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Efficacy and safety of neoadjuvant immunotherapy in non-small cell lung cancer: a systematic review and meta-analysis

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Background: Several studies have been conducted to confirm the efficacy and safety of neoadjuvant immunotherapy. However, the effects and safety of different types of immune checkpoint inhibitors (ICIs) and drug combinations are still uncertain due to the limited results published. Furthermore, a discussion of possible biomarkers needs to be put on the agenda. Consequently, an analysis of the latest research is urgently needed.

Methods: PubMed, OVID, Cochrane Library, and international conferences up to October 1, 2021, were searched. Radiologic outcomes [objective response rate (ORR)], pathologic outcomes [major pathological response (MPR), pathological complete response (pCR)], surgical outcomes [surgical resection rate, R0 surgical resection rate (R0 rate), the incidence of surgical complications, surgical delay rate], and adverse events [treatment-related adverse event (TRAE), 3–5 grade TRAE] were extracted. Possible biomarkers in connection with pathologic response were also explored.

Results: Our study contained 19 trials, with 859 patients included. The efficacy of neoadjuvant immunotherapy was higher than neoadjuvant chemotherapy published earlier. In subgroup analysis, the combined strategy (immunotherapy plus chemotherapy) exhibited better performance. Compared with immunotherapy alone, combined treatment performed better in ORR (64.8% *vs.* 11.9%), MPR (64.1% *vs.* 23.6%), and pCR (35.4% *vs.* 5.2%) though with more adverse events. Programmed cell death protein 1 (PD-1) inhibitor was associated with fairly higher effectiveness (ORR: 43.1% *vs.* 32.0%) and lower incidence of 3–5 grade TRAE [14.1%; 95% confidence interval (CI), 5.1–26.6%] compared with programmed cell death protein ligand 1 (PD-L1) inhibitor (27.0%; 95% CI, 0–89.8%). The rate of MPR in the PD-L1 positive group was significantly higher [relative risk (RR) =1.56; 95% CI, 1.06–2.29]. High-expression group also performed well (RR =3.38; 95% CI, 1.20–9.52). When we compared the group with objective response and the group without objective response, RR reached 3.19 (95% CI, 2.17–4.69), indicating ORR was probably in connection with MPR as well. We found no significant results in other factors such as smoking status, histological type, gender, and clinical stage. Similar results were found in patients with pCR.

Conclusions: Our study further confirmed that neoadjuvant immunotherapy combined with chemotherapy had preferable efficacy and acceptable safety. Based on combined therapy, applying PD-1 inhibitor were preferred in clinical practice. Furthermore, our study proved that PD-L1 expression level may be the possible biomarker in connection with the pathologic response of either MPR or pCR.

Keywords: Non-small cell lung cancer (NSCLC); neoadjuvant immunotherapy; meta-analysis; efficacy; safety

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Introduction

Lung cancer ranks first in morbidity and mortality in males among all malignant tumors worldwide (1), of which non-small cell lung cancer (NSCLC) accounts for nearly 80%. Surgery is always the basic treatment of early-stage NSCLC (2). However, the 5-year survival rate ranges from 36% to 92% with a high probability of recurrence, especially distant metastasis (3). Recently, researchers applied chemotherapy before surgery and achieved elevation in progression-free survival (PFS) and overall survival (OS) (4). However, with the development of neoadjuvant therapy, surgery, and adjuvant therapy, the prognosis is still not satisfactory. As we know, only a 5% improvement in the 5-year survival rate is observed (5). Also, accompanied by improved efficacy, adverse events happened more frequently.

Recently, immune checkpoint inhibitors (ICIs), a kind of antitumor drug, have been proven to have satisfactory effects in advanced NSCLC (6,7). The high response rate in stage IV NSCLC urges researchers to explore the efficacy and safety of ICIs in early-stage NSCLC. In recent years, many trials have been conducted such as LCMC3, NEOSTAR, NEOMUN, and so on. Studies showed exciting short-term outcomes. However, side effects occurred frequently. In NADIM, 93% of the participants receiving chemotherapy and ICIs underwent side effects and 30% were 3–5 grade treatment-related adverse event (TRAE). ChiCTR-OIC-17013726 also reported one grade 5 pneumonitis related to sintilimab. Consequently, we needed to analyze the efficacy and safety of neoadjuvant immunotherapy and combination strategies. Regrettably, most trials with data published online are phase 2 and single-arm studies, reporting short-term results. Few long-term survival data have been published (8). A previous study showed that histopathologic response related strongly to long-term OS. As a result, we utilized pathologic response and radiologic response as surrogate end points (9,10). Our meta-analysis aims to integrate the clinical data and pathologic data of recently published studies, predict survival and give evidence to guide clinical practice. We present the following article in accordance with the PRISMA reporting checklist (available at https://amj.amegroups.com/article/view/10.21037/amj-22-88/rc).

Highlight box

Key findings

- Neoadjuvant immunotherapy combined with chemotherapy has preferable efficacy and acceptable safety. Patients with high PD-L1 expression [tumor proportional score (TPS) >50%] are more likely to benefit from neoadjuvant immunotherapy.

What is known and what is new?

- Neoadjuvant immunotherapy displays high pathologic response rate and admissible side effects.
- Neoadjuvant immunotherapy combined with chemotherapy shows better effectiveness and acceptable safety compared with immunotherapy alone. PD-1 inhibitors are preferable. PD-L1 expression level and radiologic response associate with pathologic response closely.

What is the implication, and what should change now?

- These data provide evidence for treatment decisions. Combined therapy and patients with high PD-L1 expression are preferred.

Methods

Search strategy and study selection

PubMed, OVID, and Cochrane Library were searched to access comprehensive studies with keywords including "NSCLC", "neoadjuvant immunotherapy" and "trials". The deadline for the search strategy is October 1, 2021. Please refer to the Appendix 1 for a detailed search strategy. On the other hand, due to the small number of published trials related, we also searched international tumor conferences such as American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), World Conference on Lung Cancer (WCLC), and other recent congresses. Thus, studies with abstracts only were also in our search list.

The population, intervention, comparator, outcome, and study (PICOS) criteria were followed and the inclusion criteria were listed as follows: (I) patients: resectable stage I–III NSCLC; (II) intervention: neoadjuvant ICIs; (III) comparator: how effective and safe are the different combinations and types of neoadjuvant treatment regimens;

(IV) outcomes: objective response rate (ORR), surgical resection rate, R0 surgical resection rate (R0 rate), the incidence of major pathological response (MPR), pathological complete response (pCR), TRAE, 3–5 grade TRAE, surgical complications, and surgical delay, etc.; (V) study design: randomized controlled trials (RCTs), non-RCTs, prospective cohort studies. Those treated with any ICIs or radiotherapy previously should be excluded. Studies not focusing on the efficacy or safety of neoadjuvant immunotherapy were also rejected. Furthermore, the search also refused reviews and case reports.

Two reviewers (XK and WXD) were assigned to screen the title and abstract of each study independently. Then, we investigated full texts of studies included after the first search round. For those with disagreements, the two reviewers discussed together or asked for the third reviewer to decide on the final inclusion.

Data abstracted

Two reviewers (XK and WXD) separately extracted detailed data. Data containing the first author, published year, name of the trial, registration number, intervention type, drug and dose, number of enrollment, and baseline characteristics of participants. Short-term outcomes such as ORR, MPR, pCR, surgical resection rate, R0 rate, TRAE, 3–5 grade TRAE, the incidence of surgical complications, and surgical delay rate were recorded. Furthermore, we extracted the detailed baseline data of patients with MPR or pCR in each trial. Nevertheless, few studies supplied survival outcomes, and some results called for calculation, so we recorded the comprehensive raw data as possible. The two reviewers read studies repeatedly to make sure the accuracy and authenticity of the recorded data.

Statistical analysis

R version 4.1.1 was applied to perform the statistical analysis. The R META package was used for the meta-analysis and meta-regression. For proportions, the R function METAPROP was applied. For the raw data, simple calculations were done and the most suitable method was chosen to ensure its normality when using the METAPROP function. All included studies were combined in a descriptive synthesis. The heterogeneity was assessed using I^2 and T^2 values and calculated the estimates for the aforementioned clinical outcomes together with their 95% confidence intervals (CIs). Determination of which model to use to calculate the estimated values was made on both the authors' assessment and statistical heterogeneity. Funnel plots were created to evaluate the publication bias of each included study. Egger's test and Begg's test were used to check for publication bias. In consideration of the limited trials included in this study, meta-regression was applied to explore the possible relationship between the duration time of surgery and MPR. Furthermore, due to the large heterogeneity, subgroup analysis was conducted based on the questions raised below: whether ICIs and chemotherapy (immunotherapy and chemotherapy or immunotherapy) should be combined and which type of ICIs [programmed cell death protein 1 (PD-1) inhibitor or programmed cell death protein ligand 1 (PD-L1) inhibitor] was preferred.

Moreover, the R function of METABIN was applied to explore the relationship between gender, smoking status, clinical stage, radiologic response, PD-L1 expression level, and pathologic response. Relative risk (RR) and 95% CI were the effective measures. Heterogeneity was assessed using the I^2 and t^2 values. The random effect model was adopted when results had significant heterogeneity; otherwise, we chose the fixed effect model.

All reported P values were two-sided and statistical significance was defined as $P<0.05$.

Assessments of publication bias and study quality

Because almost all the studies are non-randomized clinical trials except CheckMate 816, the Methodologic Index for Nonrandomized Studies (MINORS) was applied to assess the bias of these trials. Two reviewers independently carried out the quality evaluation. When encountering disagreement, the resolution strategy was the same as that conducted before.

Results

Results of search

After an advanced search of 3 databases (PubMed, OVID, and Cochrane Library), 487 studies were retrieved from the first round. Together with 215 studies obtained from other sources, 702 studies were included in the total. Following the removal of 226 duplicate articles, we excluded 444 articles by browsing titles and abstracts. Thirty-two articles went into the last round. Then 14 articles were excluded after viewing the full text. They were excluded for different main points or updated data. The study selection process

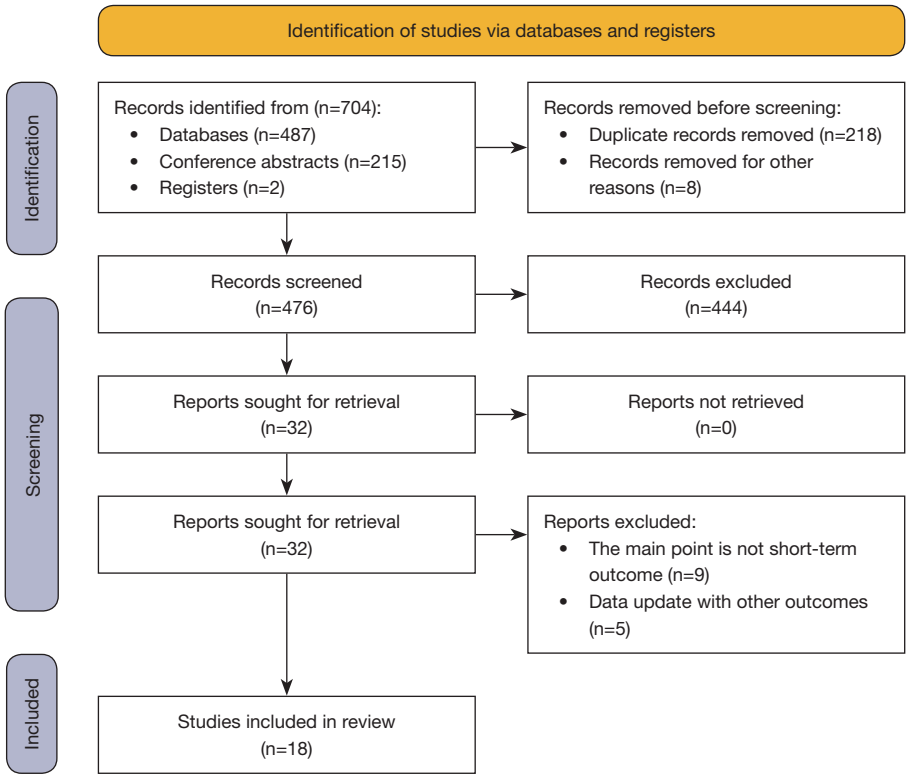

Figure 1 Flow diagram of the study selection process.

is shown in *Figure 1*. Ultimately, 18 articles (8,11-27), with 859 patients were included in the final meta-analysis. *Table 1* provides detailed information on the 18 records (19 trials) involved. As we can see in the table, only one phase 3 dual-arm open-label RCT, CheckMate 816, is included in the final meta-analysis.

Primary outcomes

Efficacy of neoadjuvant immunotherapy

ORR is defined as a radiologic response according to the RECIST version 1.1 criteria (28,29). Fourteen studies reported specific data on ORR (*Figure 2*). The mean result was 39.1% (95% CI, 24.3–54.0%). In the pooled surgical resection rate, the percentage of patients who successfully underwent surgery was 90.7% (95% CI, 85.3–95.1%) of the 19 trials involved. As for the R0 rate, the 15 trials' average result was 97.8% (95% CI, 94.8–99.6%). In terms of pathologic response, we applied MPR and pCR as the research objects. The definition of MPR was less than 10% of viable tumor cells in both resected primary tumor beds and lymph nodes. On this basis, pCR was completely absent of viable tumor cells. Pooled MPR based on 15 studies was 44.4% (95% CI, 29.9–59.4%) and pCR of 16 trials involved reached 23.3% (95% CI, 14.4–32.2%) (Figure S1).

Safety of neoadjuvant immunotherapy

We obtained specific information on the incidence of TRAE, the incidence of 3–5 grade TRAE, the incidence of surgical complications, and the surgical delay rate. Based on these data, we could conclude whether ICIs were safe when they were used before surgery. In these studies, investigators decided whether adverse events were treatment-related according to the study protocol and standard regulatory requirements. They also decided on the definition of surgical complications and surgical delay. After the analysis, the pooled results were 38.9% (95% CI, 23.6–64.0%), 19.0% (95% CI, 6.4–36.3%), 17.9% (95% CI, 6.8–29.1%) and 3.2% (95% CI, 0.4–8.7%), respectively. Detailed information can be found in *Figure 3* and Figure S2.

Subgroup analysis

Due to the huge heterogeneity, we divided the studies into different groups to figure out the underlying reason. When

Table 1 Summary of characteristics of studies of neoadjuvant immunotherapy in resectable NSCLC

First author	Year	Clinical trail	NCT number	Phase	ICIs	Main inclusion criteria	Enrollment	Cycles	Median age (years)
Shugeng Gao	2020	ChiCTR-OIC-17013726	–	Ib	Sintilimab	IA–IIIB	40	2	62
B. Besse	2020	PRINCEPS	NCT02994576	2	Atezolizumab	IA–IIIA	30	1	64
David P. Carbone	2020	LCMC3	NCT02927301	2	Atezolizumab	IB–IIIB	181	2	65.1
Catherine A Shu	2020	MAC	NCT02716038	2	Atezolizumab	IB–IIIA	30	4	–
Mariano Provencio	2020	NADIM	NCT03081689	2	Nivolumab	IIIA	46	3	63
Tina Cascone	2021	NEOSTAR	NCT03158129	2	Nivolumab	IA–IIIA	23	3	65.6
Tina Cascone	2021	NEOSTAR	NCT03158129	2	Nivolumab + ipilimumab	IA–IIIA	21	3	65.6
Ralph Zinner	2020	–	NCT03366766	2	Nivolumab	IB–IIIA	13	1	69
Jonathan Spicer	2021	CheckMate 816	NCT02998528	3	Nivolumab	IB–IIIA	179	3	–
P. M. Forde	2018	CheckMate 159	NCT02259621	1	Nivolumab	I–IIIA	21	2	67
Chi-Fu Jeffrey Yang	2017	TOP1201 IPI	NCT01820754	2	Ipilimumab	II–IIIA	24	2	65
Zerui Zhao	2021	NeoTPD01	NCT04304248	2	Toripalimab	IIIA–IIIB	33	3	61
M. Wislez	2020	IONESCO	NCT03030131	2	Durvalumab	IB–IIIA	46	3	61
Sacha I. Rothschild	2021	SAKK 16/14	NCT02572843	2	Durvalumab	IIIA	67	2	–
N. Ready	2019	MK3457-233	–	NR	Pembrolizumab	IB–IIIB	30	2	–
A. Ben Nun	2019	MK3475–223	NCT02938624	1	Pembrolizumab	I–II	10	2	70.5
Florian Eichhorn	2021	NEOMUN	NCT03197467	2	Pembrolizumab	II–IIIA	15	2	59.8
TOP1501	2021	TOP1501	NCT02818920	2	Pembrolizumab	IB–IIIA	35	2	71
Y. Zhang	2021	–	MCT4144608	NR	Toripalimab	IIIA–IIIB	15	2	57

NSCLC, non-small cell lung cancer; ICIs, immune checkpoint inhibitors; NR, not recorded.

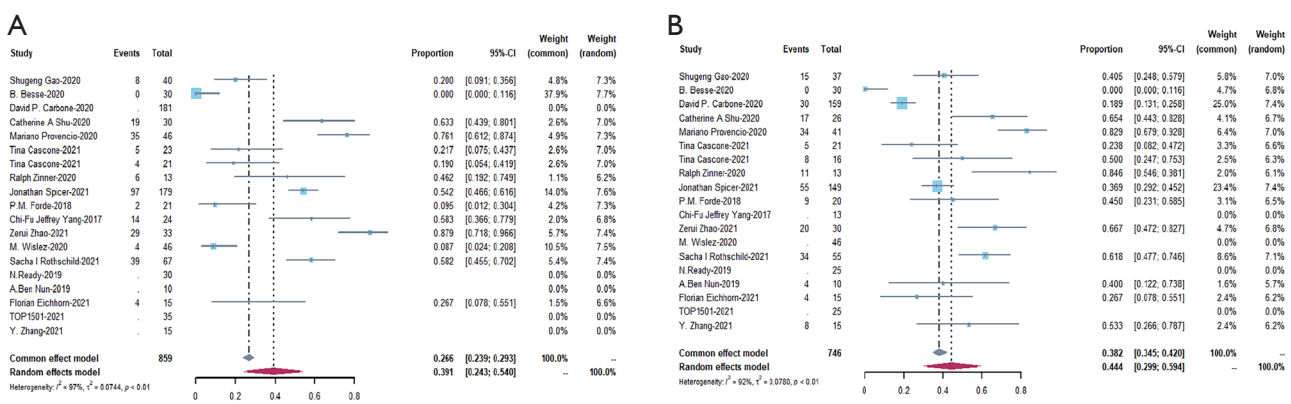

Figure 2 Meta-analysis of pooled efficacy. Forest plot for the efficacy of neoadjuvant immunotherapy. (A) ORR. (B) MPR. CI, confidence interval; ORR, objective response rate; MPR, major pathological response.

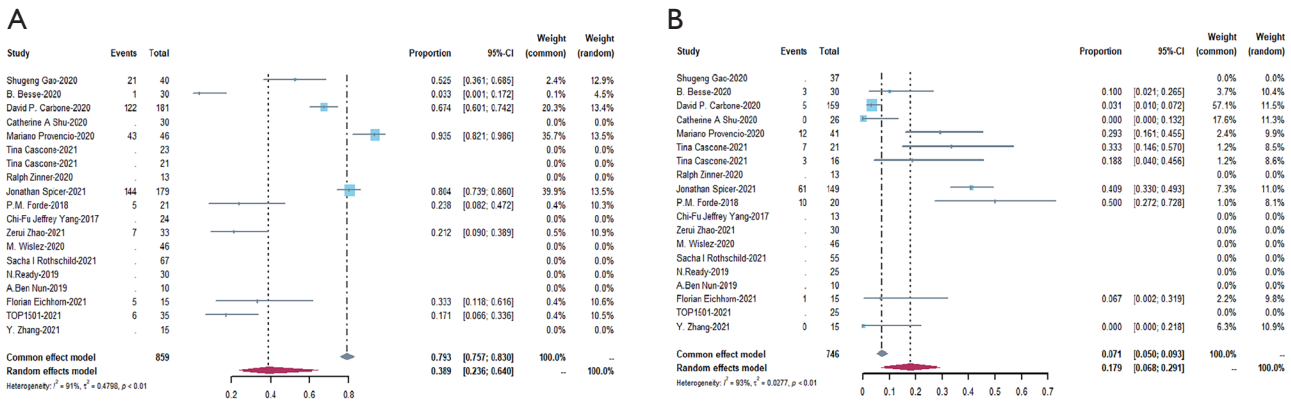

Figure 3 Meta-analysis of pooled safety. Forest plot for the safety of neoadjuvant immunotherapy. (A) TRAE. (B) The incidence of surgical complications. CI, confidence interval; TRAE, treatment-related adverse event.

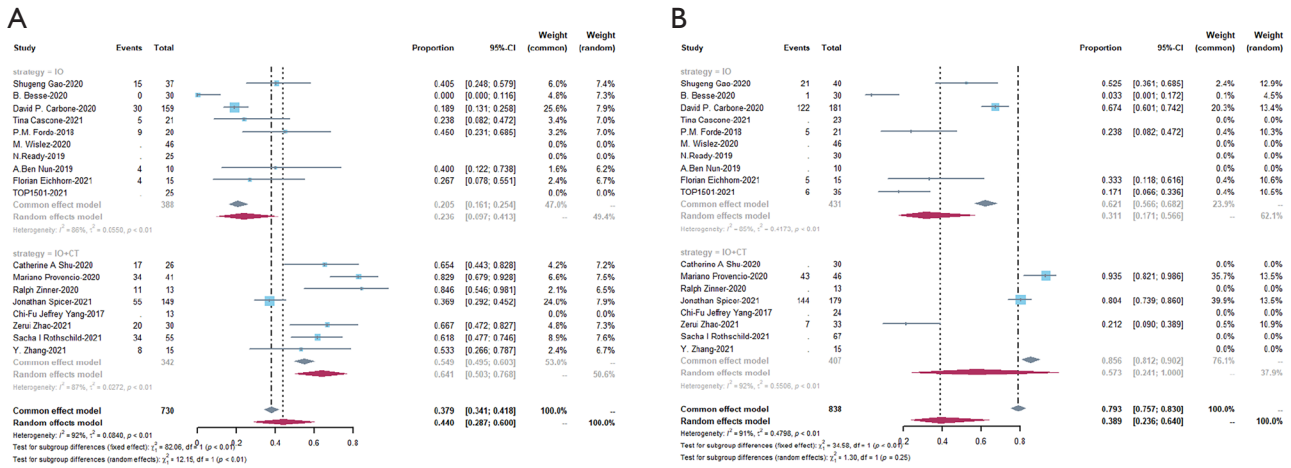

Figure 4 Subgroup analysis of safety and efficacy among different combination therapies. Subgroup analysis of safety and efficacy based on combination types. (A) MPR. (B) TRAE. CI, confidence interval; IO, immunotherapy; CT, chemotherapy; MPR, major pathological response; TRAE, treatment-related adverse event.

we compared studies using only ICIs and those combining chemotherapy and ICIs, the difference was obvious. Generally, combination therapy obtained superior efficacy, reflected by the higher ORR (68.4% *vs.* 11.9%), MPR (64.1% *vs.* 23.6%) (*Figure 4*), and pCR (35.4% *vs.* 5.2%) (Figure S2). However, TRAE (57.3% *vs.* 31.1%) and high-grade TRAE (37.3% *vs.* 8.4%) increased. The differences between other outcomes were comparable.

When we changed the focus from the combination strategy of ICIs and chemotherapy to the type of ICIs, the same tendency appeared between PD-1 inhibitors and PD-L1 inhibitors. In terms of radiologic response and pathologic response, PD-1 inhibitors showed better performance compared with PD-L1 inhibitors. Pooled ORR, MPR (*Figure 5*), and pCR (Figure S3) for PD-1 inhibitor was 43.1% (95% CI, 23.0–63.3%), 50.5% (95% CI, 36.4–64.6%) and 26.8% (95% CI, 14.8–38.8%), separately. For PD-L1 inhibitor, outcome was 32.0% (95% CI, 0–64.1%), 29.5% (95% CI, 2.0–71.2%) and 13.9% (95% CI, 0–29.0%), respectively. As for safety, TRAE in the PD-1 inhibitor subgroup was 41.1%, and the other one was 17.6% (*Figure 5*). Additionally, the surgical complication was 25.8% in PD-1 inhibitor and 2.8% in PD-L1 inhibitor. However, 3–5 grade TRAE in PD-1 inhibitor (14.1%; 95% CI, 5.1–26.6%) showed an inferior performance compared with PD-L1 inhibitor (27.0%; 95% CI, 0–89.8%). The

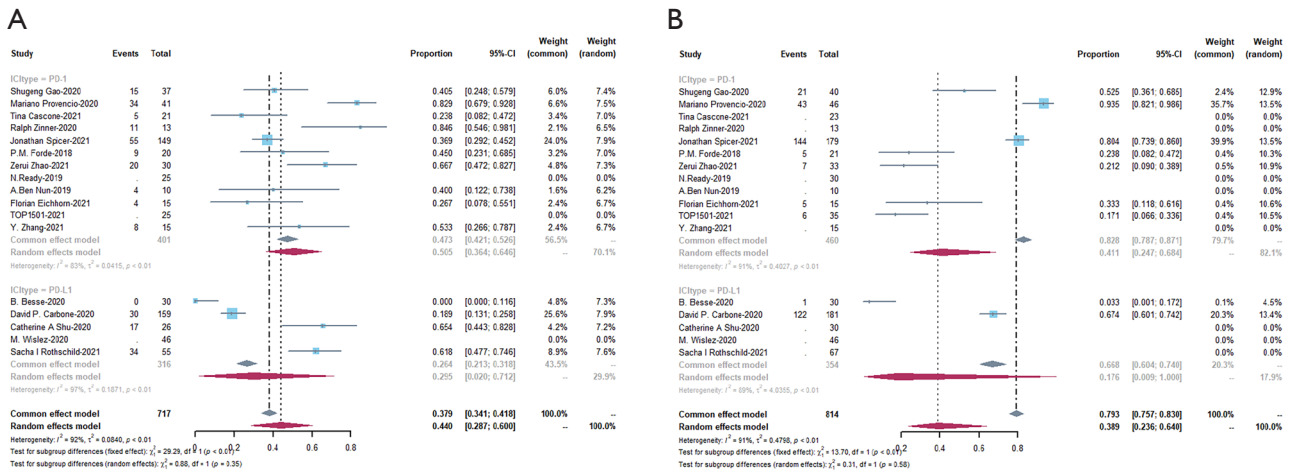

Figure 5 Subgroup analysis of safety and efficacy among different types of ICIs. Subgroup analysis of safety and efficacy based on ICIs types. (A) MPR. (B) TRAE. CI, confidence interval; ICI, immune checkpoints inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; MPR, major pathological response; TRAE, treatment-related adverse event.

combined outcomes in the R0 rate, surgical complication, and surgical resection rate were similar between groups (Figure S3).

Exploratory analysis

To further identify the possible biomarkers predicting prognosis, we conducted a meta-analysis of possible factors affecting pathologic response. First of all, the PD-L1 tumor proportion score (TPS) was a significant biomarker in advanced lung cancer. In this article, we explored whether PD-L1 TPS related to short-term outcomes, MPR, or pCR, which could be closely relevant to long-term prognosis in chemotherapy. Via R, we compared those with PD-L1 expression positive (≥1%) and those with PD-L1 expression negative (<1%) in participants with MPR. The combined RR of 8 trials was 1.56 (95% CI, 1.06–2.29) (*Figure 6*). When comparing PD-L1 high-expressing patients with PD-L1 low-expressing patients, the pooled RR was 3.38 (95% CI, 1.20–9.52) (*Figure 6*). We also considered those with low PD-L1 expression and those with PD-L1 negative expression. The average RR was 0.85 (95% CI, 0.25–2.87) (Figure S4). In terms of the relationship between radiologic response and pathologic response, except for one individual trial, individual RRs of the other 6 trials were in favor of patients with ORR (pooled ORR: 3.19; 95% CI, 2.17–4.69) (*Figure* 7). It indicated patients with ORR could get higher MPR than those without ORR. As for other possible factors such as smoking status, histological type, gender, and clinical stage, we found no significant results by meta-analysis of limited data (Figure S5). In particular, no difference was found in MPR between patients with stage III disease and those with early-stage tumors. Because data regarding stage I and IB were limited, we could not give relatively accurate results.

Similar results could be found when we compared those factors in patients with pCR (Figure S6). The average RR was 2.03 (95% CI, 1.15–3.58) when considering those with PD-L1 positive expression and those with PD-L1 negative expression. As to patients with radiologic responses and those without, the combined RR of 7 trials was 3.36 (95% CI, 1.89–5.98). No significant results were found when considering histological type or gender.

Analysis through meta-regression

Except for subgroup analysis, we also conducted meta-regression to define how many cycles were more recommended and when should operators do surgery after the first dose of ICIs. The analysis found no relationship between different cycles (P=0.16), the median duration of surgery (P=0.37), and MPR. Not median duration (P=0.09), cycles (P=0.02) had a relatively close relationship with pCR.

Study heterogeneity and risk of bias

We applied funnel plots to evaluate heterogeneity due to the huge values of I^2. Results implied that the publication bias of the studies included was tolerable. Subgroup analysis also indicated the possible sources of bias.

Because all the trials included were phase 2 studies except

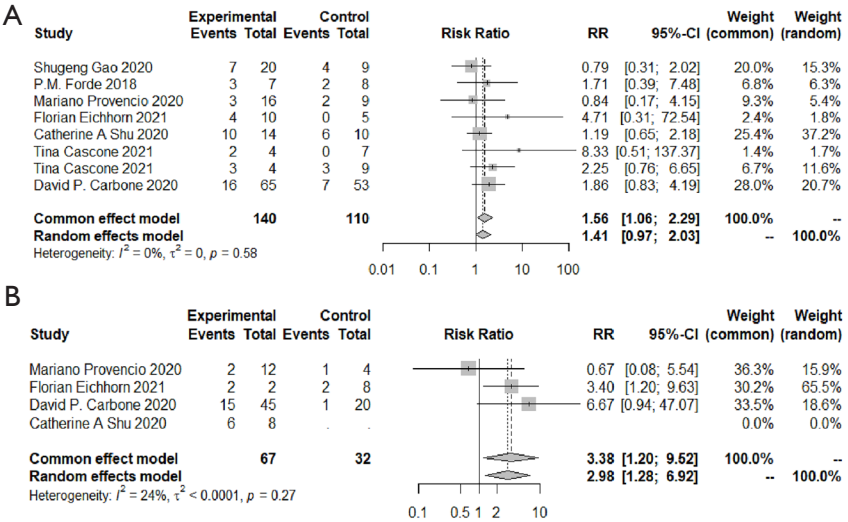

Figure 6 Exploratory analysis of relationship between MPR and PD-L1 expression level. Exploratory analysis of MPR between different PD-L1 expression groups. (A) MPR between PD-L1 positive expression group and PD-L1 negative expression group. Experiment events means the number of patients with MPR in those PD-L1 expression positive. The total means the number of patients who overcame surgery in those PD-L1 expression positive. The control group means events in negative PD-L1 expression group. (B) MPR between group with low PD-L1 expression level and group with high PD-L1 expression level. Experiment events means the number of patients with MPR in those with high PD-L1 expression. The total means the number of patients who overcame surgery in those PD-L1 expression positive. The control group means events in low PD-L1 expression group. RR, relative risk; CI, confidence interval; MPR, major pathological response; PD-L1, programmed cell death protein ligand 1.

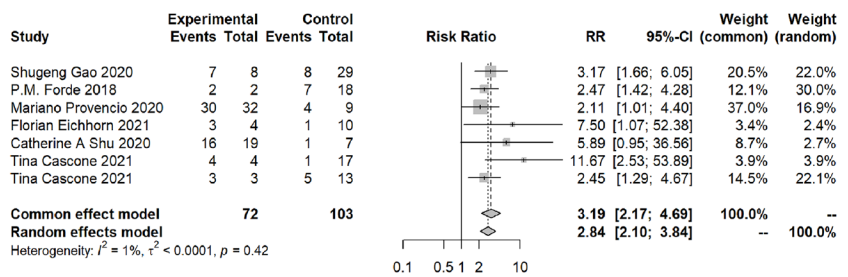

Figure 7 Exploratory analysis of relationship between MPR and ORR. Exploratory analysis of MPR between different radiologic response groups. MPR between group with objective response and group without. Experiment events means the number of patients with MPR in those with objective response. The total means the number of patients who overcame surgery in those with objective response. The control group means events in patients with radiologic stable disease. RR, relative risk; CI, confidence interval; MPR, major pathological response; ORR, objective response rate.

CheckMate 816, most of which were non-RCTs. Thus, we utilized MINORS to make the assessment and found a low risk of bias (Figure S7).

Discussion

Our study did a relatively comprehensive update with 19 trials included. Compared with chemotherapy, immunotherapy gained better outcomes in pathologic response, surgical outcomes, and even adverse events. As to radiologic response, chemotherapy seemed to be better, the same as the previous meta-analysis (30). What's more, we did abundant subgroup analysis and found the outstanding efficacy of combined therapy accompanied by worse adverse

events as we discussed prior. It was finally proved that 3 cycles of nivolumab were preferred. When it comes to pathologic response, PD-L1 expression level may be the possible biomarker. Also, radiologic response reflected pathologic response to some extent.

Two meta-analyses evaluating the feasibility of neoadjuvant immunotherapy have been applied in resectable NSCLC (30,31). However, due to the limited data available, less than 10 trials were included. Different from our article, a study published in 2020 (31) reached only one conclusion that the safety and efficacy of neoadjuvant immunotherapy were supported owing to the relatively higher rate of pCR in several trials and lower pooled incidence of TRAE. However, in that article, few indicators were defined to measure effectiveness and safety due to a lack of data. Also, subgroup analysis didn't compare single-drug immunotherapy and therapy combined ICIs and chemotherapy. Our research did a more comprehensive analysis. Considering the interference of chemotherapy, we divided all trials into two subgroups. According to our analysis, accompanied by better performance in radiologic response and pathologic response, the incidence of adverse events increased in the combined group. Furthermore, information extracted from 18 articles gave us a chance to conduct more detailed subgroup analyses and exploratory analyses. On the other hand, another article in 2021 (30) focused on short-term efficacy and surgical efficacy, lacking data on safety. Several trials gained a high incidence of TRAE, which could not be ignored. For example, in NADIM (17), a trial applying nivolumab and chemotherapy, 93.5% of participants had TRAE and 30.4% of participants suffered from 3–5 grade TRAE, which was considerably higher than that in neoadjuvant chemotherapy (32). Regardless of the numerous TRAE, our study showed the endurable pooled results in the incidence of surgical complication and delay no matter how the trials were grouped. Moreover, detailed subgroup analyses such as type of ICIs and treatment cycles were unable to conduct. The conclusion that the combined therapy was more recommended was consistent with ours to some extent. What is worth learning is that the article extracted data on neoadjuvant chemotherapy, giving a more straightforward comparison between chemotherapy and immunotherapy. Furthermore, possible biomarkers are lacking in discussion in the 2 articles mentioned. In our research, PD-L1 level and radiologic response were discussed for the first time. To sum up, our research updated from the previous 2 articles is worth conducting.

Choosing between PD-1 inhibitor and PD-L1 inhibitor was not analyzed in previous studies due to the deficiency of data. In our study, including 5 trials applying PD-L1 inhibitor, we found inferior performance. The rate of MPR gained 50.5% in the PD-1 inhibitor group whereas the PD-L1 inhibitor group gained only 29.5%. Interestingly, though the incidence of adverse events was higher the in PD-1 inhibitor group, the incidence of 3 to 5 grade TRAE was lower (14.1% *vs.* 27.0%), indicating feasibility when we applied PD-1 in clinical practice.

In previous trials exploring neoadjuvant chemotherapy, the researchers preferred to use MPR as their surrogate endpoint on the basis that histopathologic response related strongly to long-term OS (9,10). Most trials exploring the efficacy of neoadjuvant immunotherapy also tended to use MPR as their surrogate endpoint. Although pCR was considered to be a favorable prognostic factor (33), the number of patients who achieved pCR was pretty low, restricting its use in neoadjuvant chemotherapy (9,34). In NADIM, all patients with MPR or pCR stayed alive after 24 months of follow-up, supporting the possibility of using them as surrogate endpoints. Though most articles used MPR or pCR as a surrogate endpoint, the real relationship between pathologic response and prognosis requests more long-term follow-up data. In this article, we utilized MPR and pCR to evaluate prognosis.

PD-L1 level is a biomarker widely used in advanced NSCLC (35-37) and several clinical trials would like to explore its use of it in neoadjuvant immunotherapy (16,17,20,21). Unfortunately, controversial results were reached in these trials because individual cases with low PD-L1 expression reached surprising results as well. For example, in NEOMUN, researchers found positive relationships while a complete responder with a PD-L1 expression level of 1% existed. Herein, we analyzed data extracted from 8 studies and concluded that PD-L1 could be a potential biomarker predicting pathologic response in neoadjuvant immunotherapy. Specifically, PD-L1 positive patients achieved higher MPR than PD-L1 negative ones. Furthermore, in those with positive expression, high expression ones (TPS >50%) could be a more advantaged group.

On the other hand, the radiologic response has been a complicated indicator when using ICIs because of the pseudoprogression (38). In our study, after analyzing 7 trials involved, we found a significant difference that radiologic response could be another potential indicator of pathologic response in neoadjuvant immunotherapy. In NEOSTAR,

researchers found positive relationships between radiologic response and pathologic response. Furthermore, because no pseudoprogression was found in NEOMUN, researchers concluded that computed tomography (CT) helped predict pathologic response. However, in chemotherapy, it was inconsistent that RECIST could be an incredible factor to predict OS or histopathologic response. Compared with ORR, pathologic response seemed more likely to be the possible predictor of prognosis (39). Moreover, in ChiCTR-OIC-17013726, researchers found a significant correlation between maximum standardized uptake value (SUVmax) reduction and pathologic response, giving credit to positron emission tomography (PET)-CT. On the other hand, about those who didn't reach MPR or pCR, almost all the participants in ChiCTR-OIC-17013726 experiencing surgery while failing to achieve pathologic response tended to have lower SUVmax reduction (mostly <30% except one) while 13 patients reaching MPR measured had SUVmax reduction of more than 30% More controlled trials should be conducted to explore these conclusions. What is the role of PET-CT can be a possible direction for researchers to explore (40).

Tumor subtype, smoking status, and gender showed no significant difference in MPR. We got the same results in the tumor stage such as stage III. It may be different from some previous individual studies such as ChiCTR-OIC-17013726, which found higher MPR in squamous carcinoma. The limitation of meta-analysis and the limited data available could be the underlying explanation.

Except for MPR, we also used pCR for the evaluation, and the results reached were similarly the same.

We do have several limitations in this meta-analysis. Firstly, most of the studies involved were single-arm trials and some of them had only abstracts published at a recent conference. Consequently, the bias of these studies could be high. Missing data added to the difficulty of analysis. More RCTs should be included in the future. Secondly, the literature search may have language bias since no non-English language databases were searched. Thirdly, our study analyzed the trend between groups and we cannot provide an accurate statistical difference between comparison groups. Furthermore, long-term data was missing in our study for limited data. As a result, we gave more attention to MPR and pCR, which could be potential indicators reflecting prognosis. In addition, several new biomarkers were lack of data such as circulating tumor DNA (ctDNA) in peripheral blood or tumor mutational burden.

Conclusions

In conclusion, our meta-analysis confirms previous studies supporting the efficacy and safety of immunotherapy compared with traditional chemotherapy. Moreover, combination therapy is preferred in efficacy and its safety is acceptable. Except for the conclusion above with more trials involved, we also consumed that the PD-1 inhibitor was better. Regarding potential biomarkers, PD-L1 expression can be a strong factor. In our study, the radiologic response also owns a close relationship with MPR. The ongoing trials may provide detailed results in the future. More analysis should be conducted to support its wider application in clinical practice.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://amj.amegroups.com/article/view/10.21037/amj-22-88/rc

Peer Review File: Available at https://amj.amegroups.com/article/view/10.21037/amj-22-88/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://amj.amegroups.com/article/view/10.21037/amj-22-88/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Appendix 1

Search strategy

#1
"Carcinoma, Non-Small-Cell Lung" OR "Carcinoma, Non Small Cell Lung" OR "Carcinomas, Non-Small-Cell Lung" OR "Lung Carcinoma, Non-Small-Cell" OR "Lung Carcinomas, Non-Small-Cell" OR "Non-Small-Cell Lung Carcinomas" OR "Nonsmall Cell Lung Cancer" OR "Non-Small-Cell Lung Carcinoma" OR "Non Small Cell Lung Carcinoma" OR "Carcinoma, Non-Small Cell Lung" OR "Non-Small Cell Lung Cancer" OR "NSCLC"
#2
"Neoadjuvant Therapy" OR "Neoadjuvant" OR "Neo-adjuvant" OR "induction treatment" OR "Perioperative" OR "Preoperative"
#3
"nivolumab" OR "opdivo" OR "ono-4538" OR "MDX-1106" OR "BMS-936558" OR "pembrolizumab" OR "lambrolizumab" OR "keytruda" OR "SCH900475" OR "MK-3475" OR "atezolizumab" OR "tecentriq" OR "RO5541267" OR "RG7446" OR "MPDL3280A" OR "durvalumab" OR "imfinzi" OR "MEDI-4736" OR "MEDI4736" OR "Avelumab" OR "barvencik" OR "MSB0010718C" OR "cemiplimab" OR "libtayo" OR "REGN2810" OR "Tislelizumab" OR "BGB-A317" OR "Sintilimab" OR "IBI 308" OR "IBI308" OR "IBI-308" OR "Ipilimumab" OR "Yervoy" OR "MDX 010" OR "Lambrolizumab" OR "Keytruda" OR "MK-3475" OR "Camrelizumab" OR "SHR-1210"
#4
"Trial" OR "Trials" OR "phase" OR "Random" OR "Randomized" OR "Controlled"
#5
("Randomized Controlled Trial" or "Clinical Trial") not "Review"
#6
#1 AND #2 AND #3 AND #4 AND #5

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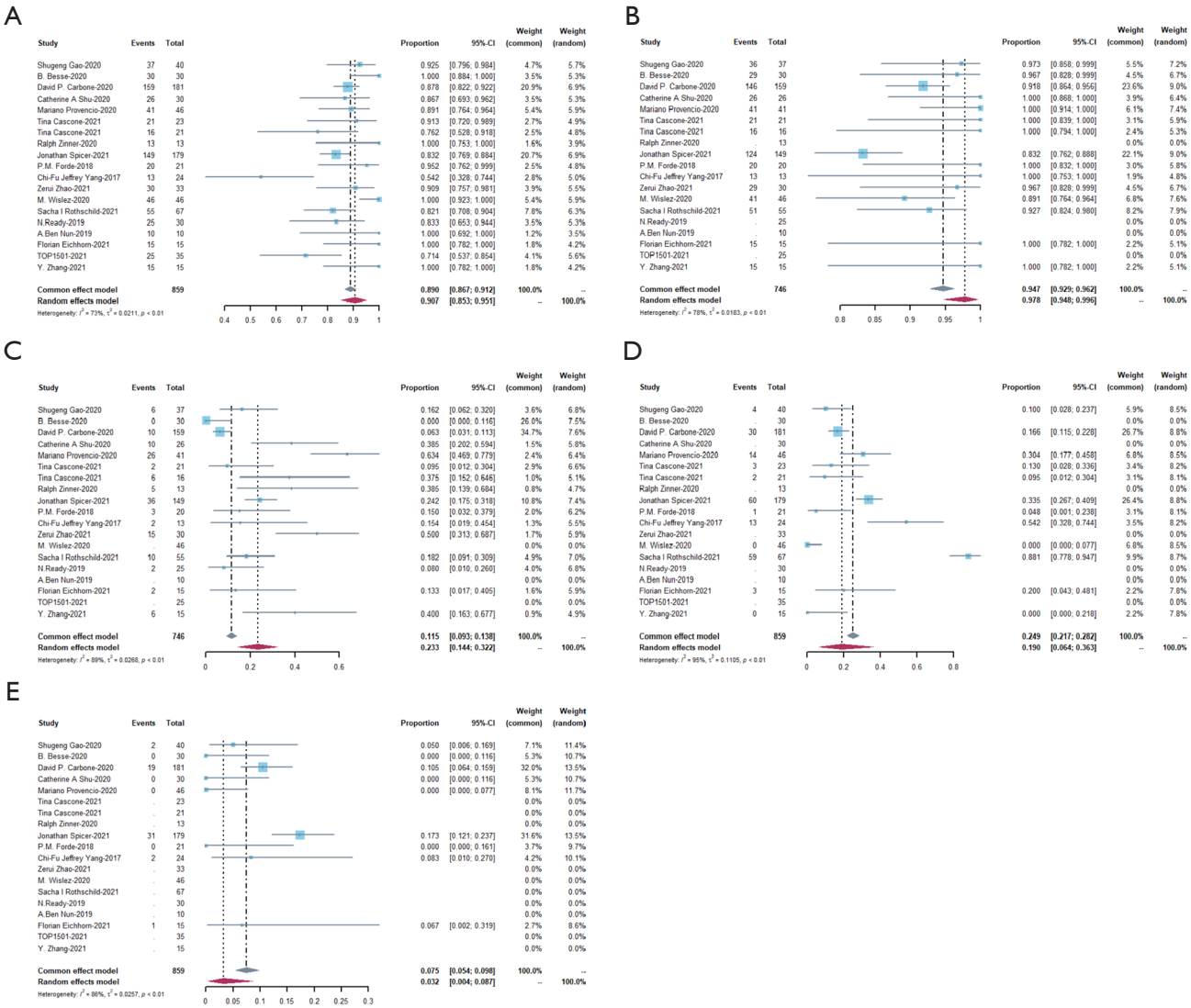

Figure S1 Meta-analysis of pooled efficacy and safety. Forest plot for the efficacy and safety of neoadjuvant immunotherapy. (A) Surgical resection rate. (B) R0 rate. (C) pCR. (D) 3–5 grade TRAE. (E) Surgical delay. CI, confidence interval; R0 rate, R0 surgical resection rate; pCR, pathological complete response; TRAE, treatment-related adverse event.

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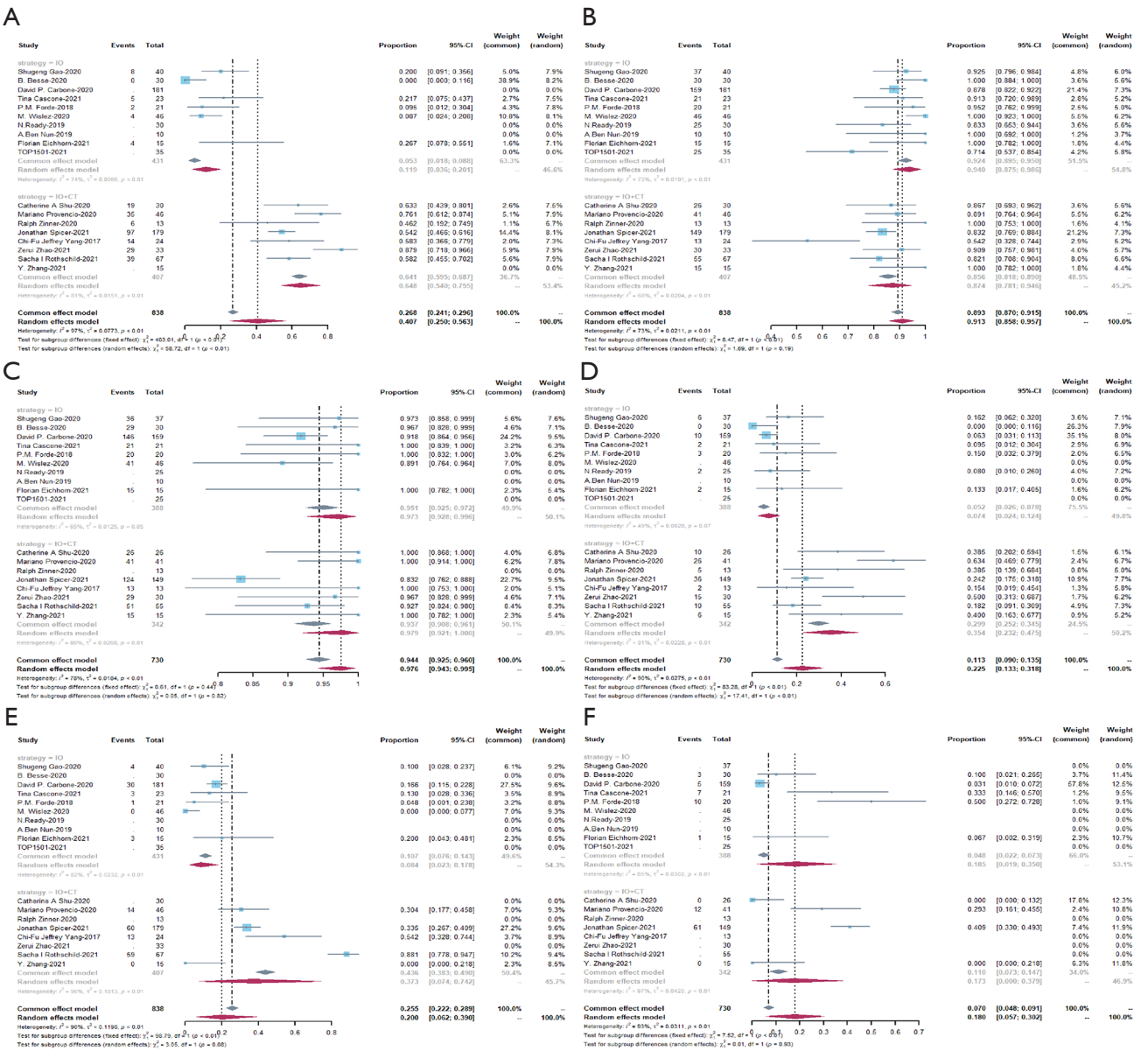

Figure S2 Subgroup analysis of safety and efficacy among different combination therapies. Subgroup analysis of safety and efficacy based on combination types. (A) ORR. (B) Surgical resection rate. (C) R0 rate. (D) pCR. (E) 3–5 grade TRAE. (F) Surgical complications. CI, confidence interval; IO, immunotherapy; CT, chemotherapy; ORR, objective response rate; R0 rate, R0 surgical resection rate; pCR, pathological complete response; TRAE, treatment-related adverse event.

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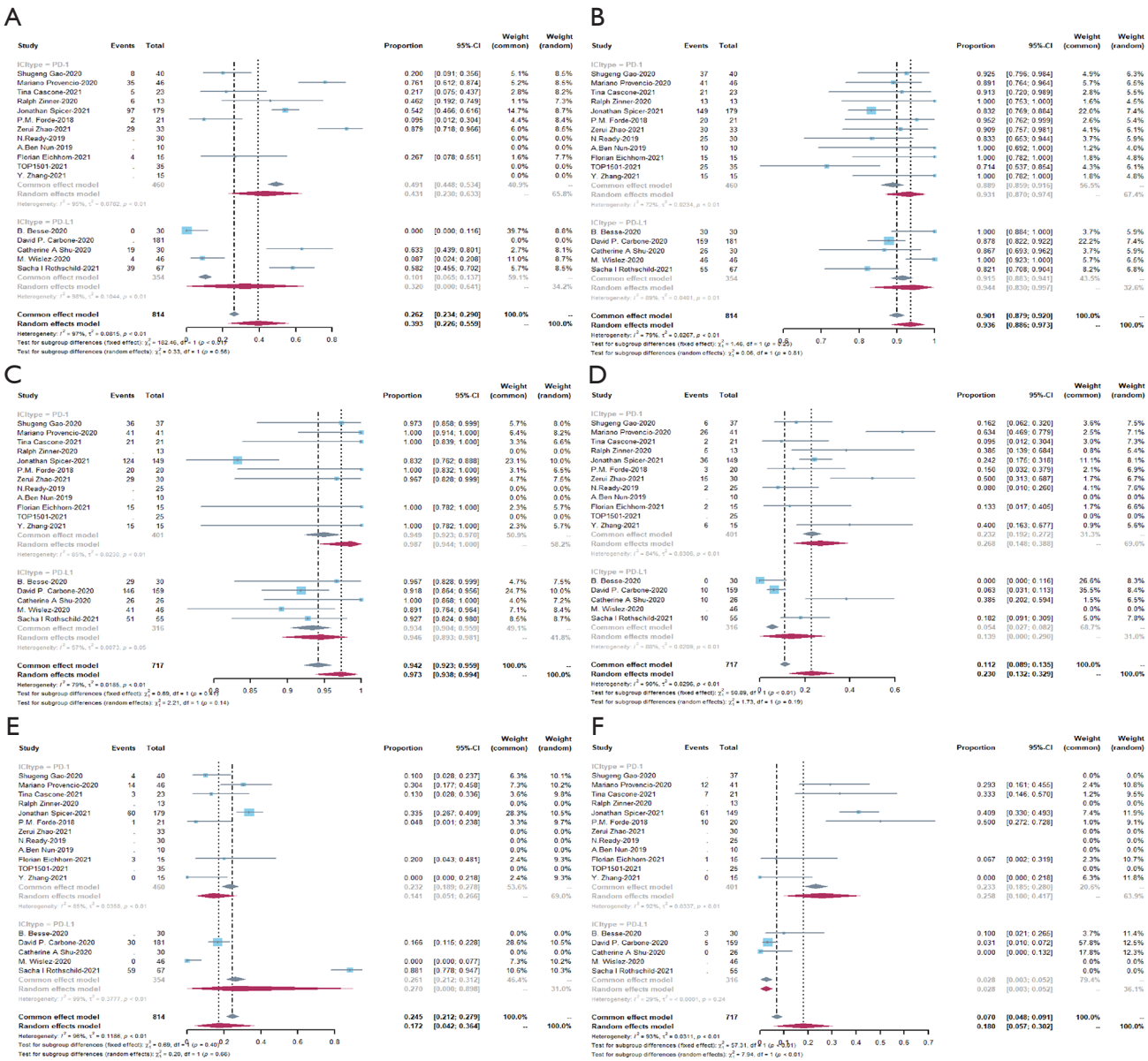

Figure S3 Subgroup analysis of safety and efficacy among different types of ICIs. Subgroup analysis of safety and efficacy based on ICIs types. (A) ORR. (B) Surgical resection rate. (C) R0 rate. (D) pCR. (E) 3–5 grade TRAE. (F) surgical complications. CI, confidence interval; ICI, immune checkpoints inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; ORR, objective response rate; R0 rate, R0 surgical resection rate; pCR, pathological complete response; TRAE, treatment-related adverse event.

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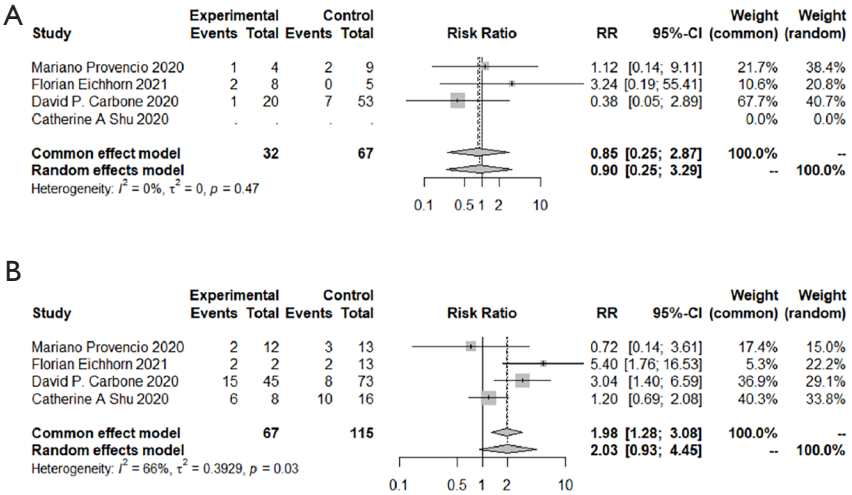

Figure S4 Exploratory analysis of relationship between MPR and PD-L1 expression level. Exploratory analysis of MPR between different PD-L1 expression groups. (A) MPR between low PD-L1 expression group and PD-L1 negative expression group. Experiment events means the number of patients with MPR in those with low PD-L1 expression. The total means the number of patients who overcame surgery in those with low PD-L1 expression. The control group means events in negative PD-L1 expression group. (B) MPR between group with high PD-L1 expression level and group with PD-L1 expression level range from 0 to 49%. Experiment events means the number of patients with MPR in those with high PD-L1 expression. The total means the number of patients who overcame surgery in those PD-L1 expression positive. The control group means events in group with PD-L1 expression level range from 0 to 49%. RR, relative risk; CI, confidence interval; MPR, major pathological response; PD-L1, programmed cell death protein ligand 1.

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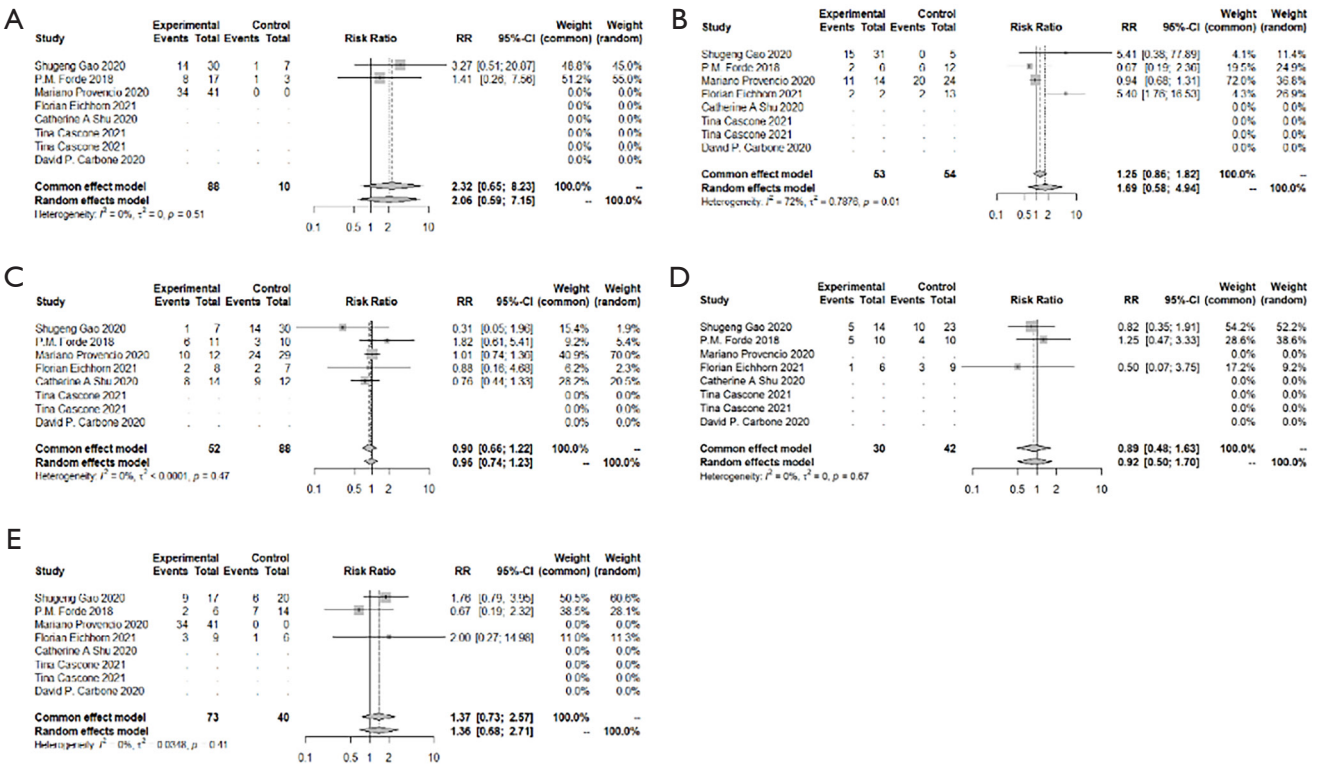

Figure S5 Exploratory analysis of relationship between MPR and clinical characteristics. Exploratory analysis of MPR between different groups. (A) MPR between smoking group and no smoking group. (B) MPR between adenocarcinoma and squamous carcinoma. (C) MPR between female and male. (D) MPR between group with stage II tumor and group with other stage tumor. (E) MPR between group with stage III tumor and group with other stage tumor. Experiment events means the number of patients with MPR in those smoking, squamous carcinoma, female, with stage II tumor, with stage III tumor, respectively. The total means the number of patients who overcame surgery. The control group means the other group in each category. RR, relative risk; CI, confidence interval; MPR, major pathological response.

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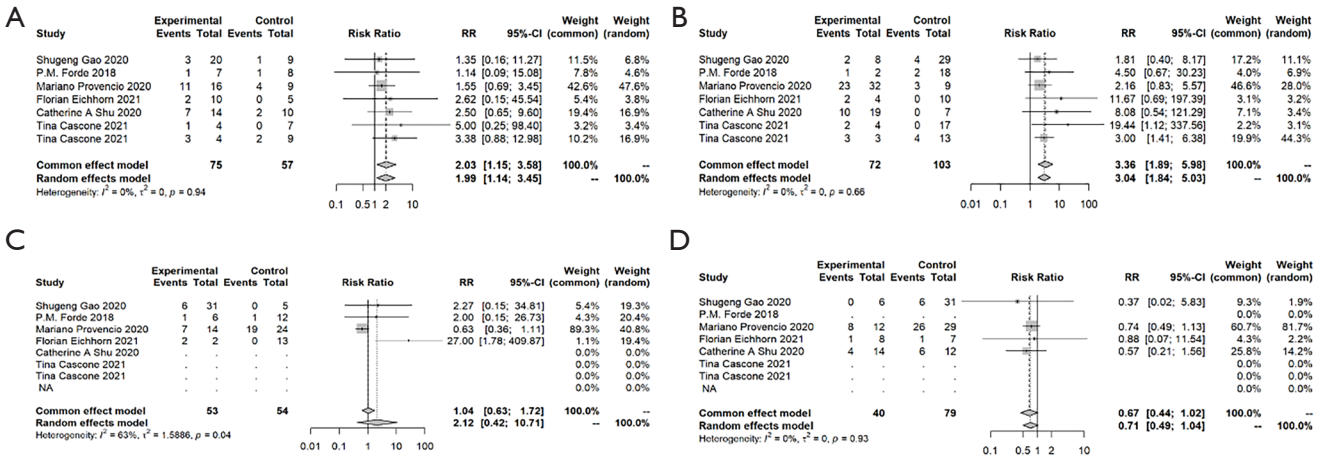

Figure S6 Exploratory analysis of pCR. Exploratory analysis of pCR between different groups. (A) pCR between PD-L1 positive expression group and PD-L1 negative expression group. (B) pCR between group with objective response and group without. (C) pCR between adenocarcinoma and squamous carcinoma. (D) pCR between female and male. Experiment events means the number of patients with pCR in those with positive PD-L1 expression, with objective response, squamous carcinoma, female, respectively. The total means the number of patients who overcame surgery. The control group means the other group in each category. RR, relative risk; CI, confidence interval; pCR, pathological complete response; PD-L1, programmed cell death protein ligand 1.

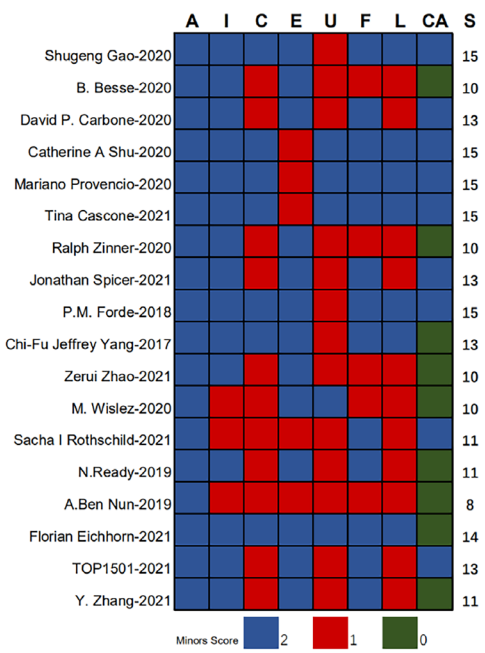

Figure S7 Risk of bias assessment for 18 trials included. Risk of bias assessment. A, a clearly stated aim; I, inclusion of consecutive patients; C, prospective collection of data; E, endpoint appropriate to the aim of study; U, unbiased assessment of the study endpoint; F, follow-up period appropriate to the aim of the study; L, loss to follow-up <5%; CA, prospective calculation of the study size.

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