Subgroup-Level Network Meta-Analysis for the Efficacy of First-Line Immunotherapy-Based Treatments in Advanced Non-Small Cell Lung Cancer

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Abstract

Background

Immunotherapy has unequal efficacies in different populations. This study aims to explore inter-subgroup differences in responses to immunotherapy in patients with advanced non-small cell lung cancer (NSCLC) and find the optimal treatments for each subgroup.

Methods

We performed (network) meta-analyses of phase III random controlled trials, in which efficacies of 10 immunotherapy-based treatments were compared with each other and chemotherapy, including anti-programmed death receptor-1 (PD-1) (+chemotherapy), anti-programmed death ligand-1 (PD-L1) (+chemotherapy), anti-PD-L1+anti-cytotoxic T-lymphocyte protein 4 (CTLA-4), anti-PD-1+anti-CTLA-4 (+chemotherapy), anti-CTLA-4+chemotherapy, anti-PD-1+anti-angiogenic therapy (AT)+chemotherapy, and anti-PD-L1+AT+chemotherapy, for 19 subgroups by sex, age, smoking status, metastatic site, histological type, and PD-L1 expression, using subgroup-level hazard ratios (HRs) for overall survival (OS) and progression-free survival (PFS) and their 95% confidence intervals (CIs).

Results

22 studies comprised of 12678 patients were included in our analyses. The results showed survival advantages of immunotherapy-based treatments in 16 out of 19 subgroups comparing with chemotherapy. In patients with PD-L1 tumor proportion score (TPS)<1%, anti-CTLA-4+anti-PD-1 and anti-PD-1+anti-CTLA-4+chemotherapy had OS benefits comparing with anti-PD-L1 monotherapy (HR 0.6, 95% CI 0.44-0.81; HR 0.6, 95% CI 0.41-0.87; respectively) and anti-PD-L1+AT+chemotherapy (HR 0.66, 95% CI 0.48-0.92; HR 0.66, 95% CI 0.45-0.98; respectively). In patients with liver metastases, anti-PD-L1+AT+chemotherapy showed PFS advantage comparing with anti-PD-L1+chemotherapy (HR 0.51, 95% CI 0.33-0.77). As for other populations, anti-PD-1+chemotherapy showed promising efficacies in multiple subgroups.

Conclusions

Patients with advanced NSCLC generally benefit from immunotherapy. Specific immunotherapy treatments should be applied according to different clinical or histological features. Meanwhile, we expect more studies to investigate treatments for populations with impaired responses towards immunotherapy.

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide.[1] Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer, and more than half of the cases are diagnosed at a late stage with the unresectable situation.[2] Platinum-based chemotherapy used to be the standard first-line treatment for driver gene-negative advanced NSCLC, whose efficacy was generally limited, and the 5-year overall survival (OS) of NSCLC patients remained poor.[3] Immunotherapy has signaled a new direction in the treatment of advanced NSCLC, with several trials showing significant advantages of immunotherapy in both first-line and subsequent-line treatments compared with chemotherapy.[4] Programmed death receptor-1 (PD-1)/programmed death ligand-1 (PD-L1) and cytotoxic T-lymphocyte protein 4 (CTLA-4) pathways play essential roles in immune escape.[5]

Various clinical and histological factors, including sex, age, smoking status, metastatic site, histological type, and PD-L1 expression could affect the response towards immunotherapy. A meta-analysis including 8 types of malignant tumors reported that males had a better efficacy from immunotherapy than females do.[6] Aging is accompanied by immune senescence and exhaustion of T cells, which could impair the efficacy of immunotherapy.[7] Smoking is associated with a high tumor mutation burden, so smokers tend to have better responses towards immunotherapy.[8] Metastases, such as liver metastases, brain metastases, and bone metastases, are associated with the poor prognosis of patients with NSCLC. There is a lack of filtration and activation of CD8⁺ T cells in the liver metastatic tumor, which can also further induce peripheral immune tolerance.[9] Brain metastases compromise the blood-brain barrier, which encourages the infiltration of immunosuppressive cells.[10] High levels of immunosuppressive cells, such as regulatory T cells and myeloid-derived suppressor cells, along with immunosuppressive cytokines in bone marrow could result in an immunosuppressive microenvironment. [11] There are more abundant CD8⁺ tumor-infiltrating lymphocytes in squamous tumors than those in non-squamous tumors, so patients with squamous tumors may have better responses to immunotherapy.[12] The level of PD-L1 expression is often used to predict the outcome of anti-PD-1/PD-L1 treatments, and there is a positive dose-response relationship between PD-L1 expression and survival benefits.[13] Although massive pre-clinical and clinical evidence has pointed out that significant heterogeneities are likely to exist among different populations, it still lacks a comprehensive meta-analysis to give the latest clinical evidence.

Given the complexity of the tumor immune microenvironment, and the distinct tolerances to chemotherapy or immunotherapy drugs among different populations, the efficacies of immunotherapy or immunotherapy combination therapy for different populations are unequal. This network meta-analysis (NMA) aims to compare the efficacy of 10 kinds of immunotherapy-based treatments, which are anti-PD-1 (with/without chemotherapy), anti-PD-L1 (with/without chemotherapy), anti-PD-L1+anti-CTLA-4, anti-PD-1+anti-CTLA-4 (with/without chemotherapy), anti-CTLA-4+chemotherapy, anti-PD-1+anti-angiogenic therapy (AT)+chemotherapy, anti-PD-L1+AT+chemotherapy, for 19 subgroups by sex, age, smoking status, metastatic site, histological type, and PD-L1 expression, with each other and chemotherapy, to find optimal treatments for each population.

Methods

This NMA is performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA-NMA) (Table S1).[14]

Search strategy

We searched PubMed, Embase, and the Cochrane databases for eligible randomized controlled trials published from the inception of each database to Aug 9, 2020. The search terms included "PD-1", "CTLA-4", "PD-L1", "immune checkpoint inhibitor", "ipilimumab", "tremelimumab", "nivolumab", "pembrolizumab", "atezolizumab", "durvalumab", "sintilimab", and "camrelizumab". The detailed search strategy is presented in supplementary Table S1. We used the Cochrane highly sensitive search strategies for identifying RCTs in PubMed and Embase (Table S1). We also reviewed abstracts and presentations from major conference proceedings, including the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the World Conference on Lung Cancer (WCLC) from 2015 to 2020.

Study selection

We included phase III randomized controlled trials (RCTs) that meet the following criteria:

Trials that enrolled adult patients with stage III/IV/recurrent NSCLC

Trials in which immunotherapy is applied in at least one of the arms

Trials that reported the hazard ratio (HR) of progression-free survival (PFS) or overall survival (OS) on at least one of the following subgroups: (1) sex: male and female; (2) smoking status: smoker (former/current smoker) and never-smoker; (3) age: patients aged 65 and over, patients aged 75 and over, and patients aged under 65; (4) histological type: squamous cancer and non-squamous cancer; (5) metastases: patients with/without liver/brain/bone metastases; (6) PD-L1 expression: TPS<1%, TPS≥1%, TPS 1%-49%, TPS≥50%.

Studies that did not meet the inclusion criteria were excluded. Meanwhile, other exclusion criteria were as follows:

Studies whose results of subgroups are not sufficient for this NMA.

Trials in which immunotherapy was used as a subsequent treatment after other therapies.

Trials that assess the efficacy of immunotherapy for subsequent-line treatment.

The process of study selection is shown in Figure 1. Two independent investigators (WT and YC) screened the full text of the included articles, and disagreements were resolved with the consensus of all investigators.

Data extraction

Two investigators (WT and YC) independently extracted the following details from every included study: study name, publication year, publication source, treatment, and treatment type of the experimental arm(s) and the control arm, treatment line, histological type, and cancer stage (Table 1). To get complete survival data of the studies, we reviewed each trial's supplement. The primary variables of interest were HRs with 95% confidence intervals (CIs) for OS or PFS in the following subgroups: (1) sex: male and female; (2) smoking status: smoker (former/current smoker) and never-smoker; (3) age: patients aged 65 and over, patients aged 75 and over, and patients aged under 65; (4) histological type: squamous cancer and non-squamous cancer; (5) metastases: patients with/without liver/brain/bone metastases; (6) PD-L1 expression: TPS<1%, TPS≥1%, TPS 1%-49%, TPS≥50%.

Table 1
Baseline characteristics of the included first-line phase III trials.

No.	Study	Year	Treatment				Histological Type	Cancer Stage
			Experimental Arm		Control Arm			
			Treatment	Drugs	Treatment	Chemotherapy Drugs		
1	CA184-104[28]	2017	Anti-CTLA-4+chemo	Ipi+Pac+Car	chemo	Pac+Car	sq.	IV / recurrent
2	CheckMate 227-Part 1[29]	2019	Anti-PD-1+chemo	Nivo+(Pem+Cis/Car or Gem+Cis/Car)	chemo	Pem+Cis/Car or Gem+Cis/Car	sq. & non-sq.	IV / recurrent
			Anti-CTLA-4+Anti-PD-1	Nivo+Ipi				
3	CheckMate 227-Part 2[30]	2020	Anti-PD-1+chemo	Nivo+(Pem+Cis/Car or Gem+Cis/Car)	chemo	Pem+Cis/Car or Gem+Cis/Car	sq. & non-sq.	IV / recurrent
4	CheckMate 9LA[31]	2020	Anti-PD-1+Anti-CTLA-4+chemo	Nivo+Ipi+chemo	chemo	Pem	sq. & non-sq.	IV / recurrent
5	CheckMate 026[32]	2017	Anti-PD-1	Nivo	chemo	Platinum-based doublet chemotherapy	sq. & non-sq.	IV / recurrent
6	IMPower110[33]	2019	Anti-PD-L1	Atezo	chemo	Pem+Cis/Car or Gem+Cis/Car	sq. & non-sq.	IV
7	IMpower130[34]	2019	Anti-PD-L1+chemo	Atezo+Car+nab-Pac	chemo	Car+nab-Pac	non-sq.	IV
8	IMpower131[35]	2020	Anti-PD-L1+chemo	Atezo+Car+nab-Pac	chemo	Car+nab-Pac	sq.	IV
9	IMpower132[36]	2018	Anti-PD-L1+chemo	Atezo+Car+Pem	chemo	Car+Pem	non-sq.	IV
10	IMpower150[37]	2018	Anti-PD-L1+AT+chemo	Atezo+Bevacizumab+Car+Pac	chemo	Bevacizumab+Car+Pac	non-sq.	IV / recurrent
			Anti-PD-L1+chemo	Atezo+Car+Pac				
11	EMPOWER-Lung 1[38]	2020	Anti-PD-1	Cemiplimab	chemo	platium-doublet chemotherapy	sq. & non-sq.	IIIB/ IV
12	TASUKI-52[39]	2020	Anti-PD-1+AT+chemo	Nivo+Bevacizumab+Car+Pac	chemo	Bevacizumab+Car+Pac	non-sq.	IIIB/ IV
13	KEYNOTE-024[40]	2016	Anti-PD-1	Pembro	chemo	Pem+Cis/Car or Gem+Cis/Car or Car+Pac	sq. & non-sq.	IV
14	KEYNOTE-407[41]	2018	Anti-PD-1+chemo	Pembro+Car+Pac/nab-Pac	chemo	Car+Pac/nab-Pac	sq.	IV
15	KEYNOTE-042[42]	2019	Anti-PD-1	Pembro	chemo	Car+Pac/Pem	sq. & non-sq.	III / IV
16	KEYNOTE-189[43, 44]	2018	Anti-PD-1+chemo	Pembro+Cis/Car	chemo	Pem+Cis/Car	non-sq.	IV
17	MYSTIC[45]	2020	Anti-PD-L1	Durva	chemo	Pem/Gem+Car	sq. & non-sq.	IV
			Anti-PD-L1+Anti-CTLA-4	Durva+Treme				
18	RATIONALE 304[46]	2020	Anti-PD-1+chemo	Tisle+Pem+Cis/Carbo	chemo	Pem+Cis/Carbo	non-sq.	IIIB/ IV
19	RATIONALE 307[47]	2020	Anti-PD-1+chemo	Tisle+Pac+Car	chemo	Pac+Car	sq.	IIIB / IV
			Anti-PD-1+chemo	Tisle+nab-Pac+Car				
20	Camel[48]	2020	Anti-PD-1+chemo	Camre +Car+Pem	chemo	Car+Pem	non-sq.	IIIB / IV

Abbr. Pac, paclitaxel; nab-Pac, nab-paclitaxel; Doc, docetaxel; Cis, cisplatin; Car, carboplatin; Pem, pemetrexed; Gem, gemcitabine; Ipi, ipilimumab; Nivo, nivolumab; Pembro, pembrolizumab; Durva, durvalumab; Treme, tremelimumab; Atezo, atezolizumab; Tisle, tislelizumab; Camre, camrelizumab; Sinti, sintilimab; sq., squamous cancer; non-sq., non-squamous cancer.

No.	Study	Year	Treatment				Histological Type	Cancer Stage
			Experimental Arm		Control Arm			
			Treatment	Drugs	Treatment	Chemotherapy Drugs		
21	Orient-11[49]	2020	Anti-PD-1+chemo	Sinti+Pem+Cis/Car	chemo	Pem+Cis/Car	non-sq.	IIIB/ IV
22	Orient-12[50]	2020	Anti-PD-1+chemo	Sinti+Pem+Cis/Car	chemo	Pem+Cis/Car	sq.	IIIB/IV
Abbr. <i>Pac</i> , paclitaxel; <i>nab-Pac</i> , nab-paclitaxel; <i>Doc</i> , docetaxel; <i>Cis</i> , cisplatin; <i>Car</i> , carboplatin; <i>Pem</i> , pemetrexed; <i>Gem</i> , gemcitabine; <i>Ipi</i> , ipilimumab; <i>Nivo</i> , nivolumab; <i>Pembro</i> , pembrolizumab; <i>Durva</i> , durvalumab; <i>Treme</i> , tremelimumab; <i>Atezo</i> , atezolizumab; <i>Tisle</i> , tislelizumab; <i>Camre</i> , camrelizumab; <i>Sinti</i> , sintilimab; <i>sq.</i> , squamous cancer; <i>non-sq.</i> , non-squamous cancer.								

Assessment of risk of bias

We used the Cochrane Risk of Bias Tool to assess the risk of bias of each study. The assessment was based on random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. The risks of bias were classified as low risk, unclear risk, or high risk (Supplementary Figure S1). Disputes of the investigators were solved through discussion.

Statistical Analysis

HRs with their corresponding 95% CIs were used to measure the relative efficacy. R software was used to analyze and process the data.

We performed meta-analyses and calculated pooled HRs for OS and PFS in the subgroups using the “meta” R package. Between-study heterogeneity was estimated using the χ^2 -based Q test. We regarded that significant heterogeneity existed when $P < 0.1$ or $I^2 > 50\%$. If there was significant heterogeneity, a random-effect model was used to calculate the pooled HR. And if there was no significant heterogeneity, a fixed-effect model was used. We performed sensitivity analyses to assess the stability of results by sequential omission of individual studies. We also evaluated publication bias by the Egger’s tests. The between-subgroup heterogeneity was also assessed by χ^2 -based Q test to give $P_{\text{heterogeneity}}$. When the $P_{\text{heterogeneity}} < 0.1$, we consider that significant heterogeneity exists between or among the subgroups.

Studies that used the same therapies were combined using traditional pairwise meta-analyses. Then the “gemtc” R package was used to perform an NMA comparing multiple therapies in a Bayesian fixed-effect model. JAGS in R was recalled for Markov chain Monte Carlo (MCMC) sampling. 200000 simulations were generated for each set of different initial values, and the first 5000 were discarded as burn-in period. The convergence of the analyses was then checked using Brooks-Gelman-Rubin diagnostic and trace plots.

Sensitivity analyses by omitting each study sequentially were performed to test the robustness of the analyses. Besides, the surface under the cumulative ranking area (SUCRA) was used to obtain the ranking probabilities for the therapies. The node-splitting method was used to test the inconsistency between direct and indirect calculations. This method separates direct and indirect evidence related to the same comparison and reports inconsistencies using P values. I^2 test was then used to evaluate the heterogeneity, with an I^2 larger than 50% indicating the existence of significant heterogeneity.

Results

Study selection and baseline characteristics

We identified a total of 3676 relevant records through database searching and conference abstract screening, in which 22 studies comprised of 12678 patients were considered suitable for the analyses after title/abstract screening and full-text screening (Figure 1). The baseline characteristics of all 22 studies with 25 immunotherapy-based treatments are listed in Table 1. Of the 22 studies, 4 studies evaluated the efficacy of anti-PD-1 monotherapy, 2 study of anti-PD-L1 monotherapy, 9 studies of anti-PD-1+chemotherapy, 4 studies of anti-PD-L1+chemotherapy, 1 study of anti-PD-1+AT+chemotherapy, 1 study of anti-PD-L1+AT+chemotherapy, 1 study of anti-PD-1+anti-CTLA-4, 1 study of anti-PD-L1+anti-CTLA-4, 1 study of anti-PD-1+anti-CTLA-4+chemotherapy, 1 study of anti-CTLA-4+chemotherapy. Treatment in control arms of all included studies is chemotherapy based on histology of NSCLC. The network structure of each subgroup is presented in Figure 2 and Figure S2. Subgroups of age ≥ 75 , PD-L1 TPS 1%-49%, and PD-L1 $\geq 50\%$ were not analyzed in the NMA section due to lacks of subgroup-level data in some studies.

Immunotherapy-based treatment vs chemotherapy

Figure 3 shows the pooled HRs of immunotherapy-based treatments vs chemotherapy for OS and PFS in 19 different subgroups, among which all the comparisons revealed significant advantages for OS or PFS of immunotherapy-based treatments comparing with chemotherapy, except OS (HR 0.81, 95% CI 0.55-1.18) and PFS (HR 0.73, 95% CI 0.51-1.07) in never-smokers, OS in ≥ 75 -year-old patients (HR 0.9, 95% CI 0.71-1.13), and OS in patients with liver metastases (HR 0.88, 95% CI 0.77-1). Inter-subgroup χ^2 -based Q test suggests that significant heterogeneities of OS in responses to immunotherapy-based therapy ($P_{\text{heterogeneity}} < 0.1$) exist in < 65 -year-old patients comparing with ≥ 75 -year-old patients ($P_{\text{heterogeneity}} = 0.07$), patients with PD-L1 TPS $\geq 50\%$ compared

with those with PD-L1 TPS<1% ($P_{\text{heterogeneity}} < 0.01$), patients with brain metastases compared with patients without brain metastases ($P_{\text{heterogeneity}} < 0.01$), patients without liver metastases comparing with patients with liver metastases ($P_{\text{heterogeneity}} < 0.01$). While significant heterogeneities of PFS in responses to immunotherapy-based therapy exist in patients with PD-L1 TPS $\geq$ 1% ($P_{\text{heterogeneity}} < 0.01$), PD-L1 TPS 1%-49% ($P_{\text{heterogeneity}} < 0.01$), and PD-L1 TPS $\geq$ 50% ($P_{\text{heterogeneity}} < 0.01$) comparing with those with PD-L1 TPS<1%, and patient without liver metastases ($P_{\text{heterogeneity}} = 0.044$) comparing with those with liver metastases. See Figure S4 for detailed information of meta-analysis in each subgroup.

NMA in subgroups by sex

The OS-NMA and PFS-NMA in subgroups by sex included data from 9 studies, respectively (Table S3 & S4). We present the results in Figure S3.

In males, immunotherapy-based treatments showed significant OS (HR 0.77, 95% CI 0.71-0.84) and PFS (HR 0.59, 95% CI 0.5-0.7) benefits compared with chemotherapy in general (Figure 3). Most immunotherapy-based therapies, including anti-CTLA-4+anti-PD-1 (HR 0.75, 95% CI 0.61-0.93), anti-PD-1 (HR 0.79, 95% CI 0.65-0.96), anti-PD-1+anti-CTLA-4+chemotherapy (HR 0.66, 95% CI 0.52-0.84), and anti-PD-1+chemotherapy (HR 0.73, 95% CI 0.62-0.88), had significant OS advantages comparing with chemotherapy. And all the immunotherapy-based therapies, including anti-PD-1 (HR 0.66, 95% CI 0.57-0.77), anti-PD-1+AT+chemotherapy (HR 0.53, 95% CI 0.41-0.69), anti-PD-1+chemotherapy (HR 0.57, 95% CI 0.49-0.65), and anti-PD-L1+chemotherapy (HR 0.67, 95% CI 0.53-0.84), had PFS advantages comparing with chemotherapy.

In females, immunotherapy-based treatments showed both significant OS (HR 0.7, 95% CI 0.52-0.94) and PFS (HR 0.68, 95% CI 0.51-0.89) benefits compared with chemotherapy generally (Figure 3). Anti-PD-1+chemotherapy and anti-PD-L1+chemotherapy had significant OS advantage (chemotherapy vs anti-PD-1+chemotherapy, HR 1.98, 95% CI 1.53-2.57; chemotherapy vs anti-PD-L1+chemotherapy, HR 1.51, 95% CI 1.07-2.16) and PFS advantage (chemotherapy vs anti-PD-1+chemotherapy, HR 2.04, 95% CI 1.64-2.55; chemotherapy vs anti-PD-L1+chemotherapy, HR 1.69, 95% CI 1.28-2.23) comparing with chemotherapy. Anti-PD-1+chemotherapy and anti-PD-L1+chemotherapy had OS advantage (HR 0.46, 95% CI 0.31-0.71; HR 0.61, 95% CI 0.37-0.99; respectively) and PFS advantage (HR 0.47, 95% CI 0.34-0.66; HR 0.57, 95% CI 0.4-0.83; respectively) comparing with anti-PD-1 monotherapy. Anti-PD-1+chemotherapy also had OS advantage (HR 0.55, 95% CI 0.38-0.81) comparing with anti-CTLA-4+anti-PD-1.

NMA in subgroups by age

The OS-NMA and PFS-NMA in subgroups by age included data from 14 and 13 studies, respectively (Table S8&S9). We present the results in Figure 4.

In <65-year-old patients, immunotherapy-based treatments showed significant OS (HR 0.73, 95% CI 0.65-0.82) and PFS (HR 0.62, 95% CI 0.54-0.71) benefits compared with chemotherapy generally (Figure 3). Anti-CTLA-4+anti-PD-1 (HR 0.7, 95% CI 0.55-0.89), anti-PD-1 monotherapy (HR 0.85, 95% CI 0.74-0.99), anti-PD-1+anti-CTLA-4+chemotherapy (HR 0.61, 95% CI 0.47-0.8), anti-PD-1+chemotherapy (HR 0.6, 95% CI 0.5-0.73), and anti-PD-L1+chemotherapy (HR 0.75, 95% CI 0.64-0.88) showed significant OS advantages comparing with chemotherapy, while anti-CTLA-4+chemotherapy (HR 0.82, 95% CI 0.64-1.05) and anti-PD-L1 monotherapy (HR 0.77, 95% CI 0.57-1.04) did not show significant OS benefits comparing with chemotherapy. All the immunotherapy-based treatments, including anti-CTLA-4+anti-PD-1 (HR 0.7, 95% CI 0.55-0.89), anti-PD-1 monotherapy (HR 0.75, 95% CI 0.63-0.89), anti-PD-1+AT+chemotherapy (HR 0.5, 95% CI 0.36-0.7), anti-PD-1+chemotherapy (HR 0.5, 95% CI 0.42-0.6), anti-PD-L1+AT+chemotherapy (HR 0.65, 95% CI 0.51-0.82), and anti-PD-L1+chemotherapy (HR 0.68, 95% CI 0.59-0.78) showed significant PFS advantages comparing with chemotherapy. Anti-PD-1+chemotherapy had significant PFS advantage comparing with anti-PD-L1+chemotherapy (HR 0.74, 95% CI 0.59-0.92). Anti-PD-1 monotherapy had inferior OS benefits to anti-PD-1+anti-CTLA-4+chemotherapy (HR 1.4, 95% CI 1.04-1.9) and anti-PD-1+chemotherapy (HR 1.42, 95% CI 1.12-1.8), as well as inferior PFS benefits to anti-PD-1+AT+chemotherapy (HR 1.49, 95% CI 1.02-2.19) and anti-PD-1+chemotherapy (HR 1.49, 95% CI 1.17-1.9). Anti-CTLA-4+chemotherapy (OS-HR 1.36, 95% CI 1-1.85) and anti-CTLA-4+anti-PD-1 (PFS-HR 1.4, 95% CI 1.04-1.88) also showed survival disadvantages comparing with anti-PD-1+chemotherapy, respectively.

In $\geq$ 65-year-old patients, immunotherapy-based treatments showed significant OS (HR 0.8, 95% CI 0.74-0.86) and PFS (HR 0.66, 95% CI 0.58-0.75) benefits compared with chemotherapy, but in $\geq$ 75-year-old patients, immunotherapy-based treatments showed non-significant OS benefit (HR 0.9, 95% CI 0.71-1.13) compared with chemotherapy (Figure 3). Chemotherapy showed OS disadvantages comparing with anti-PD-1 monotherapy (HR 1.2, 95% CI 1.02-1.4), anti-PD-1+anti-CTLA-4+chemotherapy (HR 1.37, 95% CI 1.04-1.81), anti-PD-1+chemotherapy (HR 1.29, 95% CI 1.07-1.55), anti-PD-L1 monotherapy (HR 1.51, 95% CI 1.1-2.07), and anti-PD-L1+chemotherapy (HR 1.41, 95% CI 1.21-1.66) and PFS disadvantages comparing with anti-PD-1 monotherapy (HR 1.27, 95% CI 1.06-1.53), anti-PD-1+AT+chemotherapy (HR 1.54, 95% CI 1.12-2.1), anti-PD-1+chemotherapy (HR 1.66, 95% CI 1.38-2.01), anti-PD-L1+AT+chemotherapy (HR 1.74, 95% CI 1.32-2.29), and anti-PD-L1+chemotherapy (HR 1.64, 95% CI 1.42-1.9). Anti-PD-L1 monotherapy (HR 0.65, 95% CI 0.44-0.97) and anti-PD-L1+chemotherapy (HR 0.7, 95% CI 0.53-0.93) had significant OS advantages comparing with anti-CTLA-4+chemotherapy. Anti-PD-1+chemotherapy (HR 0.66, 95% CI 0.49-0.89), anti-PD-L1+AT+chemotherapy (HR 0.63, 95% CI 0.44-0.91), and anti-PD-L1+chemotherapy (HR 0.67, 95% CI 0.51-0.88) had significant PFS advantages comparing with anti-CTLA-4+anti-PD-1. Anti-PD-L1+chemotherapy had significant PFS advantages comparing with anti-PD-1 monotherapy (HR 0.77, 95% CI 0.61-0.98).

NMA in subgroups by smoking status

The OS-NMA and PFS-NMA in subgroups by smoking status included data from 8 studies, respectively (Table S4&S5). We present the results in Figure S2.

In smokers, immunotherapy-based treatments have OS (HR 0.79, 95% CI 0.69-0.89) and PFS (HR 0.62, 95% CI 0.52-0.75) advantages generally compared with chemotherapy (Figure 3). Almost all the immunotherapy-based therapies, including anti-CTLA-4+anti-PD-1 (OS-HR 0.77, 95% CI 0.64-0.92), anti-CTLA-4+chemotherapy (OS-HR 0.88, 95% CI 0.8-0.97), anti-PD-1+anti-CTLA-4+chemotherapy (OS-HR 0.62, 95% CI 0.5-0.77), anti-PD-1+chemotherapy (OS-HR 0.63, 95% CI 0.53-0.77; PFS-HR 0.51, 95% CI 0.43-0.59), anti-PD-L1+chemotherapy (OS-HR 0.82, 95% CI 0.69-0.97; PFS-HR 0.63, 95% CI 0.55-0.72), and anti-PD-1+AT+chemotherapy (PFS-HR 0.56, 95% CI 0.44-0.72), had OS or PFS advantages comparing with chemotherapy. Anti-PD-1 monotherapy also showed OS disadvantages comparing with anti-PD-1+anti-CTLA-4+chemotherapy (HR 1.74, 95% CI 1.27-2.39), anti-PD-1+chemotherapy (HR 1.7, 95% CI 1.26-2.3), and anti-CTLA-4+ anti-PD-1 (anti-CTLA-4+ anti-PD-1 vs anti-PD-1, HR 0.71, 95% CI 0.53-0.96), and PFS disadvantages comparing with anti-PD-1+AT+chemo (HR 1.54, 95% CI 1.13-2.09), anti-PD-1+chemotherapy (HR 1.7, 95% CI 1.34-2.16), and anti-PD-L1+chemotherapy (HR 1.37, 95% CI 1.1-1.72).

In never-smokers, immunotherapy-based treatments showed non-significant OS (HR 0.81, 95% CI 0.55-1.18) and PFS (HR 0.73, 95% CI 0.51-1.07) benefits compared with chemotherapy in general (Figure 3). None of the included immunotherapy-based treatments provide significant OS benefit comparing with chemotherapy, and anti-PD-L1 showed significant OS advantage comparing with anti-CTLA-4+anti-PD-1 (HR 0.49, 95% CI 0.24-0.98). Anti-PD-1 monotherapy also showed PFS disadvantages when compared with anti-PD-1+AT+chemotherapy (HR 0.3, 95% CI 0.13-0.69), anti-PD-1+chemotherapy (HR 0.28, 95% CI 0.14-0.56), anti-PD-L1+chemotherapy (HR 0.24, 95% CI 0.11-0.51), and chemotherapy (HR 0.44, 95% CI 0.23-0.81). Chemotherapy had significant PFS disadvantages comparing with Anti-PD-1+chemotherapy (HR 1.56, 95% CI 1.17-2.08) and anti-PD-L1+chemotherapy (HR 1.81, 95% CI 1.2-2.7).

NMA in subgroups by metastatic site

The OS-NMA and PFS-NMA in subgroups by brain metastases included data from 5 studies, respectively. The OS-NMA and PFS-NMA in subgroups by liver metastases included data from 8 and 6 studies, respectively. The OS-NMA in subgroups by bone metastases included data from 3 studies (Table S12&S13). We present the results in Figure 5.

Generally, immunotherapy-based treatments showed OS and PFS benefits both in patients with brain metastases (OS-HR 0.52, 95% CI 0.36-0.76; PFS-HR 0.55, 95% CI 0.39-0.77) and in patients without brain metastases (OS-HR 0.75, 95% CI 0.68-0.82; PFS-HR 0.57, 95% CI 0.5-0.65) compared with chemotherapy (Figure 3). In patients with brain metastases, anti-PD-1+anti-CTLA-4+chemotherapy (HR 0.38, 95% CI 0.24-0.6) and anti-PD-1+chemotherapy (HR 0.58, 95% CI 0.39-0.86) provided significant OS benefits comparing with chemotherapy. Anti-PD-1 monotherapy (HR 0.51, 95% CI 0.3-0.85) provided significant PFS benefit comparing with chemotherapy. In patients without brain metastases, chemotherapy is significantly inferior to all the evaluated immunotherapy-based treatments, including anti-CTLA-4+anti-PD-1 (OS-HR 1.22, 95% CI 1.02-1.46), anti-PD-1 monotherapy (OS-HR 1.41, 95% CI 1.08-1.84; PFS-HR 1.41, 95% CI 1.24-1.6), anti-PD-1+anti-CTLA-4+chemotherapy (OS-HR 1.33, 95% CI 1.09-1.64), anti-PD-1+chemotherapy (OS-HR 1.43, 95% CI 1.2-1.69; PFS-HR 0.54, 95% CI 0.44-0.67), in terms of OS or PFS. Anti-PD-1+chemotherapy provided a significant PFS advantage comparing with anti-PD-1 alone (HR 0.76, 95% CI 0.6-0.98).

Immunotherapy-based treatments showed significant OS (HR 0.73, 95% CI 0.67-0.8) and PFS (HR 0.58, 95% CI 0.5-0.66) benefits in patients without liver metastases generally, but in patients with liver metastases, immunotherapy showed non-significant OS benefit (HR 0.88, 95% CI 0.77-1) compared with chemotherapy in general (Figure 3). In patients with liver metastases, anti-PD-1+chemotherapy and anti-PD-L1+AT+chemotherapy provided significant OS advantages comparing with anti-PD-L1+chemotherapy (HR 0.65, 95% CI 0.46-0.94; HR 0.65, 95% CI 0.45-0.95; respectively) and chemotherapy (HR 0.68, 95% CI 0.51-0.9; HR 0.68, 95% CI 0.47-0.99; respectively). Anti-PD-1+chemotherapy and anti-PD-L1+AT+chemotherapy also provided significant PFS advantages comparing with chemotherapy (HR 0.52, 95% CI 0.34-0.8; HR 0.41, 95% CI 0.27-0.62; respectively). Also, anti-PD-L1+AT+chemotherapy showed a significant PFS advantage comparing with anti-PD-L1+chemotherapy (HR 0.51, 95% CI 0.33-0.77). As for patients without liver metastases, chemotherapy provided significantly inferior benefits comparing with all the evaluated immunotherapy-based treatments, including anti-CTLA-4+anti-PD-1 (OS-HR 1.32, 95% CI 1.09-1.59), anti-PD-1+anti-CTLA-4+chemotherapy (OS-HR 1.56, 95% CI 1.22-2.01), anti-PD-1+chemotherapy (OS-HR 1.4, 95% CI 1.19-1.65; PFS-HR 2.08, 95% CI 1.69-2.56), and anti-PD-L1+chemotherapy (OS-HR 1.3, 95% CI 1.14-1.49; PFS-HR 1.64, 95% CI 1.47-1.83), in terms of OS or PFS.

In general, immunotherapy-based treatments showed significant OS benefits in both patients with bone metastases (HR 0.82, 95% CI 0.69-0.98) and patients without bone metastases (HR 0.75, 95% CI 0.66-0.85) (Figure 3). In patients with bone metastases, the 4 treatments, including anti-CTLA-4+anti-PD-1, anti-PD-1+anti-CTLA-4+chemotherapy, and anti-PD-1+chemotherapy, showed non-significant OS benefits with each other. However, in patients without bone metastases, chemotherapy showed significant OS disadvantages comparing with all the 3 immunotherapy-based treatments, including anti-CTLA-4+anti-PD-1 (HR 1.23, 95% CI 1.02-1.5), anti-PD-1+anti-CTLA-4+chemotherapy (HR 1.54, 95% CI 1.21-1.95), and anti-PD-1+chemotherapy (HR 1.32, 95% CI 1.04-1.67).

NMA in subgroups by histological type

The OS-NMA and PFS-NMA in subgroups of squamous and non-squamous cancer included data from 12 and 18 studies, respectively (Table S6&S7). We present the results in Figure S2.

Generally, immunotherapy-based treatments provided significant OS and PFS benefits both in patients with squamous tumor (OS-HR 0.74, 95% CI 0.64-0.85; PFS-HR 0.6, 95% CI 0.51-0.7) and patients with non-squamous tumor (OS-HR 0.79, 95% CI 0.68-0.93; PFS-HR 0.63, 95% CI 0.54-0.74) (Figure 3).

In terms of squamous cancer, anti-PD-1 (OS-HR 0.65, 95% CI 0.49-0.85; PFS-HR 0.58, 95% CI 0.46-0.72), anti-PD-1+chemotherapy (OS-HR 0.67, 95% CI 0.57-0.79; PFS-HR 0.53, 95% CI 0.47-0.72), anti-PD-1+anti-CTLA-4+chemotherapy (OS-HR 0.67, 95% CI 0.49-0.92), and anti-PD-L1+chemotherapy (PFS-HR 0.71, 95% CI 0.6-0.85) had OS or PFS advantages comparing with chemotherapy, while anti-CTLA-4+chemotherapy showed neither OS (HR 0.91, 95% CI 0.77-1.07) nor PFS (HR 0.87, 95% CI 0.75-1.01) advantage comparing with chemotherapy, and anti-PD-L1+chemotherapy did not show significant OS advantage (HR 0.88, 95% CI 0.73-1.06) comparing with chemotherapy. What's more, anti-PD-1+chemotherapy had significant OS (HR 0.76, 95% CI 0.59-0.98) and PFS (HR 0.75, 95% CI 0.6-0.93) advantage comparing with anti-PD-L1+chemotherapy. Anti-CTLA-4+chemotherapy showed inferior OS benefits to anti-PD-1 monotherapy (HR 1.41, 95% CI 1.02-1.95), anti-PD-1+anti-CTLA-4+chemotherapy (HR 1.47, 95% CI 1.02-2.13), and anti-PD-1+chemotherapy (HR 1.36, 95% CI 1.07-1.72), as well as inferior PFS benefits to anti-PD-1 monotherapy (HR 1.51, 95% CI 1.16-1.97) and anti-PD-1+chemotherapy (HR 1.64, 95% CI 1.35-1.99).

In terms of non-squamous cancer, chemotherapy showed OS disadvantages comparing with anti-PD-1+anti-CTLA-4+chemotherapy (HR 1.45, 95% CI 1.13-1.85), anti-PD-1+chemotherapy (HR 1.37, 95% CI 1.2-1.57), anti-PD-L1+chemotherapy (HR 1.24, 95% CI 1.06-1.46) and PFS disadvantages comparing with anti-PD-1 (HR 1.22, 95% CI 1.05-1.42), anti-PD-1+chemotherapy (HR 1.72, 95% CI 1.54-1.92), anti-PD-L1+chemotherapy (HR 1.6, 95% CI 1.41-1.82), and anti-PD-1+AT+chemotherapy (HR 1.79, 95% CI 1.39-2.3), while anti-PD-1 monotherapy did not show significant OS benefit comparing with chemotherapy (HR 0.97, 95% CI 0.79-1.19). Anti-PD-1 monotherapy showed inferior OS benefits when compared with anti-PD-1+anti-CTLA-4+chemotherapy (HR 0.67, 95% CI 0.49-0.92), anti-PD-1+chemotherapy (HR 0.71, 95% CI 0.55-0.9), as well as inferior PFS benefits when compared with anti-PD-1+chemotherapy (HR 0.71, 95% CI 0.59-0.85), anti-PD-L1+chemotherapy (HR 0.76, 95% CI 0.63-0.93), and anti-PD-1+AT+chemotherapy (HR 0.68, 95% CI 0.51-0.92).

Generally, immunotherapy-based treatments provided significant OS and PFS benefits both in patients with squamous tumor (OS-HR 0.74, 95% CI 0.64-0.85; PFS-HR 0.6, 95% CI 0.51-0.7) and patients with non-squamous tumor (OS-HR 0.79, 95% CI 0.68-0.93; PFS-HR 0.63, 95% CI 0.54-0.74) (Figure 3).

NMA in subgroups by PD-L1 expression

The OS-NMA and PFS-NMA in subgroups by PD-L1 expression included data from 9 and 11 studies, respectively (Table S10&S11). We present the results in Figure 6.

In general, immunotherapy-based treatments provided significant OS and PFS benefits in patients with various levels of PD-L1 expression (Figure 3). In patients with PD-L1 TPS<1%, anti-CTLA-4+anti-PD-1 (HR 0.62, 95% CI 0.49-0.79), anti-PD-1+anti-CTLA-4+chemotherapy (HR 0.62, 95% CI 0.45-0.85), anti-PD-1+chemotherapy (HR 0.69, 95% CI 0.56-0.85), and anti-PD-L1+anti-CTLA-4 (HR 0.68, 95% CI 0.49-0.94) showed significant OS advantages comparing with chemotherapy, and anti-CTLA-4+anti-PD-1 (HR 0.74, 95% CI 0.59-0.92), anti-PD-1+AT+chemotherapy (HR 0.55, 95% CI 0.38-0.79), anti-PD-1+chemotherapy (HR 0.71, 95% CI 0.62-0.82), anti-PD-L1+AT+chemotherapy (HR 0.77, 95% CI 0.6-0.98), and anti-PD-L1+chemotherapy (HR 0.7, 95% CI 0.6-0.81) showed PFS advantages comparing with chemotherapy. It is notable that anti-CTLA-4+anti-PD-1 and anti-PD-1+anti-CTLA-4+chemotherapy had significant OS benefit comparing with anti-PD-L1 monotherapy (HR 0.6, 95% CI 0.44-0.81; HR 0.6, 95% CI 0.41-0.87; respectively) and anti-PD-L1+AT+chemotherapy (HR 0.66, 95% CI 0.48-0.92; HR 0.66, 95% CI 0.45-0.98; respectively). Anti-PD-1+chemotherapy also showed significant OS advantage comparing with anti-PD-L1 monotherapy (HR 0.66, 95% CI 0.5-0.88).

In patients with PD-L1 TPS≥1%, chemotherapy presented with OS disadvantages comparing with anti-CTLA-4+anti-PD-1 (HR 1.27, 95% CI 1.04-1.54), anti-PD-1+anti-CTLA-4+chemotherapy (HR 1.56, 95% CI 1.22-2), anti-PD-1+chemotherapy (HR 1.51, 95% CI 1.27-1.81), anti-PD-L1 monotherapy (HR 1.23, 95% CI 1.06-1.43), anti-PD-L1+AT+chemotherapy (HR 1.27, 95% CI 1.02-1.6), along with PFS disadvantages comparing with anti-CTLA-4+anti-PD-1 (HR 1.61, 95% CI 1.14-2.28), anti-PD-1+AT+chemotherapy (HR 1.7, 95% CI 1.27-2.28), anti-PD-1+chemotherapy (HR 2.06, 95% CI 1.8-2.37), anti-PD-L1+AT+chemotherapy (HR 2, 95% CI 1.56-2.56), and anti-PD-L1+chemotherapy (HR 1.62, 95% CI 1.39-1.89). Anti-PD-L1+anti-CTLA-4 showed OS disadvantages comparing with anti-PD-1+anti-CTLA-4+chemotherapy (HR 1.52, 95% CI 1.12-2.06) and anti-PD-1+chemotherapy (HR 1.47, 95% CI 1.14-1.89). Anti-PD-L1+chemotherapy had inferior PFS benefit comparing with anti-PD-1+chemotherapy (HR 1.27, 95% CI 1.03-1.57).

Heterogeneity and inconsistency assessment

In the subgroup-level meta-analyses comparing immunological therapies with chemotherapy, heterogeneity assessments suggested minimal ($I^2=0$) or low ($I^2<50\%$) heterogeneities in half of the subgroups. However, significant heterogeneities ($I^2\geq 50\%$) were found in the following subgroups: <65-year-old patients for OS (55%), patients with brain metastases for OS (54%), females for OS (74%), never-smokers for OS (62%), patients with non-squamous tumors for OS (71%), patients with PD-L1 TPS≥1% for OS (52%), smokers for OS (67%), patients with squamous tumors for OS (51%), <65-year-old patients with for PFS (65%), ≥65-year-old patients with for PFS (56%), females for PFS (74%), males for PFS (71%), never-smokers for PFS (67%), patients with no liver metastases for PFS (50%), patients with non-squamous tumors for PFS (78%), smokers for PFS (76%), patients with squamous tumors for PFS (73%).

In the intra-subgroup network meta-analyses comparing the efficacies of various immunotherapy-based treatments, heterogeneity assessments suggested minimal ($I^2=0$) or low ($I^2<50\%$) heterogeneities in more than half of the comparisons, while significant heterogeneities were found in the following comparisons:

OS: chemotherapy vs anti-PD-1 (54.3%) and chemotherapy vs anti-PD-1+chemotherapy (75.2%) in <65-year-old patients, chemotherapy vs anti-PD-1 (52.6%) and chemotherapy vs Anti-PD-1+Anti-CTLA-4+chemotherapy (75.5%) in ≥65-year-old patients, chemotherapy vs anti-PD-1+chemotherapy (81.5%) in patients with brain metastases, anti-PD-1+chemotherapy (85.7%) in females, chemotherapy vs anti-PD-1 (78.5%) in males, chemotherapy vs anti-PD-1+chemotherapy (89.7%) in never-smokers, chemotherapy vs anti-PD-1+chemotherapy (79.8%) in patients with no brain metastases, chemotherapy vs anti-

PD-1+chemotherapy (79.1%) in patients with no liver metastases, chemotherapy vs anti-PD-1 (60.0%) and chemotherapy vs anti-PD-1+chemotherapy (87.6%) in patients with non-squamous tumors, chemotherapy vs anti-PD-1+chemotherapy (70.2%) in patients with PD-L1 TPS $\geq$ 1%, chemotherapy vs anti-PD-1+chemotherapy (59.1%) in smokers, chemotherapy vs anti-PD-1 (56.6%) in patients with squamous tumors.

PFS: chemotherapy vs anti-PD-1 (86.8%) in <65-year-old patients, chemotherapy vs anti-PD-1 (87.9%) in $\geq$ 65-year-old patients, chemotherapy vs anti-PD-1 (65.3%) in females, chemotherapy vs anti-PD-1 (90.3%) in males, chemotherapy vs anti-PD-1+chemotherapy (54.7%) in never-smokers, chemotherapy vs anti-PD-1 (84.9%) in patients with no brain metastases, chemotherapy vs anti-PD-1 (92.2%) in patients with non-squamous tumors, chemotherapy vs anti-PD-L1+chemotherapy (74.0%) in patients with PD-L1 TPS $\leq$ 1%, chemotherapy vs anti-PD-1 (82.5%) in smokers, chemotherapy vs anti-PD-1+chemotherapy in squamous tumors.

The inconsistency analyses were not available because there are no closed loops in the structures of all our NMAs, suggesting that there are no comparisons to assess for inconsistency.

Sensitivity analysis and assessment of publication bias

We conducted sensitivity analyses to assess the robustness of our results from the meta-analyses. As for the OS-meta-analysis conducted in patients with liver metastases, when CheckMate 227-Part1, Impower130, Impower131, or Impower150 was omitted, the pooled HRs showed a significant advantage of immunotherapy-based treatment. As for the PFS-meta-analysis conducted in never-smokers, when omitting CheckMate 026, the pooled HR showed a significant advantage of immunotherapy-based treatment. As for the PFS-meta-analysis conducted in $\geq$ 75-year-old patients, when omitting Impower 131, the HR became non-significant. The rest of the results were robust (Figure S6).

We assessed publication bias by the Egger's tests and found significant publication bias ($P<0.1$) in the following subgroups: no brain metastases for OS ($P=0.03$), PD-L1 TPS $\geq$ 1% for OS ($P=0.08$), squamous tumor for OS ($P=0.01$), never-smokers for OS ($P<0.01$), squamous tumor for PFS ($P=0.03$) (Figure S5).

Discussion

Various factors are associated with the efficacy of immunotherapy. The results of our subgroup-level meta-analyses show that immunotherapy-based treatments had better efficacies for patients with advanced NSCLC comparing with chemotherapy overall. Yet we have discovered indisposed efficacies in some subgroups, including never-smokers, patients aged over 75, and patients with liver metastases. The inter-subgroup comparisons suggest that significantly different efficacies may exist between different age groups (<65-year-old vs >75 -year-old), patients with different levels of PD-L1 expression ($\geq$ 1%, 1%-49%, vs $\geq$ 50%), patients without/with brain metastases, patients with/without liver metastases.

The network meta-analyses aim to explore the optimal strategy of immunotherapy for each subgroup. Our results suggest the following optimal treatment (or treatments) for the corresponding subgroup. Anti-PD-1+chemotherapy and anti-PD-1+anti-CTLA-4+chemotherapy provide the best OS for smokers. Anti-PD-1+chemotherapy provides the best PFS for patients with squamous cancer. Anti-PD-L1+AT+chemotherapy and PD-1+chemotherapy provide the best OS and Anti-PD-L1+AT+chemotherapy provides the best PFS for patients with liver metastases. What's more, we also noticed that adding chemotherapy to anti-PD-1/PD-L1 therapy could improve the efficacies in most subgroups.

Although a previous meta-analysis showed that males benefit more from immunotherapy than females do in patients with various types of cancer, our results do not support such heterogeneity between sexes in patients with NSCLC, and immunotherapy could improve OS and PFS for both male and female patients with NSCLC.[6] Aging is associated with changes in the immune system and therefore decreases the response towards immunotherapy.[15] A previous meta-analysis showed that improvements of OS and PFS are consistent between $\geq$ 65-year-old and <65-year-old-patients with various types of cancer.[16] Our results reveal significant heterogeneity of improvement in OS between $\geq$ 75-year-old and <65-year-old patients, yet the data of $\geq$ 75-year-old subgroup are rather insufficient, making this finding precarious. Smoking is associated with high tumor mutation burden in NSCLC, suggesting that smokers have better responses towards immunotherapy than never-smokers do, and indeed, our results show that never-smokers may not benefit from immunotherapy, while no significant heterogeneity of efficacy is found between smokers and never-smokers, which is consistent with the results from a previous meta-analysis.[17]

As regards patients with metastases, we found that patients with liver metastases have worse responses to immunotherapy compared with patients without liver metastases, and such difference does not exist between patients with/without brain metastases or bone metastases. Similar to our result, a meta-analysis comparing the efficacies of immunotherapy in patients with/without liver metastases revealed that patients with liver metastases received a relatively lower benefit.[18] The mechanism for impaired efficacy of immunotherapy in patients with liver metastases is complicated and not yet clarified. The unique composition and abundance of antigen-presenting cells create an immune microenvironment where T lymphocytes are activated poorly.[19] Liver metastases could reduce the infiltration of CD8⁺ T lymphocytes, and an increased proportion of monocyte-derived macrophages, which can induce the apoptosis of effector T cells.[9] Furthermore, liver-induced peripheral tolerance can also impair the efficacy of immunotherapy in patients with liver metastases.[20] Our results showed that anti-PD-L1+AT+chemotherapy could be the most ideal treatment so far for patients with liver metastases. The abundant immunosuppressive cells and molecules in bone marrow form an immunosuppressive tumor microenvironment, which could play a negative role in treatments with immunotherapy agents.[21] Although our result indicates no difference between patients with/without bone metastases in the OS benefit from immunotherapy-based treatments comparing with chemotherapy, the survival data in patients with/without bone metastases are limited, which comes from only 3 trials. And all the 3 treatments compared (anti-CTLA-4+anti-PD-1, anti-PD-1+anti-CTLA-4+chemotherapy, and anti-PD-1+chemotherapy) are consistent in the OS benefit compared with chemotherapy for both patients with and without bone metastases. Although our result suggests that

patients with brain metastases receive better OS benefit than those without brain metastases do, significant heterogeneity exists in the OS-HR data in patients with brain metastases from 5 studies, and data of patients with no brain metastases come from only 3 studies, making this estimate unconvincing. It's reported that NSCLC patients with brain metastases benefit equally as the overall population in terms of OS, suggesting that there are no differences in immunotherapy efficacy between patients with/without brain metastases.[22] Our result suggests that anti-PD-1+chemotherapy and anti-PD-1+anti-CTLA-4+chemotherapy may be the best treatments for patients with brain metastases.

Despite the differences in CD8⁺ T lymphocyte infiltration between squamous tumor and non-squamous tumor,[12] our results suggest that the survival benefits towards immunotherapy are consistent in patients with squamous and non-squamous cancer. The anti-PD-1 monoclonal antibodies block the interaction between PD-1 and PD-L1/PD-L2, thus prevent the immune escape of tumor cells. Therefore, the level of PD-L1 expression has been used as an indicator to predict the efficacy of anti-PD-1/PD-L1 therapy. A meta-analysis evaluating the efficacy of second-line immunotherapy in advanced NSCLC patients with different PD-L1 expression showed that the benefit from anti-PD-1+chemotherapy is limited to patients with PD-L1 TPS>1%.[23] However, based on our results, although there are significant differences of efficacy between patients with various levels of PD-L1 expression, patients with PD-L1 TPS<1% can also benefit from immunotherapy for first-line treatment. And anti-PD-1+anti-CTLA-4+(chemotherapy) could most possibly provide the best OS for these patients.

Anti-PD-1 antibodies can bind to PD-1 on the membrane of tumor cells and block the interaction between not only PD-1 and PD-L1 but also PD-1 and PD-L2, while anti-PD-L1 antibodies can only block the interaction between PD-1 and PD-L1, suggesting that anti-PD-1 therapy may be more effective than anti-PD-L1 therapy.[24] A meta-analysis comparing anti-PD-1 with anti-PD-L1 therapy in second-line treatment for patients with advanced NSCLC revealed that anti-PD-1 therapy was superior to anti-PD-L1 therapy.[25] Regarding our results, we have noticed similar OS or PFS advantages of anti-PD-1+chemotherapy comparing with anti-PD-L1+chemotherapy in smokers, squamous cancer, <65-year-old patients, and patients with liver metastases.

Chemotherapy can modulate tumor immunity by enhancing antigen presentation, increasing expression of costimulatory molecules, and downregulating PD-L1, suggesting a strong synergetic effect of combining immunotherapy and chemotherapy.[26] A meta-analysis comparing immunotherapy and immunotherapy+chemotherapy as first-line treatment in patients with advanced NSCLC revealed that the combination had enhanced efficacy than immunotherapy alone.[27] According to our results, anti-PD-1 monotherapy is generally inferior to most immunotherapy-based treatments in multiple subgroups.

Besides, this study has several limitations. First, although the overall number of studies is satisfactory, the data in some subgroups are not sufficient as the HR data of these subgroups in most included studies are unavailable, and the data of some treatments come from only one trial. Second, in most studies, immunotherapy-based treatments are directly compared with chemotherapy, making us unable to test the consistency of the direct and indirect comparisons. Third, moderate to high heterogeneities are detected in multiple comparisons as we mentioned above.

Conclusions

In this subgroup-level network meta-analysis evaluating the efficacy of first-line immunotherapy-based treatments in patients with advanced NSCLC, we notice that immunotherapy-based treatments are superior to chemotherapy in general, while there are populations where the efficacy is impaired, including never-smokers, ≥75-year-old patients, and patients with liver metastases. Besides, our results suggest adopting different immunotherapy-based treatments for people with different characteristics. Therefore, we expect that more pre-clinical and clinical studies focus on populations whose efficacy of immunotherapy is impaired. Our findings still need more verifications from clinical studies.

Declarations

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Ethical approval statement

Not applicable. This study involves no human or animal subjects.

Data availability statement

The dataset supporting the conclusions of this article is included within the article (and its additional file)

Competing interest

The authors report no conflict of interest to this work.

Author contribution statement

WT performed the search, extraction, and formal analyses of the data, the selection and evaluation of the studies, and wrote the original draft. CC processed the images. JK performed the extraction of the data. NT performed the extraction of the data. YC performed the extraction of the data, and the

selection and evaluation of the studies. YZ helped perform the analyses. YP helped process the images. XL helped with the data searching. LZ helped with the data searching. LS helped revise the draft. JL helped revise the draft. FW contributed to the conception of the study, and supervised the whole process of this work.

Consent for publication

Not Applicable.

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Figures

Figure 1

Selection for trials included in the meta-analyses and network meta-analyses.

Figure 2

Network structures in subgroups by age, PD-L1 expression, and metastases. Each node represents a treatment. Each line represents a head-to-head comparison of the two connected treatments, and the thickness of the line represents the number of trials which made the comparison. Abbr. chemo, chemotherapy.

Figure 3

Pooled hazard ratios for death and disease progression comparing immunotherapy-based treatments and chemotherapy by different subgroups and assessment of inter-subgroup heterogeneity. * $P<0.1$

		≥65-year-old						
< 65-year-old	Anti-CTLA-4 +Anti-PD-1	1.11 (0.8-1.54)	0.92 (0.69-1.21)	0.8 (0.56-1.14)	0.85 (0.63-1.15)	0.73 (0.49-1.07)	0.78 (0.59-1.03)	1.1 (0.87-1.38)
	0.85 (0.61-1.2)	Anti-CTLA-4 +chemo	0.82 (0.62-1.09)	0.72 (0.5-1.04)	0.77 (0.57-1.04)	0.65 (0.44-0.97)	0.7 (0.53-0.93)	0.99 (0.78-1.25)
	0.82 (0.62-1.08)	0.96 (0.72-1.27)	Anti-PD-1	0.87 (0.63-1.2)	0.93 (0.73-1.19)	0.79 (0.56-1.13)	0.85 (0.68-1.06)	1.2 (1.02-1.4)
	1.15 (0.8-1.64)	1.34 (0.94-1.93)	1.4 (1.04-1.9)	Anti-PD-1+ Anti-CTLA-4+ chemo	1.07 (0.76-1.49)	0.91 (0.6-1.38)	0.97 (0.71-1.34)	1.37 (1.04-1.81)
	1.16 (0.86-1.57)	1.36 (1-1.85)	1.42 (1.12-1.8)	1.01 (0.73-1.4)	Anti-PD-1+ chemo	0.85 (0.59-1.23)	0.91 (0.71-1.16)	1.29 (1.07-1.55)
	0.91 (0.62-1.34)	1.07 (0.72-1.58)	1.11 (0.79-1.56)	0.79 (0.53-1.19)	0.78 (0.55-1.12)	Anti-PD-L1	1.07 (0.75-1.52)	1.51 (1.1-2.07)
	0.93 (0.7-1.24)	1.09 (0.82-1.46)	1.14 (0.92-1.41)	0.81 (0.6-1.1)	0.8 (0.63-1.02)	1.02 (0.73-1.44)	Anti-PD-L1+ chemo	1.41 (1.21-1.66)
	0.7 (0.55-0.89)	0.82 (0.64-1.05)	0.85 (0.74-0.99)	0.61 (0.47-0.8)	0.6 (0.5-0.73)	0.77 (0.57-1.04)	0.75 (0.64-0.88)	chemo
		≥65-year-old						
< 65-year-old	Anti-CTLA-4+Anti-PD-1	0.86 (0.64-1.16)	0.71 (0.48-1.05)	0.66 (0.49-0.89)	0.63 (0.44-0.91)	0.67 (0.51-0.88)	1.1 (0.87-1.38)	
	0.94 (0.7-1.26)	Anti-PD-1	0.83 (0.57-1.19)	0.76 (0.59-1)	0.73 (0.52-1.02)	0.77 (0.61-0.98)	1.27 (1.06-1.53)	
	1.4 (0.92-2.12)	1.49 (1.02-2.19)	Anti-PD-1+ AT+chemo	0.92 (0.64-1.33)	0.88 (0.58-1.35)	0.94 (0.66-1.32)	1.54 (1.12-2.1)	
	1.4 (1.04-1.88)	1.49 (1.17-1.9)	1 (0.68-1.46)	Anti-PD-1+ chemo	0.96 (0.68-1.34)	1.01 (0.8-1.28)	1.66 (1.38-2.01)	
	1.08 (0.77-1.51)	1.15 (0.86-1.54)	0.77 (0.51-1.16)	0.77 (0.58-1.03)	Anti-PD-L1+ AT+chemo	1.06 (0.77-1.44)	1.74 (1.32-2.29)	
	1.03 (0.78-1.37)	1.1 (0.88-1.38)	0.74 (0.51-1.07)	0.74 (0.59-0.92)	0.96 (0.73-1.26)	Anti-PD-L1+ chemo	1.64 (1.42-1.9)	
	0.7 (0.55-0.89)	0.75 (0.63-0.89)	0.5 (0.36-0.7)	0.5 (0.42-0.6)	0.65 (0.51-0.82)	0.68 (0.59-0.78)	chemo	

Figure 4

Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) of the network meta-analysis in subgroups by age. (A) Pooled HRs and 95% CIs for overall survival in ≥65-year-old patients (upper right triangle) and <65-year-old patients (lower left triangle). (B) Pooled HRs and 95% CIs for progression-free survival in ≥65-year-old patients (upper right triangle) and <65-year-old patients (lower left triangle). Data in each cell represent HR and 95% CI for the comparison of column-defining treatment versus row-defining treatment. The data whose 95% CIs do not contain 1 are in bold. Abbr. chemo, chemotherapy; AT, anti-angiogenic therapy.

A	Brain Metastases	No Brain Metastases			
		Anti-CTLA-4+ Anti-PD-1	0.87 (0.63-1.19)	0.91 (0.69-1.2)	0.86 (0.67-1.1)
		1.55 (0.57-4.17)	Anti-PD-1	1.06 (0.75-1.48)	0.99 (0.72-1.35)
		1.79 (0.91-3.52)	1.16 (0.44-3.08)	Anti-PD-1+ Anti-CTLA-4+chemo	0.94 (0.72-1.22)
		1.17 (0.62-2.21)	0.76 (0.29-1.96)	0.65 (0.36-1.19)	Anti-PD-1+ chemo
		0.68 (0.41-1.12)	0.44 (0.19-1.04)	0.38 (0.24-0.6)	0.58 (0.39-0.86)
	Liver Metastases	No Liver Metastases			
		Anti-CTLA-4+ Anti-PD-1	0.84 (0.62-1.15)	0.94 (0.73-1.21)	-
		1.26 (0.76-2.11)	Anti-PD-1+ Anti-CTLA-4+chemo	1.21 (0.83-1.5)	-
		1.54 (0.98-2.43)	1.22 (0.76-1.95)	Anti-PD-1+ chemo	-
		1.54 (0.93-2.58)	1.22 (0.72-2.07)	1 (0.62-1.6)	Anti-PD-L1+AT+ chemo
		1.01 (0.67-1.52)	0.8 (0.52-1.23)	0.65 (0.46-0.94)	0.65 (0.45-0.95)
	Bone Metastases	No Bone Metastases			
		Anti-CTLA-4+ Anti-PD-1	0.8 (0.59-1.09)	0.94 (0.69-1.28)	1.23 (1.02-1.5)
		1.01 (0.65-1.59)	Anti-PD-1+Anti-CTLA-4+chemo	1.17 (0.84-1.64)	1.54 (1.21-1.95)
		0.77 (0.5-1.19)	0.76 (0.49-1.19)	Anti-PD-1+ chemo	1.32 (1.04-1.67)
		0.75 (0.55-1.03)	0.74 (0.53-1.03)	0.97 (0.72-1.31)	chemo
B	Brain Metastases	No Brain Metastases			
		Anti-PD-1	-	0.76 (0.6-0.98)	1.41 (1.24-1.6)
		0.78 (0.35-1.71)	Anti-PD-1+ AT+chemo	-	-
		1 (0.42-2.35)	1.28 (0.52-3.15)	Anti-PD-1+ chemo	1.85 (1.5-2.28)
		0.51 (0.3-0.85)	0.65 (0.36-1.18)	0.51 (0.26-1)	chemo
	Liver Metastases	No Liver Metastases			
		Anti-PD-1+AT+ chemo	-	-	-
		1.06 (0.43-2.62)	Anti-PD-1+ chemo	-	1.27 (1-1.61)
		1.34 (0.55-3.27)	1.27 (0.7-2.3)	Anti-PD-L1+AT+ chemo	-
		0.68 (0.3-1.54)	0.64 (0.4-1.04)	0.51 (0.33-0.77)	Anti-PD-L1+ chemo
		0.55 (0.25-1.22)	0.52 (0.34-0.8)	0.41 (0.27-0.62)	0.81 (0.66-1)

Figure 5

Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) of the network meta-analysis in subgroups by metastatic site. (A) Pooled HRs and 95% CIs for overall survival in patients without brain/liver/bone metastases (upper right triangle) and patients with brain/liver/bone metastases (lower left triangle). (B) Pooled HRs and 95% CIs for progression-free survival in patients without brain/liver metastases (upper right triangle) and patients with brain/liver metastases (lower left triangle). Data in each cell represent HR and 95% CI for the comparison of column-defining treatment versus row-defining treatment. The data whose 95% CIs do not contain 1 are in bold. Abbr. chemo, chemotherapy; AT, anti-angiogenic therapy.

A		PD-L1 TPS≥1%						
PD-L1 TPS<1%	Anti-CTLA-4+Anti-PD-1	0.81 (0.59-1.11)	0.84 (0.64-1.09)	1.03 (0.8-1.32)	1.23 (0.94-1.6)	0.99 (0.74-1.34)	1.04 (0.79-1.37)	1.27 (1.04-1.54)
	1 (0.67-1.49)	Anti-PD-1+Anti-CTLA-4+chemo	1.03 (0.76-1.4)	1.27 (0.95-1.7)	1.52 (1.12-2.06)	1.23 (0.88-1.71)	1.28 (0.93-1.76)	1.56 (1.22-2)
	0.9 (0.66-1.24)	0.9 (0.62-1.32)	Anti-PD-1+chemo	1.23 (0.98-1.56)	1.47 (1.14-1.89)	1.19 (0.89-1.59)	1.24 (0.95-1.62)	1.51 (1.27-1.81)
	0.6 (0.44-0.81)	0.6 (0.41-0.87)	0.66 (0.5-0.88)	Anti-PD-L1	1.19 (1-1.43)	0.96 (0.77-1.21)	1.01 (0.78-1.3)	1.23 (1.06-1.43)
	0.92 (0.61-1.37)	0.92 (0.58-1.45)	1.01 (0.69-1.5)	1.53 (1.11-2.1)	Anti-PD-L1+Anti-CTLA-4	0.81 (0.62-1.06)	0.84 (0.64-1.1)	1.03 (0.86-1.23)
	0.66 (0.48-0.92)	0.66 (0.45-0.98)	0.74 (0.54-1)	1.11 (0.88-1.39)	0.73 (0.5-1.05)	Anti-PD-L1+AT+chemo	1.05 (0.77-1.41)	1.27 (1.02-1.6)
	0.74 (0.54-1)	0.74 (0.51-1.07)	0.82 (0.61-1.08)	1.23 (0.94-1.61)	0.8 (0.55-1.17)	1.11 (0.82-1.49)	Anti-PD-L1+chemo	1.22 (1-1.49)
	0.62 (0.49-0.79)	0.62 (0.45-0.85)	0.69 (0.56-0.85)	1.03 (0.86-1.25)	0.68 (0.49-0.94)	0.93 (0.74-1.17)	0.84 (0.7-1.02)	chemo
B		PD-L1 TPS≥1%						
PD-L1 TPS<1%	Anti-CTLA-4+Anti-PD-1	0.95 (0.6-1.5)	0.78 (0.54-1.14)	0.81 (0.53-1.24)	0.99 (0.68-1.46)	1.61 (1.14-2.28)		
	1.34 (0.88-2.05)	Anti-PD-1+AT+chemo	0.82 (0.6-1.14)	0.85 (0.58-1.25)	1.05 (0.75-1.46)	1.7 (1.27-2.28)		
	1.04 (0.84-1.29)	0.77 (0.52-1.14)	Anti-PD-1+chemo	1.03 (0.78-1.37)	1.27 (1.03-1.57)	2.06 (1.8-2.37)		
	0.96 (0.69-1.33)	0.72 (0.46-1.1)	0.92 (0.7-1.22)	Anti-PD-L1+AT+chemo	1.23 (0.92-1.65)	2 (1.56-2.56)		
	1.06 (0.81-1.39)	0.79 (0.53-1.16)	1.02 (0.83-1.26)	1.1 (0.83-1.47)	Anti-PD-L1+chemo	1.62 (1.39-1.89)		
	0.74 (0.59-0.92)	0.55 (0.38-0.79)	0.71 (0.62-0.82)	0.77 (0.6-0.98)	0.7 (0.6-0.81)	chemo		

Figure 6

Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) of the network meta-analysis in subgroups by PD-L1 expression. (A) Pooled HRs and 95% CIs for overall survival in PD-L1 tumor proportion score (TPS)≥1% (upper right triangle) and PD-L1 TPS<1% (lower left triangle). (B) Pooled HRs and 95% CIs for progression-free survival in PD-L1 tumor proportion score (TPS)≥1% (upper right triangle) and PD-L1 TPS<1% (lower left triangle). Data in each cell represent HR and 95% CI for the comparison of column-defining treatment versus row-defining treatment. The data whose 95% CIs do not contain 1 are in bold. Abbr. chemo, chemotherapy; AT, anti-angiogenic therapy; TPS, tumor proportion score.

Supplementary Files

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- [supplementatrymaterial.pdf](#)