’s test or Egger’s test for the above analysis.
A total of seven eligible studies including 741 patients evaluated the efficacy of an immune checkpoint inhibitor combined with chemotherapy in NSCLC patients, and the ORRs ranged from 21.4% to 63.4% (median ORR was 54.2%). The combined ORR was 47.0% (95% CI: 34.2% - 60.2%) with modestly significant heterogeneity (Q statistic, 0.978; I², 0.464; p < 0.001). A random-effect model was performed. The analysis revealed that the combined DCR was 80.9% (95% CI: 69.4% - 88.7%) with good homogeneity (Q statistic, 0.976; I², 0.460; p < 0.001) using a random-effects model. Five of the seven studies reported the PFSR₆m. The combined PFSR₆m was 50.2% (95% CI: 21.9% - 78.4%), but significant heterogeneity was observed (Q statistic, 16373.121; I², 1.000; p < 0.001). Significant heterogeneity was also observed (Q statistic, 158.881; I², 0.981; p < 0.001) for the OSR₁y in four studies. The combined OSR₁y was 56.4% (95% CI: 39.1% - 73.7%). Because of the significant heterogeneity, we further detected the efficacy of anti-PD1/PD-L1 antibodies or anti-CTLA4 antibody combined with chemotherapy in NSCLC (data are shown in Table 2).

Only two studies reported the potential benefit of two immune checkpoint inhibitors in NSCLC patients. A total of 137 patients were enrolled. Only the ORR and the DCR were available to combine in the two studies. The combined ORR was 29.6% (95% CI: 11.4% - 57.8%), and the DCR was 48.7% (95% CI: 16.8% - 81.7%). In both analyses a random-effects model was applied because significant heterogeneity was detected.

Two studies including 521 patients investigated the efficacy of a PD-1 antibody combined with chemotherapy in SCLC patients. The combined ORR and DCR were 65.4% (61.1% - 69.5%) and 87.6% (84.5% - 90.2%), respectively. The combined PFSR₆m and OSR₁y were 30.7% (21.2% - 40.3%) and 36.9% (33.3% - 40.5%), respectively.

The combined ORR, DCR and PFSR₆m were 41.3% (21.0% - 65.1%), 88.3% (63.2% - 97.1%) and 49.2% (23.8% - 74.5%), respectively, for patients treated with chemotherapy based on gemcitabine in NSCLC. The analyses were performed using a fixed-effects model because good homogeneities were detected. Similar results were obtained in patients treated with chemotherapy based on pemetrexed in NSCLC. The combined ORR and DCR were 41.7% (28.9% - 55.8%) and 78.2% (63.8% - 87.9%), respectively. In contrast, the combined PFSR₆m was 55.0% (31.0% - 79.0%), and a random-effects model was used.

**Toxicity and tolerability**

Side effects were generally tolerable. The most commonly reported treatment-related adverse events (AEs) of any grade for the combination of anti-PD1/PD-L1 antibodies and chemotherapy were decreased appetite, nausea, fatigue, alopecia, and hematological toxicities (neutropenia, anemia, and thrombocytopenia). The most common treatment-related severe AEs were pneumonitis, fatigue, anemia and neutropenia. The most commonly reported AEs in the combination of PD1/PD-L1 antibodies and CTLA4 antibody treatments were skin, GI, renal, hypothyroidism, hyperthyroidism and pulmonary issues.

**Sensitivity analysis and publication bias**

Sensitivity analysis was performed to detect the impact of uncertain factors. Omission of any single
The trial did not significantly alter our results, which indicates that the survival benefits of immune checkpoint inhibitor combination strategies were still detected when studies with a high risk of bias were omitted.

The potential of publication bias for ORR, DCR, PFSR_{6m} and OSR_{1y} of the immune checkpoint inhibitor combination treatments in NSCLC and SCLC patients was observed using a funnel plot (data not shown). One possible reason is the small number of trials.

**Discussion**

Several antibodies directed toward the PD-1 receptor (nivolumab and pembrolizumab) or its ligand PD-L1 (atezolizumab) are approved for use in clinical practice for the treatment of lung cancer, and other drugs are in preclinical development. Checkpoint inhibitors and chemotherapy are approved treatment options for oncogene-driven advanced lung cancer in the first-line setting. Therefore, these strategies have attracted great interest in the identification of optimal combination strategies for advanced lung cancer patients. The aim of combination strategies is to mediate antitumor efficacy or reduce side effects. New combinations of PD1/PD-L1 antibodies with chemotherapy or other immune checkpoint inhibitors have been investigated as first-line treatments. However, the most efficacious of these therapeutic strategies in lung cancer is not known. We performed this meta-analysis to investigate potential treatment strategies using combinations of PD-1/PD-L1 inhibitors with chemotherapy or other CTLA4 inhibitors in the first-line setting for lung cancer patients.

The benefits of cytotoxic chemotherapy have reached a platform stage. The ORR is only approximately 20%, and the OS_{1y} ranges from 31-36%. These rates suggest considerable room for improvements in prognosis. Checkpoint inhibitors in combination with chemotherapy exhibited synergistic effects in preclinical and clinical studies. The combination strategy induced immunogenic cell death, inhibited immunosuppressive cells, non-specifically activated macrophages, up-regulated recognition molecules and enhanced the performance of antigen-presenting cells in the tumor microenvironment. Our results revealed an impressive efficacy of the combination of checkpoint inhibitors with chemotherapy as a first-line treatment, with tolerable side effects. There was a significant improvement in PFS but not in OS. Our subgroup analysis demonstrated no significant difference between chemotherapy regimens (gemcitabine and pemetrexed) in NSCLC. The pemetrexed subgroup was associated with a longer PFS in NSCLC. The Keynote-021 study resulted in FDA approval of pembrolizumab combined with a pemetrexed and carboplatin regimen as a first-line therapy for non-squamous cell lung cancer regardless of PD-L1 expression. However, there was no significant difference in OS between groups. Whether pembrolizumab and pemetrexed maintenance therapy improves survival benefits remains controversial. Therefore, further study is needed to verify the efficacy of the anti-PD-L1/PD1 and chemotherapy combination strategy in non-squamous cell lung cancer.

Notably, debates regarding the superiority of checkpoint inhibitors simultaneously or sequentially in combination with chemotherapy remain. Only one study investigated both concurrent ipilimumab
plus chemotherapy and phased ipilimumab plus chemotherapy in NSCLC. The results demonstrated that the phased ipilimumab group exhibited improved PFS compared to the control but not the concurrent ipilimumab group. In extensive-disease SCLC, the phased ipilimumab group still showed advantages in PFS, whereas the concurrent ipilimumab group did not. Therefore, checkpoint inhibitors sequentially in combination with a chemotherapy regimen deserves further exploration, and potential mechanisms must be elucidated.

Preclinical evidence has demonstrated that PD-1/PD-L1 antibodies and CTLA4 antibodies may be synergistically combined. The PD-1/PD-L1 and CTLA4 pathways use different but complementary mechanisms to modulate T-cell activation and proliferation. The PD-1/PD-L1 and CTLA4 antibodies combination down-regulates the function of immune-suppressive cells, including regulating T cells, to produce its dominant synergistic effects. However, unlike melanoma, the combined ORR and DCR of the combination of PD-1/PD-L1 and CTLA4 inhibitors were lower than the combination of PD-1/PD-L1 inhibitors with chemotherapy in NSCLC in our study. The combined ORR and DCR for double checkpoint inhibitors in NSCLC were 29.6% and 48.7%, respectively, which is superior to those for traditional chemotherapy. However, the superiority of double checkpoint inhibitor therapy compared with standard first-line chemotherapy in NSCLC requires further investigation.

A higher response rate to first-line chemotherapy treatment for SCLC patients was initially observed, but most SCLC patients exhibited chemoresistance in a short period of time, and the prognosis was poor. The PFS was approximately 6 months, and the median survival was shorter than 1 year. A whole-exon sequencing study demonstrated a high mutation rate (7.4 mut/Mb) in SCLC compared with other tumor types. SCLC may be a highly immunogenic tumor that may benefit from treatment with immune checkpoint inhibitors.

Therefore, checkpoint inhibitors are likely to improve the prognosis of advanced SCLC patients as a new treatment option. The combined ORR (65.4%) and DCR (87.6%) of the combination of CTLA4 antibody and chemotherapy in SCLC are promising. Unfortunately, the benefits of the ORR and the DCR did not transfer into survival benefits, including the PFSR (30.7%) and the OSR (36.9%). The superiority of the first-line combination of a checkpoint inhibitor, especially anti-PD1/PD-L1, and chemotherapy in SCLC requires more randomized, multi-center, and large sample studies to confirm. The only included study (CheckMate 032) investigated nivolumab plus ipilimumab in recurrent SCLC and revealed that the response rate and 2-year OS rate of nivolumab plus ipilimumab were superior to nivolumab. However, the response rate (21%) of double checkpoint inhibitor therapy is not satisfactory. New combinations with other therapeutic agents must be examined.

Although few studies were enrolled in our meta-analysis, this is the first meta-analysis to assess the efficacy and safety of the combination of PD-1/PD-L1 inhibitors with a CTLA4 inhibitor or chemotherapy as treatment strategies in lung cancer. We minimized the influence of heterogeneity using the random-effects model and performed exploratory subgroup analyses based on the type of chemotherapy regimen, pathological type and the combination strategy.

However, the present meta-analysis had several limitations. First, most of the studies had small sample
sizes because, to date, studies focusing on immune checkpoint inhibitors in combination with other agents are rare. Second, most of the research involved single-arm studies, and no randomization or blinding was used. Third, the random-effects model was used widely in our analysis, which may increase the effects of small samples with poor quality studies. Fourth, a potential impact of publication bias existed. Finally, individual participant data are the gold standard, but our study was limited to published literature, and selection bias was unavoidable. These limitations may have affected the final results.

The data in the present study are insufficient, but various trials are ongoing. The efficacy of pembrolizumab plus chemotherapy combination therapy and its relationship with PD-L1 expression is being evaluated in two ongoing phase III trials, including KEYNOTE-407 and KEYNOTE-189 (NCT02775435 and NCT02578680) 48. Several phase III randomization trials, including IMpower 132, IMpower 131 and IMpower 150 (NCT02657434, NCT02367794, and NCT02366143), are investigating the efficacy of first-line treatment with atezolizumab combined with chemotherapy for NSCLC 48. Combination therapy is a promising option and may become a new standard treatment. Phase III (NCT02279732 and NCT01285609) studies are ongoing to assess the efficacy of ipilimumab combined with first-line chemotherapy for advanced lung squamous cell carcinoma 48-50. The anti-tumor effect of PD-1/PD-L1 antibody plus CTLA4 antibody on NSCLC was sustained and effective. Numerous studies to evaluate the efficacy of double checkpoint inhibitors in lung cancer are ongoing, such as the NEPTUNE study and the CheckMate 227 study 48. These results will elucidate the efficacy of a first-line treatment of combined immunotherapy in advanced NSCLC. However, toxicity may limit the use of combination therapy in the entire population.

The recent results of the MYSTIC study were promulgated. The MYSTIC study was a randomized, open-label, international multicenter phase III study that compared the efficacy and safety of durvalumab single-agent or durvalumab (anti-PD-L1 antibody) plus tremelimumab (anti-CTLA4 antibody) with standard platinum-based chemotherapy in treatment-naïve metastatic NSCLC (stage IV) patients. However, this trial failed to achieve its primary endpoint. The Ventana PD-L1 (SP263) kit was used to detect PD-L1 expression in this study. Durvalumab combined with tremelimumab treatment did not prolong PFS compared with standard chemotherapy in patients with > 25% expression of PD-L1. OS data are not yet available. Whether PD-L1 expression is an ideal biomarker to predict the efficacy of anti-PD-L1 antibody is still in dispute. The optimal cutoff value for PD-L1 status is undefined. Therefore, identification of a specific biomarker for checkpoint inhibitor therapy remains a challenge.

A review of the included studies 22-24,29-35 revealed that single agent immunotherapy was relatively safe 51. However, toxicity increased, but remained tolerable, when immune checkpoint inhibitors and chemotherapy were combined.

Our meta-analysis suggests that combination treatment with PD-1/PD-L1 inhibitors plus chemotherapy or a CTLA4 inhibitor is an effective and tolerable option as a first-line treatment for lung cancer, especially NSCLC. Further prospective, multi-center, randomized control trials are urgently needed to validate our results. PD-L1 status should be considered in the design of future studies that examine immune checkpoint inhibitor combination therapies as a first-line treatment. The costs of these strategies together with patients’ quality of life should also be carefully evaluated.
References


Figure legends

Figure 1. Flowchart of the study selection procedure.

Figure 2. Forest plot of the combined overall response rate (ORR), disease control rate (DCR), six-month progression-free survival rate (PFSR_{6m}) or one-year overall survival rate (OSR_{1y}) of anti-PD-1/PD-L1 antibodies combined with chemotherapy or CTLA4 antibody as a first-line treatment for advanced lung cancer.

The pooled ORR for nine studies that provided at least one-arm data for anti-PD-1/PD-L1 antibodies combined with chemotherapy or CTLA4 antibody as a first-line treatment for advanced NSCLC. Among the nine studies, seven studies assessed anti-PD-1/PD-L1 antibodies combined with chemotherapy, and two studies assessed a double immunotherapy regimen (A). The pooled DCR for the nine studies is shown in (B). Five studies provided the PFSR_{6m} and the OSR_{1y}, and the pooled PFSR_{6m} and OSR_{1y} are shown in (C) and (D). All data were extracted from a single arm.

Figure 3. Forest plot of the combined overall response rate (ORR), disease control rate (DCR), six-month progression-free survival rate (PFSR_{6m}) or one-year overall survival rate (OSR_{1y}) of anti-PD-1/PD-L1 antibodies combined with chemotherapy or CTLA4 antibody as a first-line treatment for SCLC.

A total of three studies examined the efficacy of anti-PD-1/PD-L1 antibodies combined with chemotherapy or CTLA4 antibody in SCLC. The combined ORR (A) and DCR (B) were promising, but the combined PFSR_{6m} (C) and OSR_{1y} (D) were poor. All data were extracted from a single arm.

Figure 4. Forest plot of the combined progression-free survival (PFS) and overall survival (OS) of anti-PD-1/PD-L1 antibodies or CTLA4 antibodies combined with chemotherapy as a first-line treatment for lung cancer.

Five studies were randomized studies that provided an HR for PFS and OS. Three studies focused on NSCLC, and two studies focused on SCLC. Sub-group analysis was conducted according to pathological type. The checkpoint inhibitors combined with chemotherapy led to a significant improvement in PFS (A) but not OS (B) compared with chemotherapy in NSCLC and SCLC.
Table 1. Characteristics of the studies included in the meta-analysis.

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<th>Study types</th>
<th>Whether randomized</th>
<th>Number of patients</th>
<th>ORR (%)</th>
<th>DCR (%)</th>
<th>PFSR6m (%)</th>
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<th>Whether provided HR (95% CI) for PFS</th>
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<td>Randomized</td>
<td>70</td>
<td>21.4</td>
<td>57.1</td>
<td>35.7</td>
<td>28.2</td>
<td>0.88 (0.61-1.27)</td>
<td>0.99 (0.67-1.46)</td>
</tr>
<tr>
<td>Ramaswamy Govindan, 2017</td>
<td>USA</td>
<td>Ipilimumab+Chemo.</td>
<td>NSCLC</td>
<td>Phase 3</td>
<td>Randomized</td>
<td>478</td>
<td>62.1</td>
<td>88.3</td>
<td>42.0</td>
<td>40.0</td>
<td>0.87 (0.75-1.01)</td>
<td>0.91 (0.77-1.07)</td>
</tr>
<tr>
<td>Matthew D Hellmann, 2016</td>
<td>USA</td>
<td>Nivolumab+ipilimumab</td>
<td>NSCLC</td>
<td>Phase 1</td>
<td>Non-randomized</td>
<td>77</td>
<td>48.5</td>
<td>76.5</td>
<td>55.8</td>
<td>65.5</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Scott Antonia, 2016</td>
<td>USA</td>
<td>Durvalumab+tremelimumab</td>
<td>NSCLC</td>
<td>Phase 1b</td>
<td>Non-randomized</td>
<td>60</td>
<td>18.3</td>
<td>30.0</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Martin Reck, 2013</td>
<td>Germany</td>
<td>Ipilimumab+PC</td>
<td>SCLC</td>
<td>Phase 2</td>
<td>Randomized</td>
<td>43</td>
<td>32.5</td>
<td>69.7</td>
<td>37.2</td>
<td>39.5</td>
<td>0.93 (0.59-1.48)</td>
<td>0.95 (0.59-1.54)</td>
</tr>
<tr>
<td>Martin Reck, 2016</td>
<td>Germany</td>
<td>Ipilimumab+EP</td>
<td>SCLC</td>
<td>Phase 3</td>
<td>Randomized</td>
<td>478</td>
<td>62.1</td>
<td>88.3</td>
<td>27.6</td>
<td>36.6</td>
<td>0.85 (0.75-0.97)</td>
<td>0.94 (0.81-1.09)</td>
</tr>
<tr>
<td>Scott J Antonia, 2016</td>
<td>USA</td>
<td>Nivolumab plus ipilimumab</td>
<td>SCLC</td>
<td>Phase 1/2</td>
<td>Non-randomized</td>
<td>115</td>
<td>20.9</td>
<td>40.0</td>
<td>16.8</td>
<td>29.2</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Table 2. Incidence and ORR of summary toxicity endpoints, including 95% CI and number of trials in each analysis.

<table>
<thead>
<tr>
<th>Analyses</th>
<th>Number of study</th>
<th>Pooled ORR and 95% CI, model</th>
<th>Pooled DCR and 95% CI, model</th>
<th>Pooled PFSR6m and 95% CI, model</th>
<th>Pooled OSR1y and 95% CI, model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Checkpoint inhibitors + chemotherapy in NSCLC</td>
<td>7</td>
<td>47.0% (34.2%-60.2%), random</td>
<td>80.9% (69.4%-88.7%), random</td>
<td>50.2% (21.9%-78.4%), random</td>
<td>56.4% (39.1%-73.7%), random</td>
</tr>
<tr>
<td>Anti-PD-1/PD-L1 antibody + chemotherapy in NSCLC</td>
<td>4</td>
<td>53.3% (44.5%-61.8%), random</td>
<td>78.2% (60.5%-89.4%), random</td>
<td>63.5% (43.2%-83.7%), random</td>
<td>69.1% (52.8%-85.4%), random</td>
</tr>
<tr>
<td>Anti-PD-1/PD-L1 antibody + CTLA4 in NSCLC</td>
<td>2</td>
<td>29.6% (11.4%-57.8%), random</td>
<td>48.7% (16.8%-81.7%), random</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Anti-CTLA4 antibody + chemotherapy in NSCLC</td>
<td>3</td>
<td>36.3% (12.2%-69.9%), random</td>
<td>87.5% (84.4%-90.1%), fixed</td>
<td>30.7% (23.6%-37.8%), random</td>
<td>40.4% (36.3%-44.5%), fixed</td>
</tr>
<tr>
<td>Treatment Type</td>
<td>ORR</td>
<td>DC</td>
<td>ORR</td>
<td>DC</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>--------------------</td>
<td>-------------------</td>
<td>--------------------</td>
<td>-------------------</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy based on gemcitabine in NSCLC</td>
<td>41.3% (21.0%-65.1%), fixed</td>
<td>88.3% (63.2%-97.1%), fixed</td>
<td>49.2% (23.8%-74.5%), fixed</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy based on pemetrexed in NSCLC</td>
<td>41.7% (28.9%-55.8%), fixed</td>
<td>78.2% (63.8%-87.9%), fixed</td>
<td>55.0% (31.0%-79.0%), random</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Anti-CTLA4 antibody + chemotherapy in SCLC</td>
<td>65.4% (61.1%-69.5%), fixed</td>
<td>87.6% (84.5%-90.2%), fixed</td>
<td>30.7% (21.2%-40.3%), random</td>
<td>36.9% (33.3%-40.5%), fixed</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Not available, NA; Overall response rate, ORR; Disease control rate, DC; Confidence interval, CI.
Figure 1. Flowchart of the study selection procedure.

227x297mm (96 x 96 DPI)
Figure 2. Forest plot of the combined overall response rate (ORR), disease control rate (DCR), six-month progression-free survival rate (PFSR6m) or one-year overall survival rate (OSR1y) of anti-PD-1/PD-L1 antibodies combined with chemotherapy or CTLA4 antibody as a first-line treatment for advanced lung cancer.

The pooled ORR for nine studies that provided at least one-arm data for anti-PD-1/PD-L1 antibodies combined with chemotherapy or CTLA4 antibody as a first-line treatment for advanced NSCLC. Among the nine studies, seven studies assessed anti-PD-1/PD-L1 antibodies combined with chemotherapy, and two studies assessed a double immunotherapy regimen (A). The pooled DCR for the nine studies is shown in (B). Five studies provided the PFSR6m and the OSR1y, and the pooled PFSR6m and OSR1y are shown in (C) and (D). All data were extracted from a single arm.
Figure 3. Forest plot of the combined overall response rate (ORR), disease control rate (DCR), six-month progression-free survival rate (PFSR6m) or one-year overall survival rate (OSR1y) of anti-PD-1/PD-L1 antibodies combined with chemotherapy or CTLA4 antibody as a first-line treatment for SCLC.

A total of three studies examined the efficacy of anti-PD-1/PD-L1 antibodies combined with chemotherapy or CTLA4 antibody in SCLC. The combined ORR (A) and DCR (B) were promising, but the combined PFSR6m (C) and OSR1y (D) were poor. All data were extracted from a single arm.
Five studies were randomized studies that provided an HR for PFS and OS. Three studies focused on NSCLC, and two studies focused on SCLC. Sub-group analysis was conducted according to pathological type. The checkpoint inhibitors combined with chemotherapy led to a significant improvement in PFS (A) but not OS (B) compared with chemotherapy in NSCLC and SCLC.