Neoadjuvant Immune Checkpoint Inhibitors in Non-small Cell Lung Cancer

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ABSTRACT

Lung cancer is the leading cause of cancer-related death worldwide. A meta-analysis was conducted to assess the benefits and risks of neoadjuvant immune checkpoint inhibitors (ICIs) in non-small cell lung cancer (NSCLC). Online databases, including PubMed, Embase, Web of Science, Cochrane Library, and clinicaltrials.gov, were retrospectively and systematically searched for eligible trials from database inception to May 2021. A total of 792 patients from 21 clinical trials were included. For surgical data, the pooled operation rate and R0 resection rate were 92% (95% CI 87-96%) and 97% (95% CI 94-99%). Additionally, neoadjuvant ICIs achieved a major pathological response (MPR) of 39% (95% CI 25-53%), including 25% (95% CI 16-36%) pathological complete response (pCR). With radiological response assessment, the pooled objective response rate (ORR) and disease control rate (DCR) were 44% (95% CI 21-68%) and 88% (95% CI 75-98%), respectively. In terms of safety, the pooled rate of any-grade and grade 3–5 treatment-related adverse effects (TRAEs) were 57% (95% CI 38-76%) and 15% (95% CI 6-28%). Eventually, the study concludes that neoadjuvant ICIs are effective and safe for patients with early-stage NSCLC.

Key Words: *Neoadjuvant therapy, Immune checkpoint inhibitors, Non-small cell lung cancer, Meta-analysis.*

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INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide.[1] In spite of tremendous advances in local and systemic therapies, cure rates of lung cancer have still increased slowly over the last decades. The estimated median 5-year overall survival (OS) rate was 36-92% for early-stage NSCLC patients, and 13-36% for unresectable stage III NSCLC patients.[2] Unfortunately, the initial diagnosis of early-stage lung cancer with localized lesion accounted for less than 39%.[3] For these patients, complete surgical resection with curative intent remains the most effective therapy.[4-6] And neoadjuvant or adjuvant chemotherapy strategies could improve benefits for patients with bulky or high-risk cancer.[5,7]

In this era of immunotherapy, ICIs have been proven to be a breakthrough and revolutionized approach to the treatment of advanced NSCLC.[8]

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However, it is unclear whether neoadjuvant ICIs could have similar definite curative effect and controlled toxicity to enhance benefit-risk expectations in early-stage NSCLC. With more available results of related trials on neoadjuvant ICIs, the objective of this meta-analysis was to investigate the efficacy and safety of neoadjuvant ICIs for patients with NSCLC using a well-designed and comparative synthesis.

METHODOLOGY

This study was registered in PROSPERO (International Prospective Register of Systematic Reviews), with the number CRD42020188978. A comprehensive systematic search of PubMed, Embase, Web of Science, Cochrane Library, and clinicaltrials.gov were conducted from database inception to May 2021. Medical Subject Headings (MeSHs) and free text terms were combined with Boolean operators. Details about procedures and methods are described in Figure 1.

Eligible studies had to satisfy all the following inclusion criteria of early-stage NSCLC patients who had received neoadjuvant ICIs and met surgical criteria and the main study outcome directly or indirectly included effects and safety indicators being prospective clinical trials. The most complete and representative studies were included, and when these were equal, the most recent study was included. Any trials with insufficient data and retrospective studies without original data were excluded.

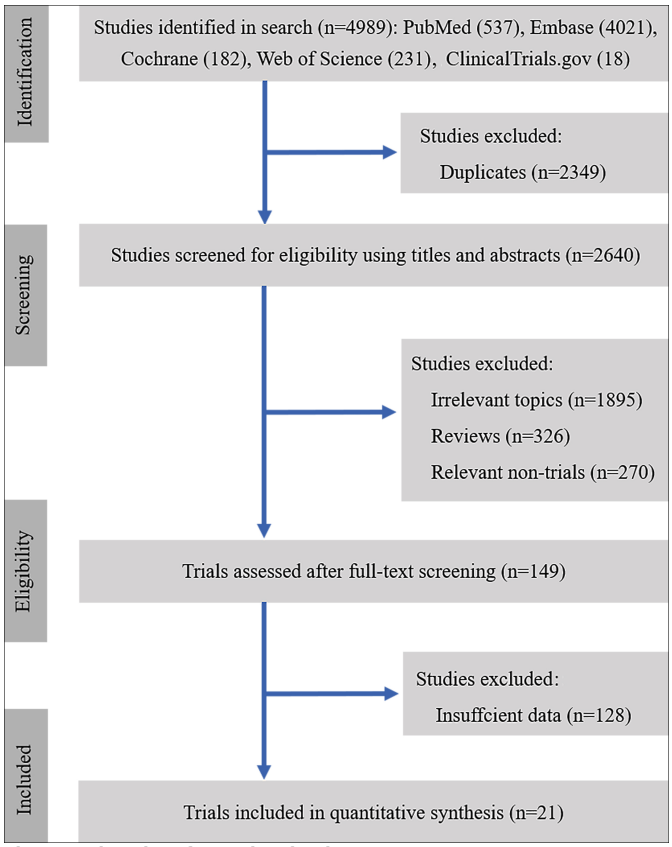

Figure 1: Flow chart for study selection.

Two independent investigators (CX and HD) performed study screening and further exploration. Any discrepancies were solved by a discussion with a third author (HC) until consensus was achieved. The variables extracted using a standardized extraction sheet included details of publications, phase of clinical study, participant characteristics, tumor histology and stage, interventions, duration of follow up, and endpoint measures. Feasibility outcomes of interest were defined as operation completion rates, R0 resection rates, pCR, MPR, ORR, DCR. Safety outcomes of interest were defined as TRAEs% of any-grade and grade 3-5.

Newcastle Ottawa Scale (NOS) was applied to assess the quality of included studies and validated independently by two authors (CX, and HD).[9] Potential publication bias among the main outcome was assessed by Begg's test.

STATA software (version 14.0) was used for all statistical analyses and the generation of the forest plots. The pooled estimates were considered statistically significant if the 95% CI did not include 1.0, with a p value of<0.05 (two-sided).[10] Statistical heterogeneity across studies was assessed using the I^2statistic and forest plots. An I^2 value of <50% indicated a low heterogeneity.[11] On the assumption that incidence data was close to 0 or 1, log-transformed event rates by the double arcsine method need to be restored to reach the final conclusion. Random-effect models were applied to reduce the influence of inter-study heterogeneity. Subgroup analyses were conducted according to the area, arms, intervention, and immune target.

RESULTS

A total of 792 patients in 3 RCTs and 18 no comparative clinical trials were deemed comparatively high quality and eligible for inclusion.[12-32] The characteristics of the included studies were showed in Table 1. But even then, large methodological heterogeneity might have existed for lack of matched groups in these single-arm trials. No publication bias was observed in those studies.

For feasibility data, the primary endpoints included operation completion rate, R0 resection rate, pCR, MPR, ORR and DCR. Just as demonstrated in Figure 2, the pooled operation completion rate and R0 resection rate were 92% (95% CI 87-96%) and 97% (95% CI 94-99%). Additionally, neoadjuvant ICIs achieved an MPR of 39% (95% CI 25-53%) including 25% (95% CI 16-36%) pCR. With radiological response assessment, the pooled ORR and DCR were 44% (95% CI 21-68%) and 88% (95% CI 75-98%), respectively.

For safety data, the pooled result of any grade and grade 3–5 TRAEs% were 57% (95% CI 38-76%) and 15% (95% CI 6-28%), respectively (Figure 3). The rate of surgical complications and operation delay was 10% (95% CI 1-26%) and 3% (95% CI 0-9%), respectively.

The main grade 3–4 AEs were blood or lymphatic system disorders (14%, 95% CI 5-23%), skin reaction (4 %, 95% CI -1-10%), diarrhea/colitis (5%, 95% CI 0-10%). Relatively common toxicities of any grade and grades 3–4 are presented in Table II in detail.

To confirm the variables attributable to heterogeneity, subgroup analysis was performed using the following classification variables: area, arms, intervention, and immune targets types. The final subgroup analysis results are demonstrated in Tables III-VI.

DISCUSSION

At present, neoadjuvant chemotherapy is an acceptable practice to reduce tumor burden for patients with operable and locally advanced NSCLC.[7] Nonetheless, the role of neoadjuvant immunotherapy is not defined. Recent preclinical studies have demonstrated that neoadjuvant ICIs could eradicate chances of distant micro-metastases by modulating the breadth and durability of tumor-specific CD8+ T-cell response.[33,34] Hence, improved antitumor efficacy help patients acquire better long-term survival.[35,36] For inoperable patients, neoadjuvant ICIs strategy, either monotherapy or in combination, could have enormous potential to improve the downstage rate and eventually improve the feasibility of surgery.[7,37-39]

In the case of neoadjuvant ICIs, assessing tumor response according to conventional radiological criteria may underestimate the pathological response. Pathological response, as an outcome measure, correlates with improved PFS and OS data.[7] And immune-related pathologic response criteria (irPRC) have been developed in the completely resected specimen.[40-42]

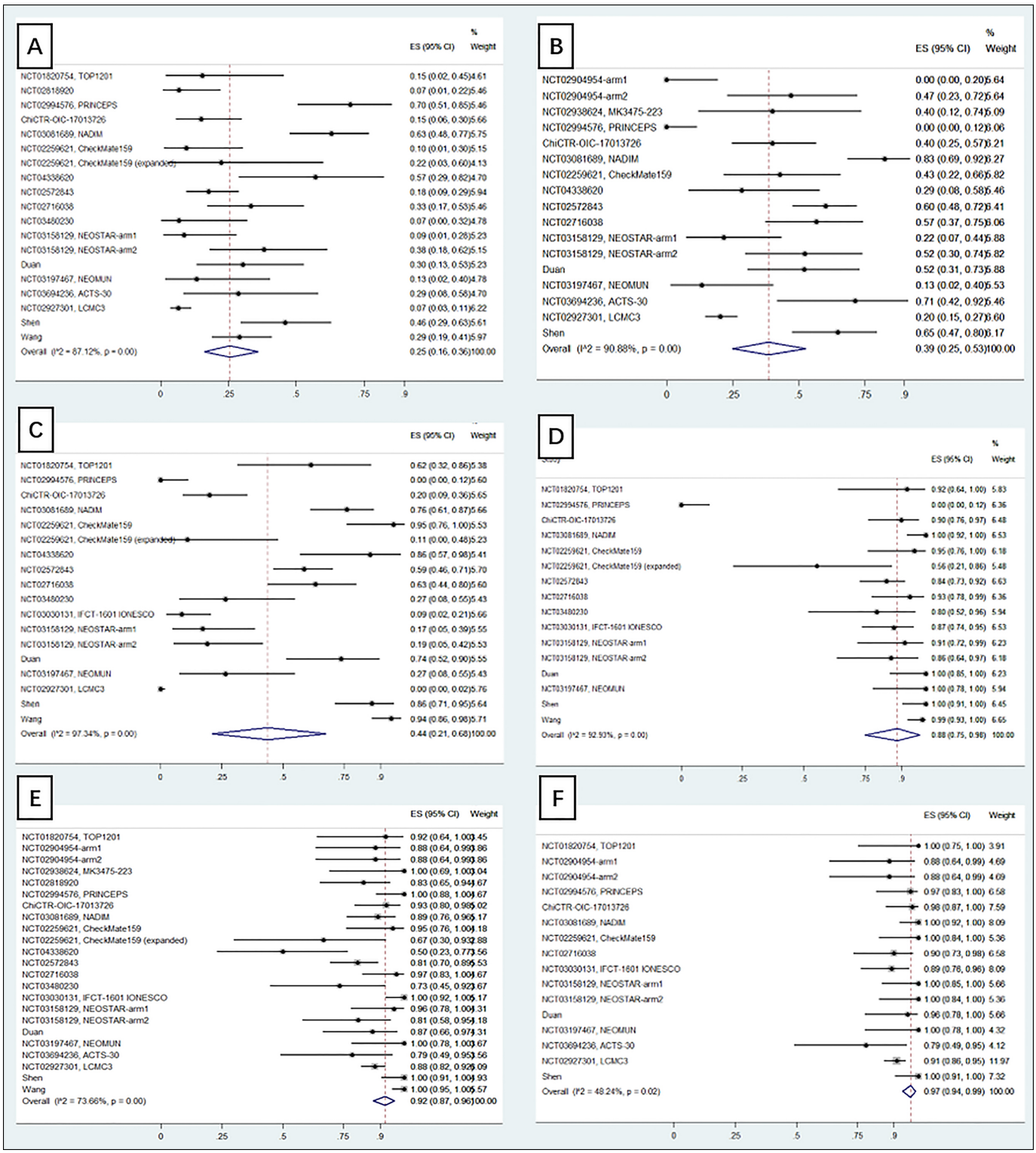

Figure 2: Forest plots depicting surgical data (A. pCR; B. MPR; C. ORR; D. DCR; E. surgical resection rate; F. R0 resection rate).

In this regard, having standardized and thorough protocols for tumor response assessment after neoadjuvant ICIs to grade responses and guide further data collection is crucial.[43-45]

To the best of the authors' knowledge, this is thus far the most comprehensive meta-analysis that has evaluated the feasibility and safety of neoadjuvant ICIs for NSCLC patients. Based on the data we collected, neoadjuvant ICIs achieved relatively improved rates of operation completion and R0 resection inoperable NSCLC patients. According to previous studies,[25,46] the median rate of pCR reviewed from 15 trials of neoadjuvant chemotherapy was 4% (range 0–16%), and MPR reported in GLCCG trials was only 7%.

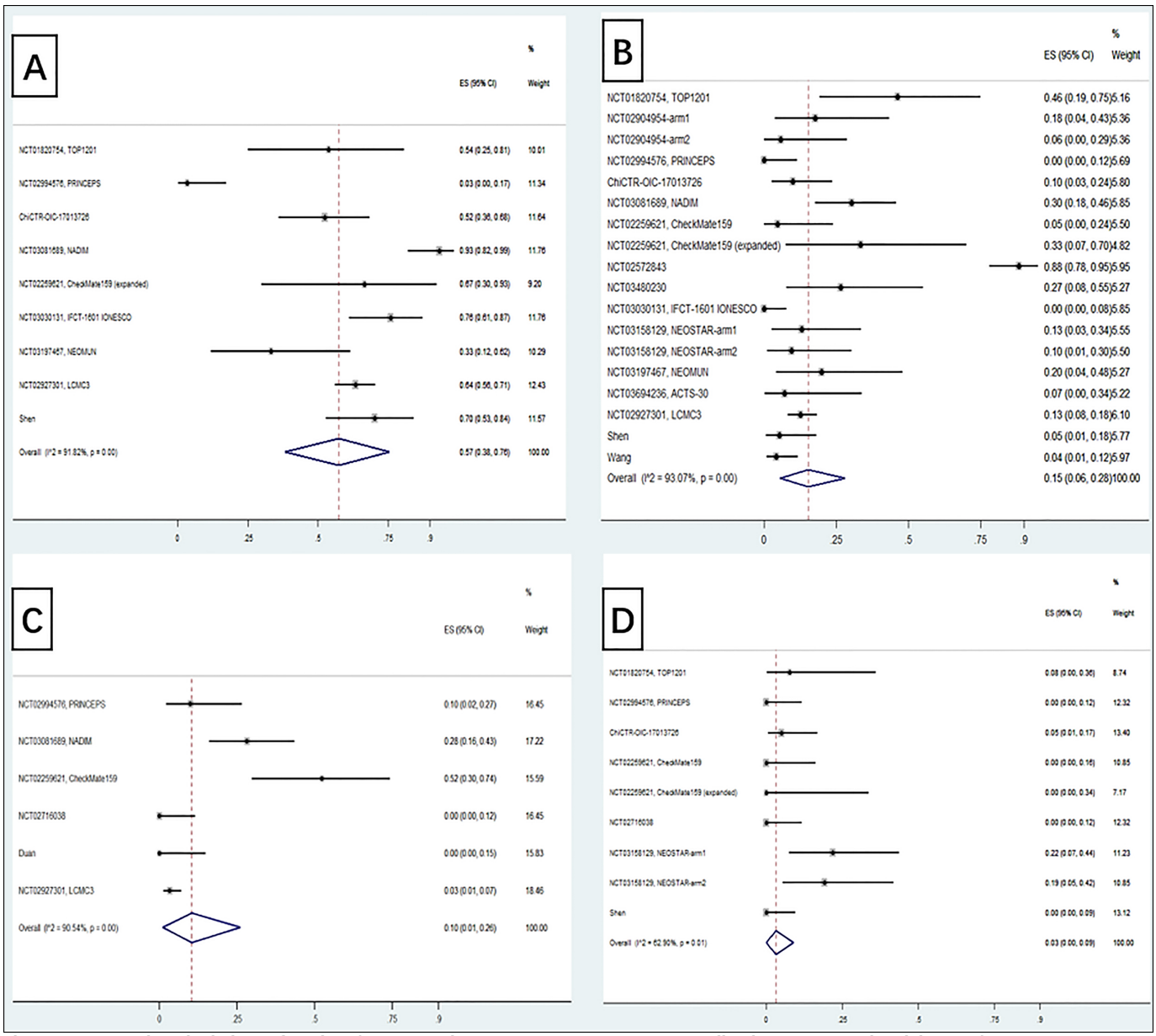

Figure 3: Forest plots depicting safety data (A. any-grade TRAEs; B. G3-5 TRAEs; C. complications; D. operation delay rate).

By comparison, our meta-analysis indicated higher pCR and MPR in neoadjuvant ICIs settings, no matter immune therapy was used alone or in combination with chemoradiotherapy. The outcome of ORR and DCR data also proved to be favorable, supporting the feasibility and obvious effects of neoadjuvant ICIs.

Another issue that we studied is the occurrence of adverse events associated with neoadjuvant ICIs modality, particularly immune-induced diarrhea/colitis and accompanying pulmonary surgical complications. Translationally, early trials also highlighted the importance of appropriate doses and schedules of neoadjuvant ICIs.[47] Currently, determining the optimal timeline and combination strategy of ICIs to achieve the highest cure rates possible requires further investigation.[6,34,48] In the trials published to date, immune-related adverse events (irAEs) induced by neoadjuvant ICIs did rarely delay the preplanned surgery, demonstrating that neoadjuvant ICIs is relatively safe.[13]

As a result, this study might have a meaningful impact on clinical practice, especially in early-stage NSCLC patients being planned to receive ICIs treatment.

This study, nonetheless, still had several potential limitations. Generally, the RCTs with high methodological quality reported better results than the noncomparative studies. To a great extent, a single-arm meta-analysis is subject to subjectivity and heterogeneity. Considerable heterogeneity across studies limited actual evidence-based recommendation grades for neoadjuvant therapy with ICIs for lack of controlled arms.

Table I: The characteristics of the included studies.

Identification	Authors	country	Phase	Stage	Arm	N	SCC	Interventions	Outcomes
NCT01820754, TOP1201	Yang, 2017	USA	II	IB-IIIA	1	13	38.46%	CT; ipilimumab+ CT	Mortality, safety, OS
NCT02904954	Altorki, 2019	USA	II	I-IIIA	1	17	41.18%	Durvalumab	DFS, safety, response rates
		USA	II	I-IIIA	2	17	41.18%	SBRT+Durvalumab	DFS, safety, response rates
NCT02938624, MK3475-223	Bar, 2019	Israel	I	I-II	1	10	60.00%	Pembrolizumab	DLT, MPR, response rate
NCT02259621, CheckMate159	Bott, 2019	USA	I	I-IIIA	1	21	23.81%	Nivolumab	Safety, MPR, ORR, DFS, OS
NCT02818920	Ready, 2019	USA	II	IB-IIIA	1	30	56.67%	Pembrolizumab	Safety, MPR, pCR
NCT02994576, PRINCEPS	Besse, 2020	France	II	IA-IIIA	1	30	16.67%	Atezolizumab	Safety, MPR, respose rate
ChiCTR-OIC-17013726	Gao, 2020	China	I	IA–IIIB	1	40	82.50%	Sintilimab	Safety, nonoperation delay rate, MPR, ORR, DFS, OS
NCT03081689, NADIM	Provencio, 2020	Spain	II	IIIA	1	46	34.78%	Nivolumab+CT	PFS, OS, MPR, respose rate, surgical outcome, and safety
NCT02259621, CheckMate159 (expanded)	Reuss, 2020	USA	II	IB-IIIA	1	9	11.11%	Nivolumab+ipilimumab; nivolumab	Safety, MPR
NCT04338620	Lei, 2020	China	II	IIIA/IIIB	2	14	NA	Camrelizumab+CT	pCR, MPR, ORR, DFS and safety
NCT02572843	Rothschild, 2020	Switzerland	II	IIIA-N2	1	68	NA	CT +durvalumab	EFS
NCT02716038	Shu, 2020	USA	II	IB–IIIA	1	30	40.00%	Atezolizumab+CT	MPR, ORR, DFS, Safety
NCT03480230	Tfayli, 2020	Lebanon	II	IB–III	1	15	13.33%	Avelumab	ORR, pCR, MPR, PFS, OS
NCT03030131, IFCT-1601 IONESCO	Wislez, 2020	France	II	IB-IIIA	1	46	41.30%	Durvalumab	Safety, OS, DFS, ORR, MPR
NCT03158129, NEOSTAR	Cascone, 2021	USA	II	I-IIIA	1	23	43.48%	Nivolumab, 3cycles	Safety, MPR, OS
		USA	II	I-IIIA	2	21	33.33%	Nivolumab+ipilimumab; nivolumab	
Duan	Duan, 2021	China	II	IIA–IIIB	1	23	17.39%	PD-1 (Pembrolizumab/Nivolumab/Sintilimab) + CT	Safety, MPR, pCR,ORR
NCT03197467, NEOMUN	Eichhorn, 2021	Germany	II	IIA-IIIA	1	15	13.33%	Pembrolizumab	Safety, DFS, OS
NCT03694236, ACTS-30	Hong, 2021	Korea	I/II	III	1	14	50.00%	Durvalumab+CRT	Safety, ORR, R0%, EFS, OS, pCR, MPR
NCT02927301, LCMC3	Lee, 2021	USA	II	IB-IIIB	1	181	38.12%	Atezolizumab	MPR and safety
Shen	Shen, 2021	China	II	IIB–IIIB	1	37	100.00%	Pembrolizumab+CT	Safety, MPR, pCR
Wang	Wang, 2021	China	II	IIIA	1	72	91.67%	Nivolumab/pembrolizumab/camrelizumab+CT	Safety□pCR□R0□ORR□complications

CT: Chemotherapy; RT: Radiotherapy; EFS: Event-free survival; pCR: Pathological complete response; MPR: Major pathological response; ORR: Objective response rate; DCR: Disease control rate; DFS: Disease free survival; PFS: Progression free survival; OS: Overall survival.

Table II: Detailed treatment-related adverse effects of neoadjuvant immunotherapy in NSCLC patients.

Types of common TRAEs	Any-grade AEs				Grade 3–4 AEs			
	Study	N	Rate	95% CI	Study	N	Rate	95% CI
Total	12	542	0.60	0.39-0.80	17	708	0.19	0.08-0.31
Blood and lymphatic system disorders	9	375	0.22	0.11-0.33	6	268	0.14	0.05-0.23
Skin reaction	9	316	0.37	0.16-0.57	4	142	0.04	-0.01-0.10
Diarrhea/colitis	8	217	0.18	0.10-0.26	5	88	0.05	0.00-0.10
Asthenia	8	278	0.36	0.23-0.50	3	141	0.02	-0.00-0.04
Dyspnea	7	279	0.03	0.01-0.05	4	167	0.02	0.00-0.04
Nausea/Vomiting	7	261	0.27	0.12-0.42	2	95	0.02	-0.01-0.04
Pneumonitis	6	188	0.04	0.01-0.07	4	165	0.03	0.00-0.06
Liver function test abnormality	6	207	0.12	0.08-0.16	4	153	0.03	0.00-0.05
Hyperthyroidism	5	109	0.07	0.02-0.12	1	15	0.13	-0.04-0.31
Lung infection	2	63	0.05	-0.01-0.10	1	40	0.03	-0.02-0.07
Cardiac disorders	3	130	0.07	0.03-0.11				

Table III: p-values and Begg's tests before and after adjustment.

Groups	p-value (unadjusted)	p-value (adjusted)	Begg's test (unadjusted)	Begg's test (adjusted)
pCR	0.115	0.124	1.57	1.54
MPR	0.520	0.553	-0.64	0.59
operation rate	0.002	0.002	-3.09	3.05
R0 resection rate	0.118	0.144	-1.56	1.46
ORR	0.471	0.499	-0.72	0.68
DCR	0.186	0.213	-1.32	1.25

pCR: Pathological complete response; MPR: Major pathological response; ORR: Objective response rate; DCR: Disease control rate.

Table IV: Subgroup analysis of any-grade and grade 3-5 (G3-5) TRAEs of neoadjuvant immunotherapy in lung cancer patients.

Group	pCR				MPR			
	No. of studies	Rate (95% CI)	P heterogeneity between groups	I2 (%)	No. of studies	Rate (95% CI)	P heterogeneity between groups	I2 (%)
Total	18	0.25 (0.16-0.36)	-	87.12	15	0.39 (0.25-0.53)	-	90.88
Area								
North America	7	0.15 (0.07-0.26)		72.10	5	0.31 (0.16-0.49)		84.96
Europe	4	0.40 (0.13-0.71)	0.10	92.87	4	0.35 (0.02-0.79)	0.20	96.76
Asia	7	0.29 (0.18-0.41)		66.25	6	0.50 (0.38-0.63)		50.50
Arms								
Single	16	0.24 (0.14-0.36)	0.63	88.17	12	0.43 (0.27-0.61)	0.26	92.61
Dual	2	0.32 (0.07-0.63)		.	3	0.26 (0.08-0.51)		81.83
Intervention								
IO	8	0.15 (0.05-0.29)		87.4	8	0.18 (0.07-0.32)		83.14
IO+IO	2	0.33 (0.17-0.52)	0.08	.	1	0.52 (0.30-0.74)	0.00	-
IO+CT/RT	9	0.35 (0.24-0.47)		75.86	8	0.60 (0.49-0.71)		63.46
Immune target								
PD-1	10	0.26 (0.14-0.40)		84.23	9	0.44 (0.28-0.61)		83.01
PD-L1	6	0.25 (0.08-0.46)	0.69	92.12	6	0.31 (0.11-0.55)	0.42	9396
CTLA-4	1	0.15 (0.02-0.45)		-		-		-
PD-1+CTLA-4	2	0.33 (0.17-0.52)		.	1	0.52 (0.30-0.74)		-

NA: Not available; IO: Immuno-oncology drugs; CT: Chemotherapy; RT: Radiotherapy.

Table V: Subgroup analysis of pathological response rate (pCR and MPR) of neoadjuvant immunotherapy in lung cancer patients.

Group	ORR				DCR			
	No. of studies	Rate (95% CI)	P heterogeneity between groups	I2 (%)	No. of studies	Rate (95% CI)	P heterogeneity between groups	I2 (%)
Total	17	0.44 (0.21-0.68)	-	97.34	15	0.88 (0.75-0.98)	-	92.93
Area								
North America	7	0.35 (0.04-0.75)		97.10	5	0.90 (0.81-0.96)		30.43
Europe	5	0.29 (0.04-0.65)	0.24	96.14	5	0.78 (0.34-1.00)	0.17	97.55
Asia	6	0.67 (0.36-0.92)		94.61	5	0.97 (0.90-1.00)		72.08
Arms								
Single	15	0.45 (0.19-0.71)	0.839	97.73	14	0.88 (0.73-0.98)	0.97	93.86
Dual	2	0.39 (0.05-0.81)		.	1	0.89 (0.77-0.97)		.
Intervention								
IO	8	0.19 (0.02-0.45)		95.53	7	0.79 (0.45-1.00)		95.73
IO+IO	2	0.16 (0.04-0.33)	0.00	.	2	0.78 (0.61-0.92)	0.00	.
IO+CT/RT	8	0.77 (0.64-0.87)		80.48	7	0.97 (0.92-1.00)		72.73
Immune target								
PD-1	9	0.67 (0.42-0.87)		93.88	8	0.98 (0.95-1.00)		35.75
PD-L1	6	0.19 (0.00-0.53)	0.00	97.44	5	0.68 (0.27-0.97)	0.00	96.78
CTLA-4	1	0.62 (0.32-0.86)		-	1	0.92 (0.64-1.00)		-
PD-1+CTLA-4	2	0.16 (0.04-0.33)		.	2	0.78 (0.61-0.92)		.

ORR: Objective response rate; DCR: Disease control rate.

Table VI: Subgroup analysis of radiological response rate (ORR and DCR) of neoadjuvant immunotherapy in lung cancer patients.

Group	Any-grade TRAEs				G3-5 TRAEs			
	No. of studies	Rate (95% CI)	P heterogeneity between groups	I2 (%)	No. of studies	Rate (95% CI)	P heterogeneity between groups	I2 (%)
Total	9	0.57 (0.38-0.76)	-	91.82	16	0.15 (0.06-0.28)	-	93.07
Area								
North America	3	0.64 (0.57-0.71)		.	6	0.14 (0.07-0.21)		42.66
Europe	4	0.52 (0.09-0.93)	0.87	96.83	5	0.21 (0.00-0.68)	0.31	97.86
Asia	2	0.61(0.50-0.72)		.	5	0.08 (0.03-0.14)		37.84
Arms								
Single	-	-	-	-	14	0.17 (0.05-0.33)	0.54	94.65
Dual	-	-		-	2	0.11 (0.05-0.20)		0.00
Intervention								
IO	5	0.45 (0.20-0.70)		93.69	9	0.08 (0.03-0.16)		70.09
IO+IO	3	0.67 (0.30-0.93)	0.23	.	2	0.15 (0.03-0.31)	0.35	.
IO+CT/RT	1	0.76 (0.50-0.96)		-	7	0.24 (0.02-0.57)		96.55
Immune target								
PD-1	4	0.66 (0.38-0.89)		90.24	7	0.11 (0.04-0.20)		68.01
PD-L1	3	0.45 (0.10-0.83)	0.81	.	7	0.15 (0.00-0.43)	0.07	96.66
CTLA-4	1	0.54 (0.25-0.81)		-	1	0.46 (0.19-0.75)		-
PD-1+CTLA-4	1	0.67 (0.30-0.93)		-	2	0.15 (0.03-0.31)		.

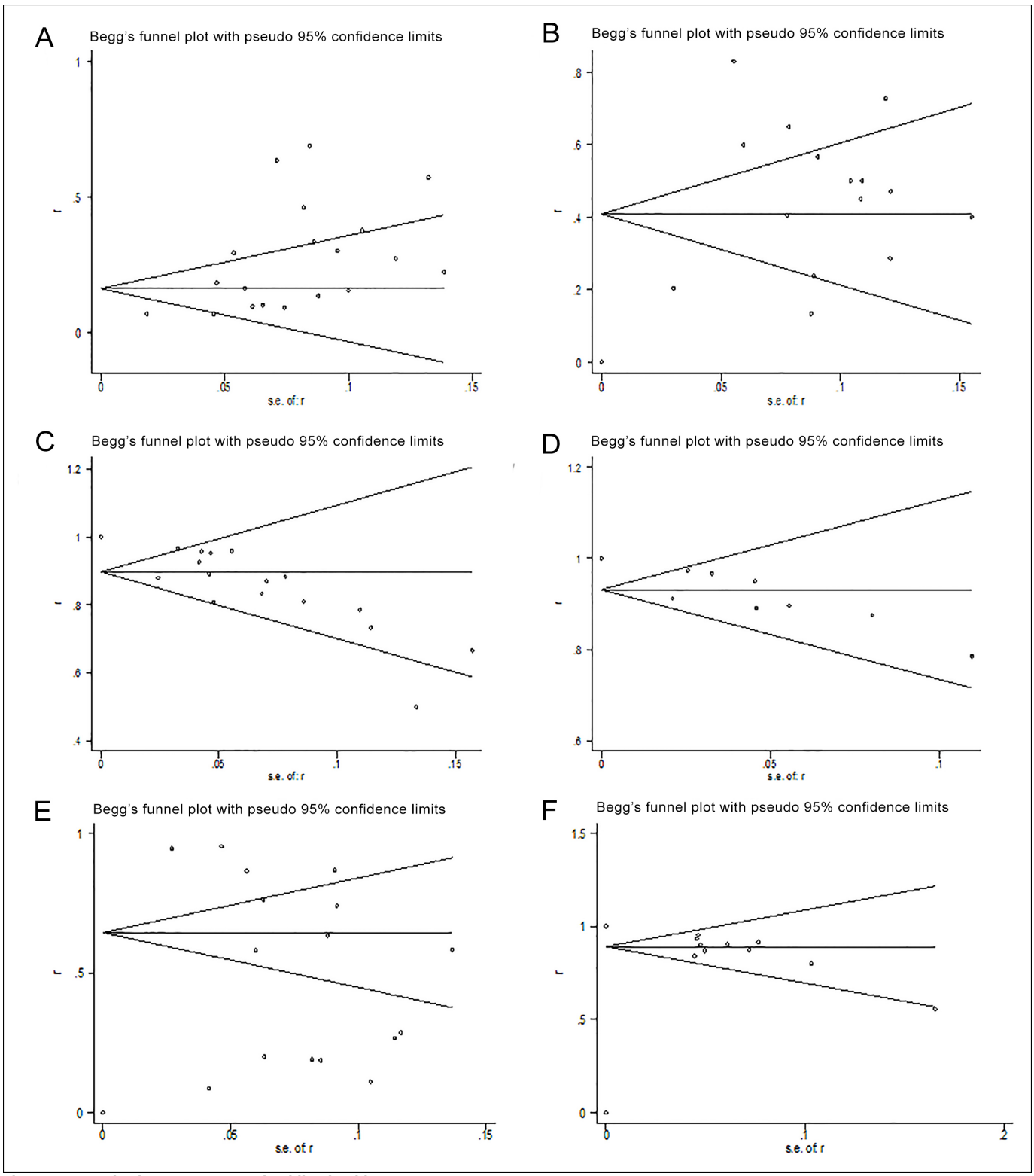

Fig S1: A quantitative assessment of publication bias.

Moreover, a significant percentage of data was not available so that it was hardly able to perform a more complete subgroup analysis. Thus, high-quality pf phase III trials with ICIs in the neoadjuvant setting are eagerly needed.

CONCLUSION

Promising clinical results indicated that neoadjuvant administration of ICIs is effective and safe. With more exciting data observed, it may further change clinical practice for early nonmetastatic NSCLC.

Appendix 1: Search strategies.

PubMed 537
#1 ((((((((((((((immun*) OR (ipilimumab)) OR (CTLA-4)) OR (pd-1)) OR (Nivolumab)) OR (pembrolizumab)) OR (sintilimab)) OR (camrelizumab)) OR (Cemiplimab)) OR (toripalimab)) OR (tislelizumab)) OR (PD-L1)) OR (Atezolizumab)) OR (durvalumab)) OR (avelumab)) OR (checkpoint inhibitors)
#2 (((((lung adenocarcinoma) OR (squamous cell lung carcinoma)) OR (large cell lung cancer)) OR (lung carcinoid)) OR (NSCLC)) OR (non small cell lung cancer[MeSH Terms])
#3 Neoadjuvant
#4 #1 AND #2 AND #3
ClinicalTrials.gov 18
Condition or disease: Non Small Cell Lung Cancer
Study type: Interventional studies (clinical trials)
Interventional/Treatment: Neoadjuvant immunotherapy
Embase 4021
#1 ('lung'/exp OR lung) AND ('adenocarcinoma'/exp OR adenocarcinoma) OR (squamous AND ('cell'/exp OR cell) AND ('lung'/exp OR lung) AND ('carcinoma'/exp OR carcinoma)) OR (large AND ('cell'/exp OR cell) AND ('lung'/exp OR lung) AND ('cancer'/exp OR cancer)) OR (('lung'/exp OR lung) AND ('carcinoid'/exp OR carcinoid)) OR nsclc OR 'non small cell lung cancer'/exp OR 'non small cell lung cancer'
#2 immun* OR ipilimumab OR 'ctla 4' OR 'pd 1' OR nivolumab OR pembrolizumab OR sintilimab OR camrelizumab OR cemiplimab OR toripalimab OR tislelizumab OR 'pd l1' OR atezolizumab OR durvalumab OR avelumab OR (checkpoint AND inhibitors)
#3 adjuvant
#4 #1 AND #2 AND #3
Cochrane Library 182
#1 ((((((((((((((immun*) OR (ipilimumab)) OR (CTLA-4)) OR (pd-1)) OR (Nivolumab)) OR (pembrolizumab)) OR (sintilimab)) OR (camrelizumab)) OR (Cemiplimab)) OR (toripalimab)) OR (tislelizumab)) OR (PD-L1)) OR (Atezolizumab)) OR (durvalumab)) OR (avelumab)) OR (checkpoint inhibitors)
#2 (((((lung adenocarcinoma) OR (squamous cell lung carcinoma)) OR (large cell lung cancer)) OR (lung carcinoid)) OR (NSCLC)) OR (non small cell lung cancer)
#3 Neoadjuvant
#4 #1 AND #2 AND #3
Web of Science 231
#1 ((((((((((((((immun*) OR (ipilimumab)) OR (CTLA-4)) OR (pd-1)) OR (Nivolumab)) OR (pembrolizumab)) OR (sintilimab)) OR (camrelizumab)) OR (Cemiplimab)) OR (toripalimab)) OR (tislelizumab)) OR (PD-L1)) OR (Atezolizumab)) OR (durvalumab)) OR (avelumab)) OR (checkpoint inhibitors)
#2 (((((lung adenocarcinoma) OR (squamous cell lung carcinoma)) OR (large cell lung cancer)) OR (lung carcinoid)) OR (NSCLC)) OR (non small cell lung cancer)
#3 Neoadjuvant
#4 #1 AND #2 AND #3

Appendix 2: Quality assessment of the included studies Newcastle-Ottawa Scale for assessing the quality of studies in meta-analysis.

Study	Selection	Comparability	Outcome/ exposure	Overall Rating (more stars= lower risk of bias)
Yang (2017)	★★	★	★★★	★★★★★★
Provencio (2020)	★★	-	★★	★★★★
Lee (2021)	★★	-	★★	★★★★
Bar (2019)	★★	-	★★	★★★★
Ready (2019)	★★	-	★★	★★★★
Altorki (2019)	★★★	★★	★★	★★★★★★★
Cascone (2021)	★★★	★★	★★	★★★★★★★
Gao (2020)	★★	-	★★★	★★★★★
Besse (2020)	★★	-	★★	★★★★
Bott (2019)	★★	-	★★★	★★★★★
Reuss (2020)	★★	-	★★★	★★★★★
Lei (2020)	★★★	★★	★★	★★★★★★★
Rothschild (2020)	★★	-	★★★	★★★★★
Shu (2020)	★★	-	★★★	★★★★★
Tfayli (2020)	★★	-	★★	★★★★
Wislez (2020)	★★	-	★★	★★★★
Duan (2021)	★★	-	★★★	★★★★★
Eichhorn (2021)	★★	-	★★★	★★★★★
Hong (2021)	★★	-	★★	★★★★
Shen (2021)	★★	-	★★★	★★★★★
Wang (2021)	★★	-	★★★	★★★★★

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ETHICAL APPROVAL:
The relevant research data was obtained from reliable published sources and free of ethical issues.

PATIENTS' CONSENT:
This study is a systematic review and meta-analysis that does not involve human specimens; therefore, doesn't involve any related patients consents issues.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

CX: Proposed the hypothesis and idea for this work with all authors contributing to its development and analysis plan.
CX, HD, YC: Literature search and reviewed studies for inclusion.
YC, XL, SZ: Performed the data extraction and checking.
CX, HD, HC: Performed all meta-analyses and wrote the initial draft.
All authors approved the final version of the manuscript to be published.

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