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Research paper

The effect of smoking status on efficacy of immune checkpoint inhibitors in metastatic non-small cell lung cancer: A systematic review and meta-analysis

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ABSTRACT

Background: It remains uncertain whether smoking status can effect efficacy of immune checkpoint inhibitors (ICIs) in metastatic non-small cell lung cancer (NSCLC). We performed a meta-analysis to address this issue.

Patients and methods: PubMed, Embase, Cochrane Library, Web of Science, and international meetings were searched until April 1, 2021, for phase 2 and 3 randomized controlled trials (RCTs) which compared ICIs with chemotherapy (CT) and reported overall survival (OS) and/or progression-free survival (PFS) data according to smoking status. This meta-analysis was registered in INPLASY platform (#INPLASY202140025). The random-effect model was used for statistical analysis.

Findings: Twenty-eight articles from 24 RCTs including 13918 patients were eligible. ICIs significantly prolonged OS than CT in smokers (hazard ratio [HR] = 0.75, 95% confidence interval [CI]: 0.69-0.81), but not in never-smokers (HR = 0.87, 95% CI: 0.74-1.04); while there was no significant treatment-smoking interaction ($P_{interaction}$ = 0.11). Significant heterogeneity was observed for both smokers (OS: I^2 = 60%, P = 0.0002; PFS: I^2 = 74%, P < 0.0001) and never smokers (PFS: I^2 = 69%, P < 0.0001). Subgroup analyses revealed that ICIs monotherapy significantly improved OS in smokers (HR = 0.76, 95% CI: 0.69-0.85) but not in never-smokers (HR = 0.93, 95% CI: 0.77-1.12, $P_{interaction}$ = 0.07), and treatment-smoking interaction was significant in patients with PD-L1 ≥50% (HR, 0.61 vs 1.18; $P_{interaction}$ = 0.005). ICIs plus CT achieved better OS either in smokers or never-smokers (HR, 0.76 vs 0.61; $P_{interaction}$ = 0.39), while dual ICIs combination prolonged OS only in smokers but never-smokers (HR, 0.68 vs 1.02; $P_{interaction}$ = 0.02).

Interpretation: Either ICIs monotherapy or combination therapy was superior to CT in smokers. While ICIs monotherapy and dual ICIs combination were less effective in never-smokers, and ICIs plus CT might be the optimal selection. Nevertheless, given the limitation of the high heterogeneity of studies included, the findings need to be confirmed by future RCTs focusing on this subject.

Funding: None.

1. Introduction

Despite immune checkpoint inhibitors (ICIs) have become the preferred regimens for advanced non-small cell lung cancer (NSCLC), only 15-25% of patients responded to this class of therapy [1], and most had primary resistance. As such, the search for clinical or molecular factors that predict benefit of ICIs is important. So far, several biomarkers such as PD-L1 expression and tumor mutation burden (TMB) have been identified as potential predictors of response to ICIs in NSCLC. In addition, patients characteristics such as gender [2], smoking status [3,4], and metastatic sites [5] are also reported to be associated with efficacy of ICIs, while their predictive value remain controversial.

Cigarette smoking is an important risk factor for lung cancer, and the tumor genomic landscape is markedly distinct according to smoking status [6]. Tumors in smokers are generally correlated with increased TMB [6] and PD-L1 expression [4]. Therefore, never smokers should obtain less benefit from ICIs compared to smokers theoretically. However, this hypothesis has not been confirmed by current ICIs trials, in which inconsistent results were observed [7–35]. Some

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Research in context

Evidence before this study

Immune checkpoint inhibitors (ICIs) have become the preferred regimens for advanced non-small cell lung cancer. However, whether smoking status can effect efficacy of ICIs remains uncertain. To date, there is still no randomized controlled trial which has specifically assessed survival benefits from ICIs in smokers and never smokers, respectively.

Added value of this study

In this meta-analysis, we found that ICIs monotherapy significantly improved overall survival compared to chemotherapy in smokers, but not in never-smokers even in the case of PD-L1 expression ≥50%. ICIs plus chemotherapy achieved better overall survival both in smokers and never-smokers, while dual ICIs combination prolonged overall survival only in smokers but never-smokers.

Implications of all the available evidence

Either ICIs monotherapy or combination therapy is superior to chemotherapy in smokers. While ICIs monotherapy and dual ICIs combination are less effective in never-smokers, and ICIs plus chemotherapy is likely to be the optimal selection. Nevertheless, given the limitation of the high heterogeneity of studies included, the findings need to be confirmed by future RCTs focusing on this subject.

previous meta-analyses [36–43] have attempted to clarify the relationship between smoking and the efficacy of ICIs in NSCLC, while the lack of statistical power due to limitations such as small number of studies, small sample size, and few subgroup analysis prevents a final conclusion.

To date, there is still no randomized controlled trial (RCT) which has specifically assessed survival benefits from ICIs in smokers and never smokers with NSCLC respectively. Whether smoking status can act as a predictive marker of response to ICIs remains uncertain. Recently, a number of new trials of ICIs in NSCLC have been published, and several previously published trials have updated their survival data. Thus, we conducted a updated meta-analysis aiming to further determine effect of smoking status on ICIs efficacy in NSCLC. In addition, the optimal treatment strategy for never smokers was also evaluated.

2. Methods

2.1. Literature search

This systematic review and meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [44] (Supplementary File: Table S1), and was registered in INPLASY international platform of registered systematic review and meta-analysis protocols (registration number: INPLASY202140025). A comprehensive literature search in PubMed, Embase, Cochrane Library, and Web of Science until April 1, 2021 was performed by two authors (LD and BJ) independently. The following terms were used: ("non-small cell lung cancer" or "non-small cell lung carcinoma" or "lung neoplasms") and ("programmed death 1" or "PD-1" or "programmed death-ligand 1" or "PD-L1" or "immunotherapy" or"immune checkpoint inhibitors" or "PD-1/PD-L1 inhibitors" or "PD-1/PD-L1 blockades" or "anti-PD-1/PDL1"). To identify unpublished studies, we searched abstracts from recent conferences including American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and World Conference on Lung Cancer (WCLC). We also manually checked the references cited in the relevant studies for additional articles. The detailed search strategy was listed in Supplementary File: Table S2.

2.2. Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) phase 2 or 3 RCTs in metastatic NSCLC; (2) compared ICIs (alone or in combination with other agents) with chemotherapy (CT); (3) reported overall survival (OS) and/or progression-free survival (PFS) data according to smoking status in each arm; (4) published in English. If multiple papers were published from the same RCT, the most recent one which reported the results according to smoking status was used.

2.3. Data extraction and Quality assessment

For each included trial, two authors (LD and BJ) independently extracted the trial name/first author, year of publication or conference presentation, design, region, number of smokers (defined as current and/or former smokers) and never smokers, interventions, hazard ratios (HRs) with 95% confidence intervals (CIs) for OS and/or PFS.

Risk of bias of individual trials was independently assessed by two authors (LD and BJ), using the Cochrane Risk of Bias Tool [45]. The studies were finally rated as low (all domains indicated as low risk), high (one or more domains indicated as high risk), and unclear risk of bias (more than three domains indicated as unclear risk).

2.4. Statistical analysis

Statistical analysis was performed using the software Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) and STATA MP 14.0 (Stata Corporation, College Station, TX, USA). The random-effect model was performed for statistical analysis. OS and PFS were the primary outcomes of interest. HRs and their 95% CIs were used as summary statistics. The heterogeneity among studies was estimated by the Chi-square (χ^2) and I-square (I^2) test with significance set at P value of less than 0.10 or I^2 greater than 50%. Subgroup analyses were performed according to treatment modality (ICIs montherapy or ICIs combination therapy), type of ICIs montherapy (PD-1 or PD-L1 inhibitors), type of ICIs combination therapy (ICIs plus CT or dual ICIs combination), ICIs montherapy in PD-L1 expression $\geq$1% or $\geq$50%, and treatment line (first-line or subsequent-line with ICIs). The difference in effect of ICIs between smokers and never smokers was assessed using a χ^2 test and expressed as P for interaction. Meta-regression analysis was conducted to search for the sources of heterogeneity. Sensitivity analysis was performed to verify the stability of the pooled results by removing the data of an individual study each time. Publication bias was evaluated by Begg's test [46], the Egger's test [47], and the funnel plot. All reported P-values were two sided, and P values less than 0.05 were considered statistically significant.

2.5. Role of funding source

There was no funding source for this study.

3. Results

3.1. Literature Search and Study Selection

In total, 10318 studies were identified on the initial literature search. After screening the abstract and/or full text, 10290 studies

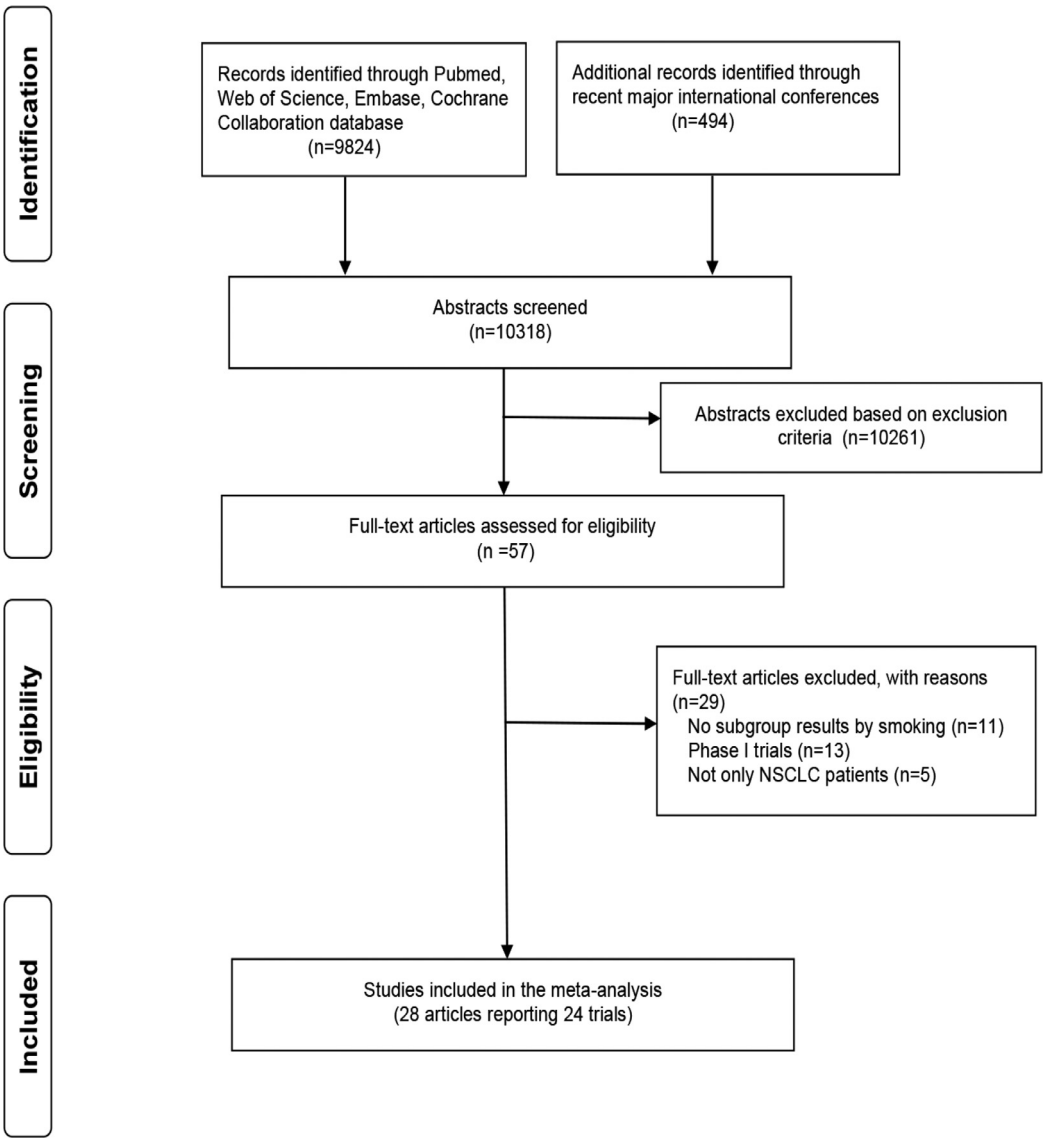

Fig. 1. Literature search and selection.

were excluded. The selection process and reasons for study exclusion are shown in Fig. 1. Finally, 28 eligible articles reporting 24 RCTs (23 phase 3 and 1 phase 2 trials) with 13918 patients (11698 of smokers and 2220 of never smokers) were eligible for inclusion [7–35]. Because one studies [10] provided pooled OS data of CheckMate-017 [9], and -057 [11], the pooled data were used instead of data from the individual trials in this meta-analysis. The main characteristics of included studies are presented in Table 1. Nineteen studies reported OS data, and eighteen studies provided PFS data. The median sample size of smokers and never smokers arm were 354 participants (range 49-1017, interquartile range [IQR] 216-614) and 73 participants (range 12-282, IQR 51-137), respectively.

3.2. Assessment of included studies and publication bias

The risk of bias of included RCTs is summarized in Supplementary File: Figure S1. Two trials were judged as unclear risk of bias [22,26]. The remaining trials were rated with a low risk of bias. The Begg's and Egger's test results indicated no publication bias in OS (smokers: P = 0.43 and P = 0.65; never smokers: P = 0.27 and P = 0.39) and PFS (smokers: P = 0.42 and P = 0.35; never smokers: P = 0.43 and P = 0.34). The funnel plot is shown in Supplementary File: Figure S2.

3.3. Effect of ICIs on OS and PFS by smoking status

ICIs were significantly associated with longer OS and PFS compared with CT in smokers (HR = 0.75, 95% CI: 0.69-0.81 and HR = 0.63, 95% CI: 0.56-0.70), but not in never smokers (HR = 0.87, 95% CI: 0.74-1.04 and HR = 0.84, 95% CI: 0.64-1.08). There were no statistically significant difference in the pooled HR for OS ($P_{interaction}$ = 0.11) and ($P_{interaction}$ = 0.05) between the two patients population. Significant heterogeneity was observed for both smokers (OS: I^2 = 60%, P = 0.0002; PFS: I^2 = 74%, P < 0.0001) and never smokers (PFS: I^2 = 69%, P < 0.0001). The detailed results are shown in Fig. 2 (OS) and Fig 3 (PFS).

3.4. Subgroup analyses

The detailed results of subgroup analyses are shown in Fig. 4 (OS) and Fig. 5 (PFS).

Table 1
Characteristics of included trials.

Trial/Year	Design	Histological type	Treatment line	Primary endpoint	Treatment	Size (smokers/nerver smokers)	CT regimen
Keynote-024/2016 [7]	3	Mixed	1	PFS	Pembrolizumab	149/5	PP/GP/PC
					CT	132/19	
Keynote-042/2019 [8]	3	Mixed	1	OS	Pembrolizumab	495/142	PC/PP
					CT	497/140	
CheckMate-017/2015 [9]	3	Squamous	≥2	OS	Nivolumab	121/10	Doctaxel
					CT	129/7	
CheckMate-057/2015 [11]	3	Non-squamous	≥2	OS	Nivolumab	231/58	Doctaxel
					CT	227/60	
CheckMate-026/2017 [12]	3	Mixed	1	PFS	Nivolumab	238/30	GP/PP
					CT	237/29	
CheckMate-078/2019 [13,14]	3	Mixed	≥2	OS	Nivolumab	236/102	Doctaxel
					CT	118/48	
IMpower110/2020 [15]	3	Mixed	1	OS	Atezolizumab	98/9	GP/PP
					CT	83/15	
OAK/2017 [16,17]	3	Mixed	≥2	OS	Atezolizumab	501/112	Doctaxel
					CT	516/96	
POPLAR/2016 [18]	2	Mixed	≥2	OS	Atezolizumab	117/27	Doctaxel
					CT	114/29	
JAVELIN Lung 200/2018 [19]	3	Mixed	≥2	OS	Avelumab	220/43	Doctaxel
					CT	224/41	
MYSTIC/2020 [20]	3	Mixed	1	OS	Durvalumab	139/24	PP/GP/PC
					CT	141/21	
Keynote-189/2018 [21]	3	Non-squamous	1	OS, PFS	Pembrolizumab+CT	362/48	PP
					CT	181/25	
Lee/2020 [22]	3	Non-squamous	1	PFS	Nivolumab+CT	214/61	PC+Bev
					CT	221/54	
Camel/2020 [23,24]	3	Non-squamous	1	PFS	Camrelizumab+CT	162/22	PP
					PC	157/23	
ORIENT-11/2020 [25]	3	Non-squamous	1	PFS	Sintilimab+CT	171/95	PP
					CT	87/44	
RATIONALE 304/2020 [26]	3	Non-squamous	1	PFS	Tislelizumab+CT	147/76	PP
					CT	66/45	
RATIONALE 307/2020 [27]	3	Squamous	1	PFS	Tislelizumab+PC	96/24	
					Tislelizumab+CnP	107/12	
					CT	98/23	PC
IMpower150/2019 [28]	3	Non-squamous	1	OS	Atezolizumab+CT	318/82	PC+Bev
					CT	323/77	
IMpower130/2019 [29]	3	Non-squamous	1	PFS/OS	Atezolizumab+CT	403/48	PC/CnP
					CT	201/17	
Impower131/2020 [30]	3	Squamous	1	PFS/OS	Atezolizumab+CT	311/32	CnP
					CT	316/23	
IMpower132/2020 [31]	3	Non-squamous	1	OS/PFS	Atezolizumab+CT	255/37	PP
					CT	256/30	
Govindan/2017 [32]	3	Squamous	1	OS	Ipilimumab+CT	339/NR	PC
					CT	317/NR	
CheckMate-227/2019 [33,34]	3	Mixed	1	OS/PFS	Nivolumab+Ipilimumab	497/79	GP/PP
					CT	499/78	
CheckMate-9LA/2021 [35]	3	Mixed	1	OS	Nivolumab+Ipilimumab+CT	315/46	PC/PP
					CT	306/52	

Abbreviations: OS, overall survival; PFS, progression-free survival; CT, chemotherapy; PP, pemetrexed-cisplatin/carboplatin; PC, paclitaxel carboplatin; CnP, nab-paclitaxel-carboplatin; GP, gemcitabine- cisplatin/carboplatin; Bev, bevacizumab; NR, not reported.

3.4.1. Subgroup analyses of ICIs montherapy by smoking status

ICIs montherapy significantly improved OS and PFS compared to CT in smokers (HR = 0.76, 95% CI: 0.69-0.85 and HR = 0.79, 95% CI: 0.66-0.94), but not in never smokers (HR = 0.93, 95% CI: 0.77-1.12 and HR = 1.51, 95% CI: 0.95-2.39). Treatment-smoking interaction was not statistically significant for OS ($P_{interaction}$ = 0.07) but was for PFS ($P_{interaction}$ = 0.01).

For patients with PD-L1 expression ≥1% or ≥50% tumors, ICIs montherapy also achieve a significant longer OS than CT in smokers (PD-L1 ≥1%: HR = 0.80, 95% CI: 0.69-0.92; PD-L1 ≥50%: HR = 0.61, 95% CI: 0.51-0.73), but not in never smokers (PD-L1 ≥1%: HR = 1.08, 95% CI: 0.80-1.45, $P_{interaction}$ = 0.07; PD-L1 ≥50%: HR = 1.18, 95% CI: 0.78-1.79, $P_{interaction}$ = 0.005).

In term of type of ICIs montherapy, either PD-1 or PD-L1 inhibitor significantly prolonged OS in smokers but neither in never smokers, while no significant treatment-smoking interactions were observed (PD-1 inhibitor: HR, 0.79 vs 0.91; $P_{interaction}$ = 0.26; PD-L1 inhibitor: HR, 0.77 vs 0.97; $P_{interaction}$ = 0.31).

3.4.2. Subgroup analyses of ICIs combination therapy by smoking status

The pooled HRs for OS and PFS were 0.73 (95% CI, 0.64-0.84) and 0.56 (95% CI, 0.50-0.62) in the smokers subgroup, and were 0.75 (95% CI, 0.53-1.06) and 0.68 (95% CI, 0.53-0.87) in the never smoker subgroup. There was no significant treatment-smoking interaction ($P_{interaction}$ = 0.89 for OS and $P_{interaction}$ = 0.15 for PFS).

Further analyses according to type of ICIs combination therapy showed that ICIs plus CT achieved significant improvements in OS and PFS either for smokers or never-smokers (OS: HR, 0.76 vs 0.61, $P_{interaction}$ = 0.39; PFS: HR, 0.55 vs 0.63, $P_{interaction}$ = 0.23), while dual ICIs combination significantly prolonged OS only in smokers but not in never-smokers (HR, 0.68 vs 1.02; $P_{interaction}$ = 0.02).

3.4.3. Subgroup analyses of first-line with ICIs by smoking status

The pooled HRs for OS and PFS were 0.75 (95% CI, 0.68-0.84) and 0.59 (95% CI, 0.52-0.67) in the smokers subgroup, and were 0.84 (95% CI, 0.67-1.06) and 0.74 (95% CI, 0.56-0.98) in the never smoker

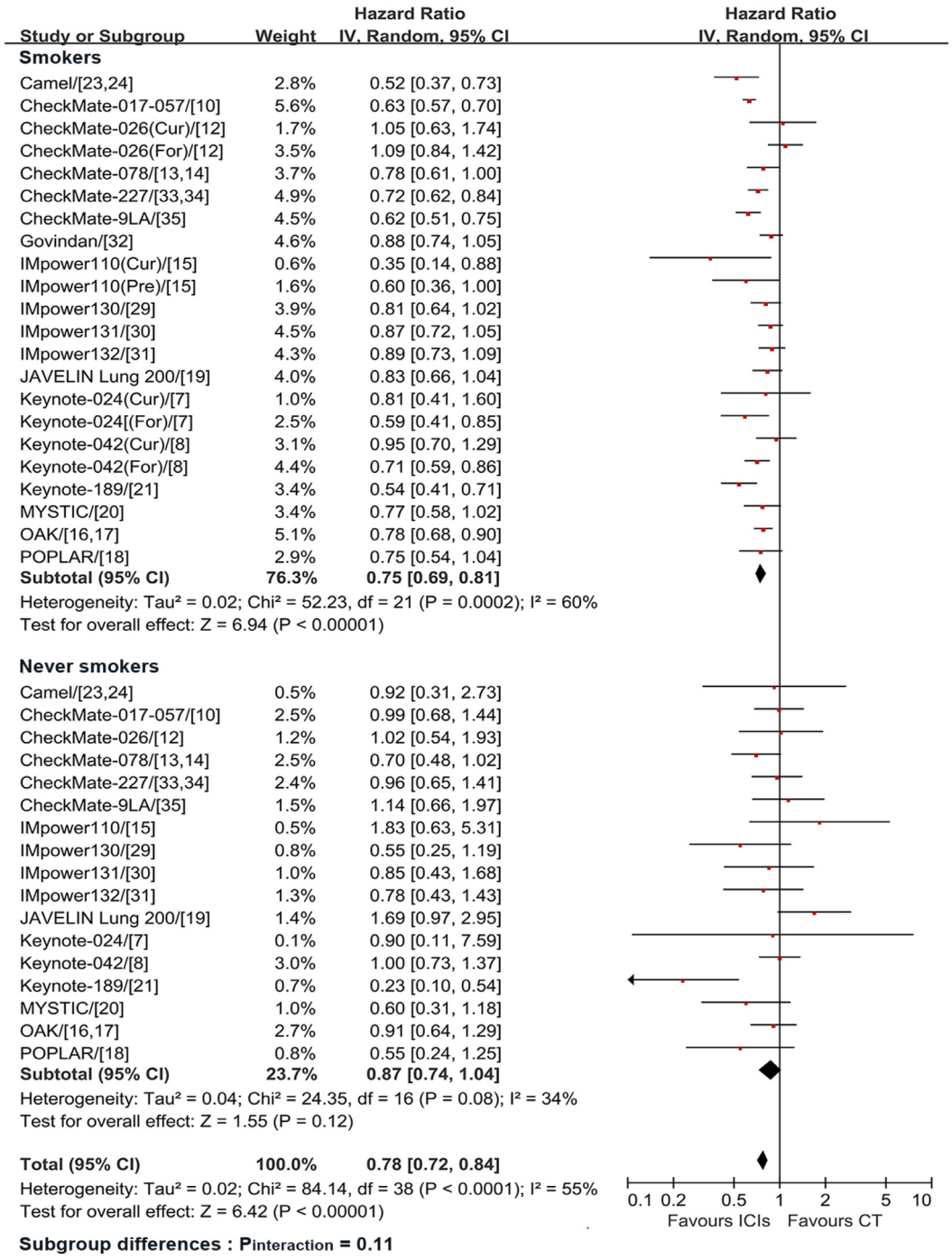

Fig. 2. Forest plot of hazard ratios comparing overall survival in patients who received ICIs vs CT. CI, confidence interval; Cur, current smokers; For, former smokers; ICIs, immune checkpoint inhibitors; CT, chemotherapy.

subgroup. No significant treatment-smoking interactions were observed ($P_{interaction}$ = 0.38 for OS and $P_{interaction}$ = 0.16 for PFS).

3.4.4. Subgroup analyses of subsequent-line with ICIs by smoking status

The pooled HRs for OS and PFS were 0.74 (95% CI, 0.65-0.84) and 0.78 (95% CI, 0.68-0.89) in the smokers subgroup, and were 0.92 (95% CI, 0.69-1.23) and 1.35 (95% CI, 0.80-2.26) in the never smoker subgroup. There was no statistically significant treatment-smoking interaction in OS ($P_{interaction}$ = 0.17) and PFS ($P_{interaction}$ = 0.05).

3.5. Meta-regression analysis

Meta-regression analysis was conducted to investigate whether treatment modality (ICIs montherapy or ICIs combination therapy) and treatment line (first-line or subsequent-line with ICIs) were the sources of heterogeneity. The results demonstrated that treatment modality was the evident contributor of heterogeneity for PFS (smokers: P = 0.002; never smokers: P = 0.007) (Supplementary File: Table S3).

3.6. Sensitivity analysis

When individual trials were removed one at a time from the analyses for OS and PFS, the corresponding pooled HRs were not

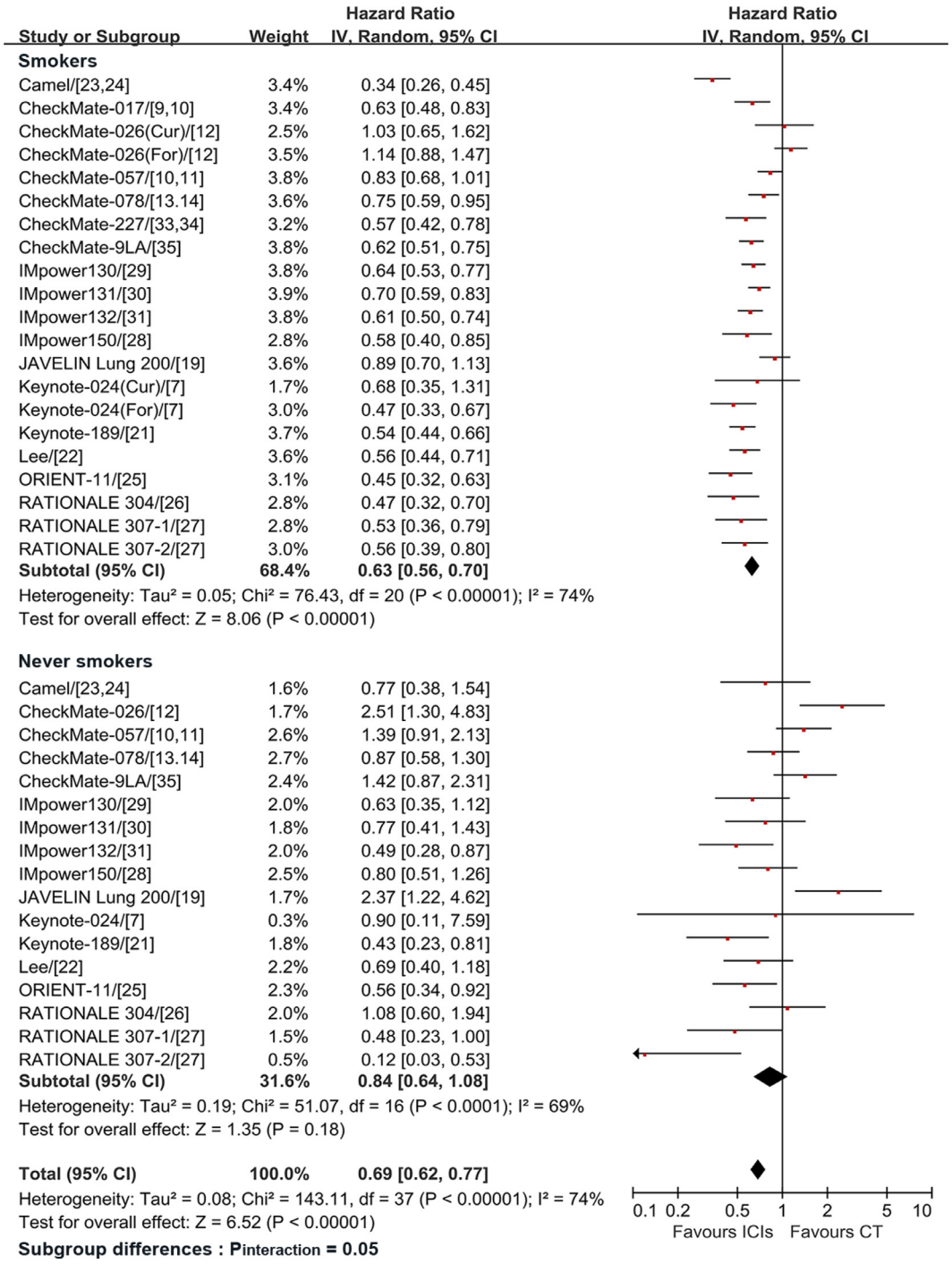

Fig. 3. Forest plot of hazard ratios comparing progression-free survival in patients who received ICIs vs CT. CI, confidence interval; Cur, current smokers; For, former smokers; ICIs, immune checkpoint inhibitors; CT, chemotherapy.

markedly altered by any single study (smokers: HR lies between 0.74 and 0.76 for OS, and between 0.61 and 0.65 for PFS; never smokers: HR lies between 0.84 and 0.92 for OS, and between 0.78 and 0.87 for PFS), indicating a relatively good stability of the presented results (Supplementary File: Figure S3).

4. Discussion

This is a comprehensive meta-analysis to assess the effect of smoking status on efficacy of ICIs in patients with metastatic NSCLC. This meta-analysis included 28 studies involving 13918 patients (11698 smokers and 2220 never smokers). It showed that ICIs were associated with significant longer OS and PFS than CT in smokers but not in never smokers, while no significant treatment-smoking interaction in OS ($P_{interaction}$ = 0.11) and PFS ($P_{interaction}$ = 0.05) was observed.

In subgroup analysis, ICIs monotherapy significantly prolonged OS and PFS in smokers but not in never smokers; the treatment-smoking interaction was significant for PFS ($P_{interaction}$ = 0.01) and was trend significant for OS ($P_{interaction}$ = 0.07). The fact that never smokers are more likely to be with relatively low TMB [6] and low tumor PD-L1 expression [4] may account for the less efficacy of ICIs monotherapy.

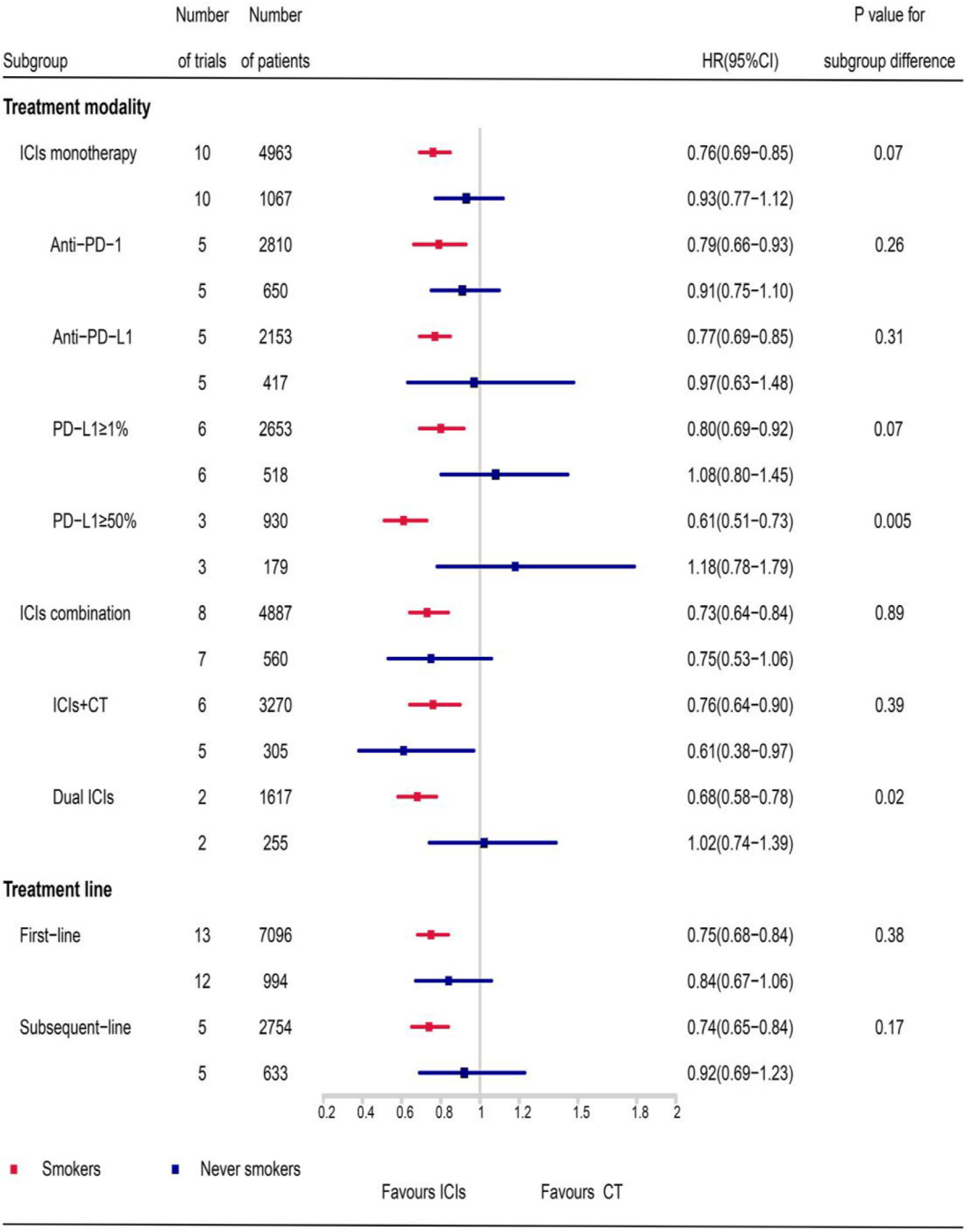

Fig. 4. Subgroup analyses for overall survival. HR, hazard ratio; CI, confidence interval; ICIs, immune checkpoint inhibitors; CT, chemotherapy.

Unexpectedly, ICIs monotherapy failed to significantly prolong OS even in never smokers with PD-L1 expression ≥1% or ≥50% in our study, and significant treatment-smoking interaction was observed ($P_{interaction}$ = 0.005 in PD-L1 ≥50% group). It had been reported that there was no association between PD-L1 expression and TMB in NSCLC patients treated with pembrolizumab or nivolumab, and patients with both high TMB and high PD-L1 expression might have greater response to nivolumab than those with only one or neither of these factors [12]. If so, the generally low TMB might account for the less efficacy of ICIs monotherapy in never-smokers with high PD-L1 expression tumors. As such, ICIs monotherapy was not likely to be a better selection for never-smokers even in those with high PD-L1 expression tumors. While, this hypothesis needs to be confirmed by future RCTs focusing on this subject.

It should be noted that there are the possibilities that tobacco exposure levels and molecular smoking signature rather than smoking history correlate with efficacy of ICIs monotherapy [48]. It had been reported that there was a positive correlation between the amount of smoking exposure and mutational burden [6], and expression levels of PD-L1 in smokers were increased by number of pack-years [4]. In a retrospective study investigating relationship between smoking status and response to nivolumab or pembrolizumab [49], heavy smokers with NSCLC had longer OS compared to light smokers (P = 0.003). Gainor, et al also found that ICIs showed a numerically shorter median PFS and median duration of response in never/light smokers compared to heavy smokers in NSCLC patients with PD-L1 TPS ≥50% [50]. In addition, the molecular smoking signature was also reported to be associated with ICIs efficacy [50]. The ORR in tumors

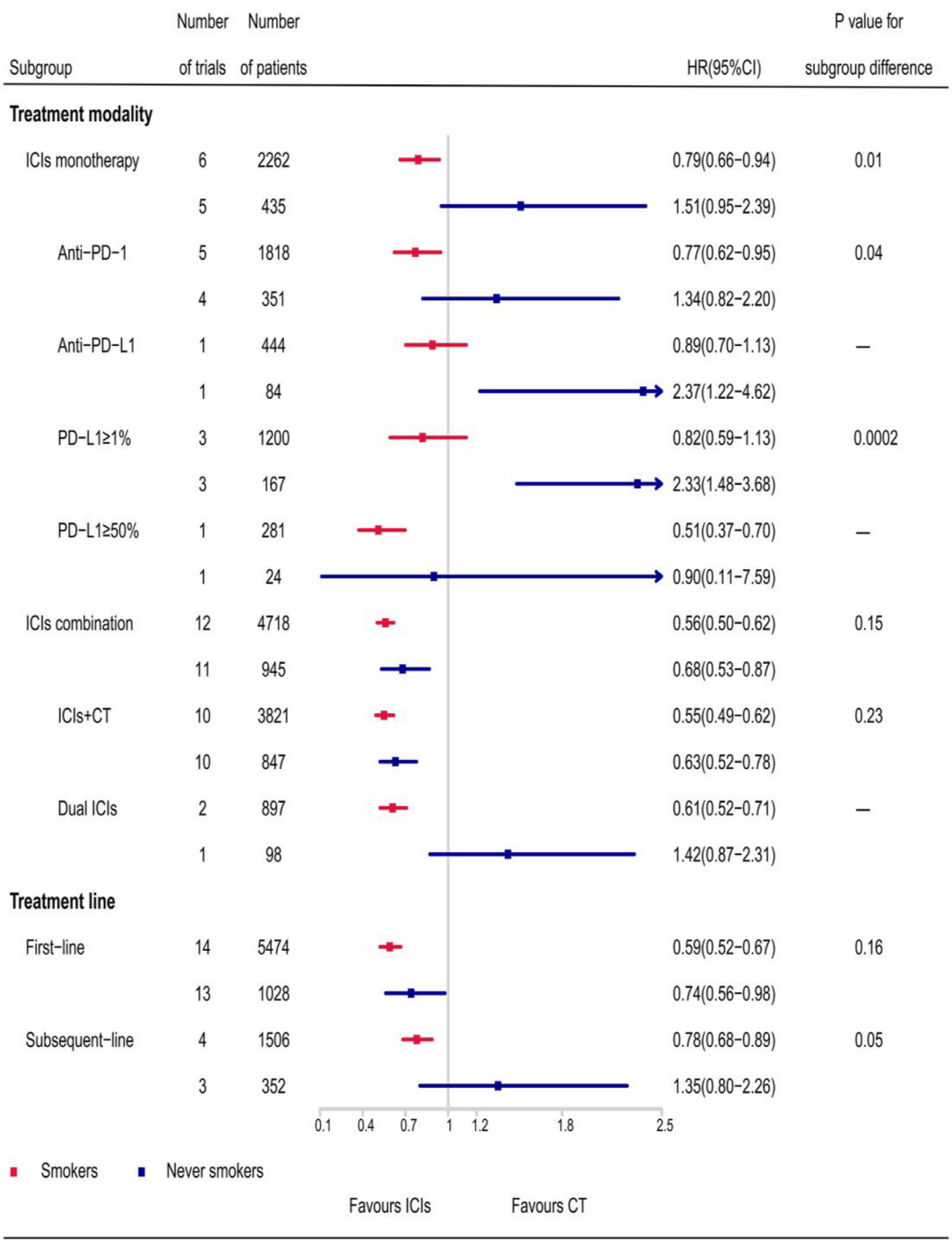

Fig. 5. Subgroup analyses for progression-free survival. HR, hazard ratio; CI, confidence interval; ICIs, immune checkpoint inhibitors; CT, chemotherapy.

with the molecular smoking signature was 56% versus 17% in those without, and the median PFS was not reached versus 3.5 months (P = 0.0001) [51]. The molecular smoking signature but self-reported smoking status was correlated with efficacy of pembrolizumab [50]. Nevertheless, the retrospective studies mentioned above has their inherent limitations, additional prospective trials are needed to validate those findings. In our meta-analysis, we were unable to assess the two factors because they were not investigated in any of trials included.

Currently, ICIs in combination with CT has been a standard first-line treatment for metastatic NSCLC patients. Dual ICIs combination such as nivolumab plus ipilimumab is also reported to be associated with superior efficacy [33–35]. While, dual ICIs combination appeared to be more effective for patients with high TMB. In Checkmate 227 trial [33,34], nivolumab plus ipilimumab was not correlated with a longer PFS than CT in patients with low TMB (<10mut/Mb) and low PD-L1 expression level (<1%), but was in those with high TMB (≥10mut/Mb) regardless PD-L1 expression status. In our study, ICIs plus CT achieved better OS either in smokers or never-smokers (HR, 0.76 vs 0.61; $P_{interaction}$ = 0.39), while dual ICIs combination prolonged OS only in smokers but never-smokers (HR, 0.68 vs 1.02; $P_{interaction}$ = 0.02). Thus, in term of combination therapy, ICIs plus CT rather than dual ICIs combination was likely to be the optimal strategy for never-smokers with NSCLC.

Some previous meta-analyses have also investigated efficacy of ICIs in NSCLC by smoking status (Supplementary File: Table S4). Except two [38,42] reporting a significant longer OS in ICIs vs CT, most of the studies found no significant survival benefit from ICIs in never-smokers. However, limited by generally small number of trials (range from 5 to 16) with few subgroup analyses, their results were not sufficiently powered. The present study with updated data included more trials (n=24) with more patients. In addition, a comprehensive subgroup analyses were performed (including treatment modality, type of ICIs montherapy, type of ICIs combination therapy, ICIs montherapy in PD-L1 expression $\geq$1%/$\geq$50%, and treatment line). Moreover, this meta-analysis had two new findings in never-smokers that ICIs monotherapy appeared to be less effective even in those with high PD-L1 expression tumors, and ICIs plus CT but dual ICIs combination correlated with the longer OS. These findings provide additional insight to better determine the treatment strategy in never smokers with NSCLC.

Nevertheless, there are several limitations in our meta-analysis. First, This meta-analysis relies on results reported from trials rather than on individual patients' data. Second, despite all included studies were RCTs, survival data of smokers and never smokers were extracted from subgroup analyses of these trials, which might be imbalance in baseline characteristics between the two sets of patients. Third, some RCTs were excluded from our study due to without reporting survival information of smokers and never-smokers, respectively. This might result in a selection bias to some extent. Fourth, there were significant heterogeneity for OS and PFS in smokers and/or never-smokers. Results of subgroup and meta-regression analysis showed that treatment modality might account for a part of heterogeneity. In addition, chemotherapy regimens were inconsistent among studies, which might also lead to heterogeneity. Fifth, the validity of smoking history can be marred by recall bias and reporting bias. Finally, we were unable to assess efficacy of ICIs according to tobacco exposure levels, because no trial had provided these information.

In conclusion, either ICIs monotherapy or combination therapy was superior to CT in smokers. While ICIs monotherapy and dual ICIs combination were less effective in never-smokers, and ICIs plus CT was likely to be the optimal selection. These findings are helpful in the treatment selection, as well as the design of future RCTs in never-smokers with NSCLC. Nevertheless, given the limitation of the high heterogeneity of studies included, the findings need to be confirmed by future RCTs focusing on this subject.

Data sharing statement

All data used and generated in this study are available within the article and/or its supplementary materials.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

Funding

None.

Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.100990.

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