Research article

Efficacy and safety of different cycles of neoadjuvant immunotherapy in resectable non-small cell lung cancer: A systematic review and meta-analysis

Linlin Ye [1], Yao Liu [1], Xuan Xiang [1], Zihao Wang, Wenbei Peng, Xiaoshan Wei, Siyu Zhang, Qianqian Xue, Qiong Zhou [*]

Department of Respiratory and Critical Care Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, 430000

ABSTRACT

Background: There is no standard consensus on the optimal number of cycles of neoadjuvant immunotherapy prior to surgery for patients with locoregionally advanced non-small cell lung cancer (NSCLC). We carried out a systematic review to evaluate the efficacy and safety of neoadjuvant immunotherapy with different treatment cycles in order to provide valuable information for clinical decision-making.

Methods: PubMed, Embase, the Cochrane Library and ClinicalTrials.gov were systematically searched before May 2023. The included studies were categorized based on different treatment cycles of neoadjuvant immunotherapy to assess their respective efficacy and safety in patients with resectable NSCLC.

Results: Incorporating data from 29 studies with 1331 patients, we found major pathological response rates of 43 % (95%CI, 34–52 %) with two cycles and 33 % (95%CI, 22–45 %) with three cycles of neoadjuvant immunotherapy. Radiological response rates were 39 % (95%CI, 28–50 %) and 56 % (95%CI, 44–68 %) for two and three cycles, respectively, with higher incidence rates of severe adverse events (SAEs) in the three-cycle group (32 %; 95%CI, 21–50 %). Despite similar rates of R0 resection between two and three cycles, the latter showed a slightly higher surgical delay rate (1 % vs. 7 %). Neoadjuvant treatment modes significantly affected outcomes, with the combination of immunotherapy and chemotherapy demonstrating superiority in improving pathological and radiological response rates, while the incidence of SAEs in patients receiving combination therapy remained within an acceptable range (23 %; 95%CI, 15–35 %). However, regardless of the treatment mode administered, an increase in the number of treatment cycles did not result in substantial improvement in pathological response rates.

Conclusion: There are clear advantages of combining immunotherapy and chemotherapy in neoadjuvant settings. Increasing the number of cycles of neoadjuvant immunotherapy from two to three primarily may not substantially improve the overall efficacy, while increasing the risk of

* Corresponding author.
E-mail addresses: yelinlinwh@126.com (L. Ye), 591895786@qq.com (Y. Liu), xiangxuan@hust.edu.cn (X. Xiang), wz_hao_whuh@hust.edu.cn (Z. Wang), pengwenbei_@hust.edu.cn (W. Peng), weixs@hust.edu.cn (X. Wei), zhangsy1996@hust.edu.cn (S. Zhang), xueqianqian0510@163.com (Q. Xue), zhouqiongtj@126.com (Q. Zhou).
[1] These authors contributed equally to this work.

adverse events. Further analysis of the outcomes of four cycles of neoadjuvant immunotherapy is necessary.

1. Introduction

Lung cancer remains the leading cause of cancer deaths worldwide with non-small cell lung cancer (NSCLC) accounting for 80 % of all lung cancers [1]. The current standard of care for patients with locoregionally advanced NSCLC includes surgical resection with adjuvant therapy or definitive chemoradiotherapy [2,3]. Despite this multimodal therapeutic approach, high rates of treatment failure and disease recurrence are responsible for poor survival outcomes [3].

In the past decade, immunotherapy has emerged as a promising treatment of metastatic or recurrent NSCLC, dramatically improving the prognosis of patients with advanced NSCLC [4]. Given the success of immunotherapy in advanced NSCLC, there is a growing interest in exploring the potential benefits in patients with earlier stages of NSCLC. The goal is to utilize immunotherapy in the neoadjuvant setting, administered before surgery, to achieve beneficial clinical outcomes. The rationale for neoadjuvant immuno-therapy derives from the early introduction of systemic therapy that can potentially reduce the risk of distant metastases and convert unresectable to resectable disease [5,6]. Ultimately, it may modify the extent of surgery and reduce surgical morbidity [7]. Tumor downstaging can also translate into reduced intensity of adjuvant therapy [7].

To date, numerous studies of neoadjuvant immunotherapy administering in patients with NSCLC have provided promising results in terms of improving the pathological response and tumor downstaging [8–10]. However, the favorable effects of immunotherapy are inevitably accompanied by undesirable adverse events that involve in a wide range of organs, some of which can be life-threatening [8–10]. Thus, balancing the clinical benefits and treatment-related toxicities for each patient is of great importance. Moreover, pre-clinical studies have reported that timely surgery following neoadjuvant treatment dramatically determined chances of long-term survival [6,11]. This implies that a shorter duration of neoadjuvant immunotherapy may not provide sufficient time for the treat-ment to reach its full potential in reducing tumor burden and activating the immune response. However, a longer duration of neo-adjuvant immunotherapy may carry the risk of tumor progression, potentially missing the window of opportunity for surgery. In this context, it is crucial to determine the optimal number of cycles of immunotherapy prior to surgery to achieve the maximum benefits while minimizing the risks. At present, most neoadjuvant trials of NSCLC administer only two or three cycles as there is no standard consensus on this issue [9,11]. To date, only one study has focused on assessing the efficacy and safety of different cycles of immuno-chemotherapy for resectable NSCLC in the neoadjuvant setting [12]. The results showed that increasing the number of cycles of neoadjuvant treatment from two to three led to a 14.5 % increase in major pathological response (MPR) with an acceptable tolerability. However, due to the small size of the research, the difference did not achieve statistical significance [12]. Therefore, it remains unclear whether increasing the number of cycles of therapy prior to surgery is ultimately more beneficial than detrimental to these patients. In light of this, we performed a meta-analysis on the available data to evaluate the efficacy and safety of different cycles of neoadjuvant immunotherapy in order to provide valuable information for clinical decision-making.

2. Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines [13] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines [14]. The detailed protocol is documented online in the International Prospective Register of Systematic Reviews registry (PROSPERO: CRD42023438413). Since this systematic review and meta-analysis did not use individualized patient data, institutional review board approval was not required.

2.1. Study selection

We conducted a systematic search in PubMed (MEDLINE), Embase, the Cochrane Library, and ClinicalTrials.gov to identify published studies on neoadjuvant immunotherapy in patients with NSCLC reported before May 2023 (detail search strategy provided in the Supplement). We also searched for unpublished data from ongoing clinical trials of neoadjuvant immunotherapy in patients with NSCLC presented at international conferences (Table S1 in the Supplement).

The following screening criteria were applied to determine eligibility: a study that 1. included patients with resectable NSCLC confirmed in tissue; 2. PD-1/PD-L1 inhibitors or CTLA-4 inhibitors were used as neoadjuvant therapy, 3. reported at least one key outcome, such as major pathological response (MPR), pathological complete response (pCR), complete response (CR), partial response (PR), treatment-related adverse events (TRAEs), severe adverse events (SAEs), surgical delay rate or R0 resection rate. Publications were excluded if they met any of the following criteria: 1. Included patients with unresectable primary or metastatic disease. 2. Did not involve the use of PD-1/PD-L1 inhibitors or CTLA-4 inhibitors. 3. Did not report any of our key outcomes. 4. Included fewer than 10 patients. 5. Repeated publications. 6. Reviews, case reports or case series. 7. Violated of any of the above inclusion criteria.

2.2. Data Extraction

Two investigators (LLY and YL) independently identified and extracted articles for potential inclusion. Disagreements were

Table 1

Summary of characteristics of studies of neoadjuvant immunotherapy in resectable NSCLC.

Source	NCT Number	Country	Study type	Study design	No. of patients	No. of complated	Patient stage	Median age	Neoadjuvant regimens	Cycles	Dose of ICI	Outcome reported	Article type
Besse et al., 2020 [26]	NCT02994576	France	Phase II Trial	Single-arm Multicenter	30	30	IA-IIIA	64	Atezolizumab	1	Atezolizumab 1200 mg IV	MPR; R0 rate; Surgical delay	Abstract
Forde et al., 2018 [23]	NCT02259621	USA	Phase II Trial	Single-arm Single-center	22	20	I-IIIA	67	Nivolumab	2	Nivolumab (3 mg/kg) IV Q2W	MPR; pCR; PR; R0 rate TRAEs; SAEs; Surgical delay	Full text
Tong et al., 2022 [27]	NCT02818920	USA	Phase II Trial	Single-arm Multicenter	35	30	IB-IIIA	72	Pembrolizumab	2	Pembrolizumab 200 mg IV	MPR; R0 rate; SAEs	Full text
Carbone et al., 2021 [10]	NCT02927301	USA	Phase II Trial	Single-arm Single-center	181	147	IB - IIIB	65.1	Atezolizumab	2	Atezolizumab 1200 mg IV Q3W	MPR; pCR; PR; R0 rate TRAEs; SAEs	Abstract
Gao et al., 2020 [28]	ChiCTR–OIC–17013726	China	Phase Ib Trial	Single-arm Single-center	40	40	IA-IIIB	59.8	Sintilimab	2	Sintilimab 200 mg IV Q3W	MPR; pCR; R0 rate TRAEs; SAEs; Surgical delay	Full text
Huang et al., 2021 [29]	/	China	Retrospective observational Study	Single-group Single-center	25	25	IIIA	62.9	Nivolumab	2	Nivolumab 3 mg/kg IV Q3W	MPR; pCR; PR; R0 rate TRAEs; SAEs; Surgical delay	Full text
Shen et al., 2021 [30]	/	China	Prospective observational study	Single-group Single-center	37	37	IIB -IIIB	62.8	Pembrolizumab[a]	2	Pembrolizumab 2 mg/kg IV Q3W	MPR; pCR; PR; R0 rate TRAEs; SAEs	Full text
Rothschild et al., 2021 [22]	NCT02572843	Switzerland	Phase II Trial	Single-arm Multicenter	67	62	I to IIIA	61	Durvalumab[a]	2	Durvalumab 750 mg IV Q2W	MPR; pCR; PR; R0 rate TRAEs; SAEs	Full text
Eichhorn et al., 2021 [31]	NCT03197467	Germany	Phase II Trial	Single-arm Single-center	15	13	II/IIIA	59.8	Pembrolizumab[a]	2	Pembrolizumab 200 mg IV Q3W	MPR; pCR; R0 rate TRAEs; SAEs	Full text

(continued on next page)

Table 1 (*continued*)

Source	NCT Number	Country	Study type	Study design	No. of patients	No. of complated	Patient stage	Median age	Neoadjuvant regimens	Cycles	Dose of ICI	Outcome reported	Article type
Chen et al., 2021 [32]	/	China	Retrospective observational study	Single-group Single-center	35	35	IIIA-IIIB	62.17	Pembrolizumab[a]	2	Pembrolizumab 2 mg/kg IV Q3W	MPR; pCR; PR; R0 rate SAEs; Surgical delay	Full text
Zhang et al., 2021 [33]	/	China	Retrospective observational study	Single-group Single-center	30	30	IIIA-IIIB	56.5	Toripalimab[a] or Pembrolizumab[a]	2	Toripalimab 200 mg IV Pembrolizumab IV	MPR; pCR; R0 rate TRAEs; SAEs	Abstract
Hong et al., 2021 [34]	NCT03694236	Korea	Phase Ib Trial	Single-arm Single-center	14	14	III	66	Durvalumab[a]	2	Durvalumab 1500 mg IV Q4W	MPR; pCR; R0 rate SAEs	Abstract
Altorki et al., 2021 [21]	NCT02904954	USA	Phases II Trial	Randomized Single-center	30	30	IA-IIIA	71	Durvalumab	2	Durvalumab 1.12 g IV Q3W	MPR; pCR; PR; R0 rate SAEs; Surgical delay	Full text
					30	27	IA-IIIA	70	Durvalumab #	2	Durvalumab 1.12 g IV Q3W	MPR; pCR; PR; R0 rate SAEs; Surgical delay	
Cascone et al., 2021 [10]	NCT03158129	USA	Phase II Trial	Randomized Single-center	23	22	IA-IIIA	66.1	Nivolumab	3	Nivolumab 3 mg/kg IV Q2W	MPR; pCR; PR; R0 rate SAEs; Surgical delay	Full text
					21	19	IA-IIIA	65	Nivolumab + Ipilimumab	3	Nivolumab 3 mg/kg IV Q2W Ipilimumab 1 mg/kg IV Q6W		
Forde et al., 2022 [8]	NCT02998528	USA	Phase III Trial	Randomized Multicenter	179	167	IB-IIIA	64	Nivolumab[a]	3	Nivolumab 360 mg IV Q3W	MPR; pCR; PR; R0 rate TRAEs; SAEs; Surgical delay	Full text
Zhao et al., 2021 [20]	NCT04304248	China	Phase II Trial	Single-arm Single-center	33	30	IIIA-IIIB	61	Toripalimab[a]	3	Toripalimab 240 mg IV	MPR; pCR; PR; R0 rate	Full text
Tfayli et al., 2020 [35]	NCT03480230	Lebanon	Phase II Trial	Single-arm Multicenter	15	15	IB-IIIA	65	Avelumab[a]	3	Avelumab 10 mg/kg IV Q2W	MPR; pCR; PR	Full text

(*continued on next page*)

Table 1 (*continued*)

Source	NCT Number	Country	Study type	Study design	No. of patients	No. of complated	Patient stage	Median age	Neoadjuvant regimens	Cycles	Dose of ICI	Outcome reported	Article type
Lei et al., 2020 [36]	NCT04338620	China	Phases II Trial	Randomized Multicenter	14	14	IIIA-IIIB	NR	Camrelizumab[a]	3	Camrelizumab 200 mg IV Q3W	MPR; pCR	Abstract
Wu et al., 2022 [37]	NCT04316364	China	Phase Ib/III Trial	Randomized Multicenter	37	37	II and IIIB	NR	SHR-1316[a]	3	SHR-1316 (PD-L1 inhibitor) 20 mg/kg IV Q3W	MPR; PR; R0 rate TRAEs; SAEs	Abstract
Provencio et al., 2020 [38]	NCT03081689	Spain	Phase II Trial	Single-arm Multicenter	46	46	IIIA	63	Nivolumab[a]	3	Nivolumab 360 mg IV Q3W	MPR; pCR; PR TRAEs; SAEs	Full text
Yang et al., 2018 [39]	NCT01820754	USA	Phase II Trial	Single-arm Single-center	24	24	II–IIIA	65	Ipilimumab[a]	3	Ipilimumab 10 mg/kg IV	PR SAEs; Surgical delay	Full text
Hou et al., 2022 [40]	/	China	Prospective observational study	Dual-arm Single-center	31	31	IIIA-IIIB	59.4	Camrelizumab[a]	3	Camrelizumab 200 mg IV Q2W	MPR; pCR; PR	Full text
Zhai et al., 2022 [41]	/	China	Retrospective observational Study	Single-group Single-center	46	46	IIIA-IIIB	63	Nivolumab[a]	3	Nivolumab 360 mg IV Q3W	MPR; pCR; PR; R0 rate TRAEs; SAEs	Full text
Shu et al., 2020 [42]	NCT02716038	USA	Phase II Trial	Single-arm Multicenter	39	30	IB–IIIA	67	Atezolizumab[a]	4	Atezolizumab 1200 mg IV Q3W	MPR; pCR; PR; R0 rate	Full text
Shao et al., 2023 [12]	NCT04459611	China	Phases II Trial	Randomized Single-center	60	55	IB-IIIA	64.5	Sintilimab[a]	2 to 3	Sintilimab 200 mg IV Q3W	MPR; pCR; PR SAEs	Full text
Duan et al., 2021 [43]	/	China	Prospective observational study	Single-group Multicenter	23	23	IIA–IIIB	61.83	Nivolumab[a] Pembrolizumab[a] Sintilimab[a] Nivolumab[a]	1 to 4	Nivolumab 360 mg IV Q2W Pembrolizumab 200 mg IV Q2W Sintilimab 200 mg IV Q2W Nivolumab 200 mg IV Q2W	MPR; pCR; PR	Full text
Zhang et al., 2022 [44]	ChiCTR1900023758	China	Phase II Trial	Single-arm Single-center	50	49	IIIA	64.84	Sintilimab[a]	1 to 4	Sintilimab 200 mg IV Q3W	MPR; pCR; PR; R0 rate TRAEs; SAEs; Surgical delay	Full text
Wu et al., 2022 [37]	/	China	Retrospective observational study	Dual-arm Single-center	76	76	I-III	62	Pembrolizumab[a]; Nivolumab[a]	2 to 4	Pembrolizumab 200 mg IV Q3W Nivolumab 360 mg IV Q3W	MPR; pCR; PR SAEs	Full text

Table 1 (*continued*)

Source	NCT Number	Country	Study type	Study design	No. of patients	No. of complated	Patient stage	Median age	Neoadjuvant regimens	Cycles	Dose of ICI	Outcome reported	Article type
Dai et al., 2022 [45]	/	China	Retrospective observational study	Single-group Single-center	23	23	II–IIIB	63.2	Pembrolizumab[a]; Sintilimab[a]; Camrelizumab[a]; Toripalimab[a];	2 to 4	Pembrolizumab IV Q3W Sintilimab IV Q3W Camrelizumab IV Q3W Toripalimab IV Q3W	MPR; pCR; PR; R0 rate TRAEs; SAEs	Full text

Abbreviations: MPR, major pathological response; pCR, pathological complete response; PR, partial response; R0 rate, R0 resection rate; TRAEs, trentment-related adverse events; SAE, severe adverse event (grade 3–5 TRAEs); iv, intravenous injection; Q2w,2 weeks using a; Q3w,3 weeks using a.

[a] with other neoadjuvant Radiotherapy; #with other neoadjuvant Chemotherapy.

resolved by referral to a third reviewer (QZ). We attempted to identify and exclude duplicate data from research studies presented in separate publications. For cases in which we identified multiple studies with duplicated or overlapping data, we selected the study with the largest or most representative sample size. If these were also similar, we present the most recent study. A summary of the characteristics of the included studies is provided in Table 1.

2.3. Quality assessment and risk of bias

The selected studies were assessed with the Agency for Healthcare Research and Quality's risk of bias tool [15], which is used to assign a rating of high, low, or unclear risk of bias for the domains of selection, performance, detection, attrition, and reporting. Summary assessment of the risk of bias (high, low, or unclear) was derived for each outcome in each trial. Two reviewers (LLY and YL) independently assessed the risk of bias. Disagreements were resolved through consensus or referral to a third reviewer (QZ) (Fig. S5 and Fig. S6 in the Supplement).

2.4. Data Synthesis and statistical analysis

The meta-analysis was performed using R version 4.1.1 (The R Foundation for Statistical Computing, MO, USA) with the open-source package meta version 6.0–0. The effect size of all pooled results was represented by 95 % CI with an upper limit and a lower limit. Heterogeneity among the studies was quantified with the χ^2 test and the heterogeneity index (I^2). If the heterogeneity was significant ($p < 0.1$) or higher than 50 %, the random effect model was adopted, if insignificant ($p > 0.1$) or lower than 50 %, the fixed effect model was adopted. Sensitivity analysis was performed by excluding each study one by one for the pooled results with high heterogeneity (Fig. S4 in the Supplement). A p-value <0.05 was considered statistically significant.

3. Results

The literature search and study selection process are illustrated in Fig. 1. The search strategy identified a total of 1755 citations. After screening the abstracts and reviewing the available full texts, 29 studies met the inclusion criteria, yielding a total number of 1331 patients for inclusion in this meta-analysis (Fig. 1). Six of those 29 studies were ongoing trials for which only the abstracts were
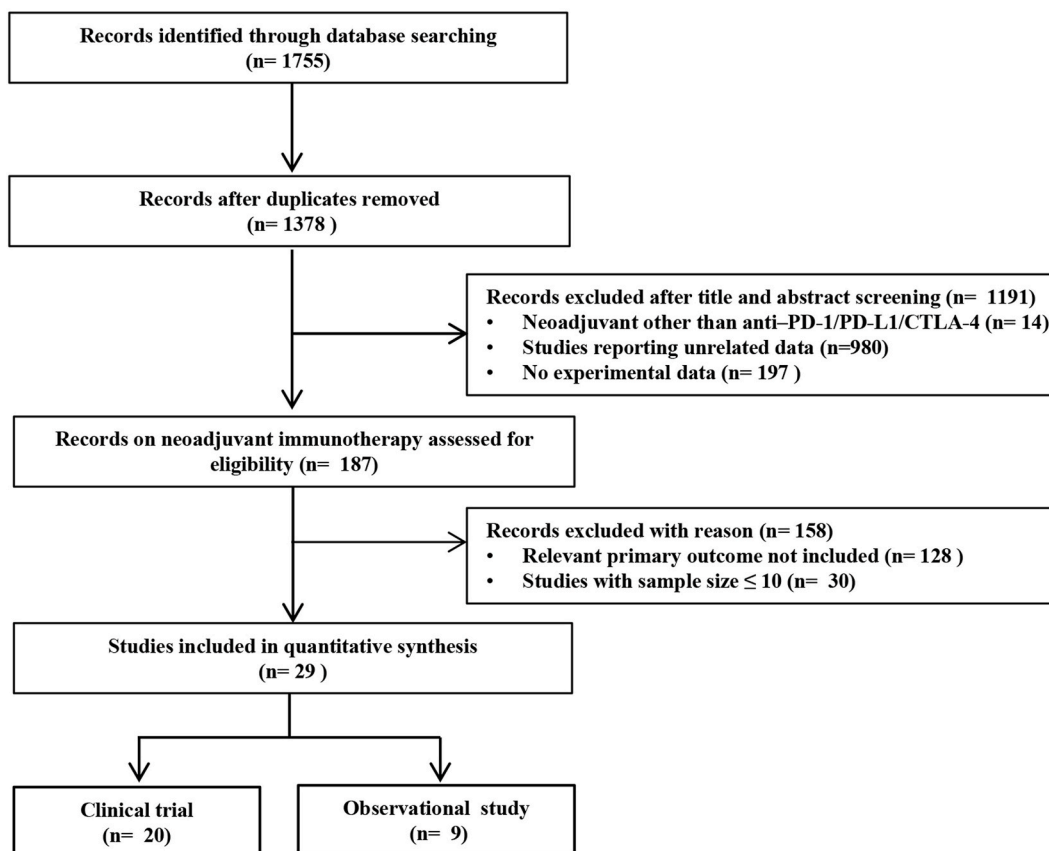

Fig. 1. PRISMA flow chart showing selection of articles for review.

available, and the remaining 23 studies were published as full-length articles. The number of cycles of neoadjuvant immunotherapy in the included studies varied from one to four. A total of 24 of the 29 studies reported outcomes for patients who received two and three cycles of neoadjuvant immunotherapy, while only two studies reported outcomes for patients who received one and four cycles of treatment. Here, the primary outcomes were pooled based on the number of cycles of neoadjuvant immunotherapy. An overview of the study characteristics is presented in Table 1.

3.1. Evaluation of efficacy outcomes

The efficacy of neoadjuvant immunotherapy can be evaluated through pathological responses, radiological response, and the outcome of the operation.

Pathological responses, which refer to the changes observed in the tumor tissue after treatment, serve as the most critical indicators
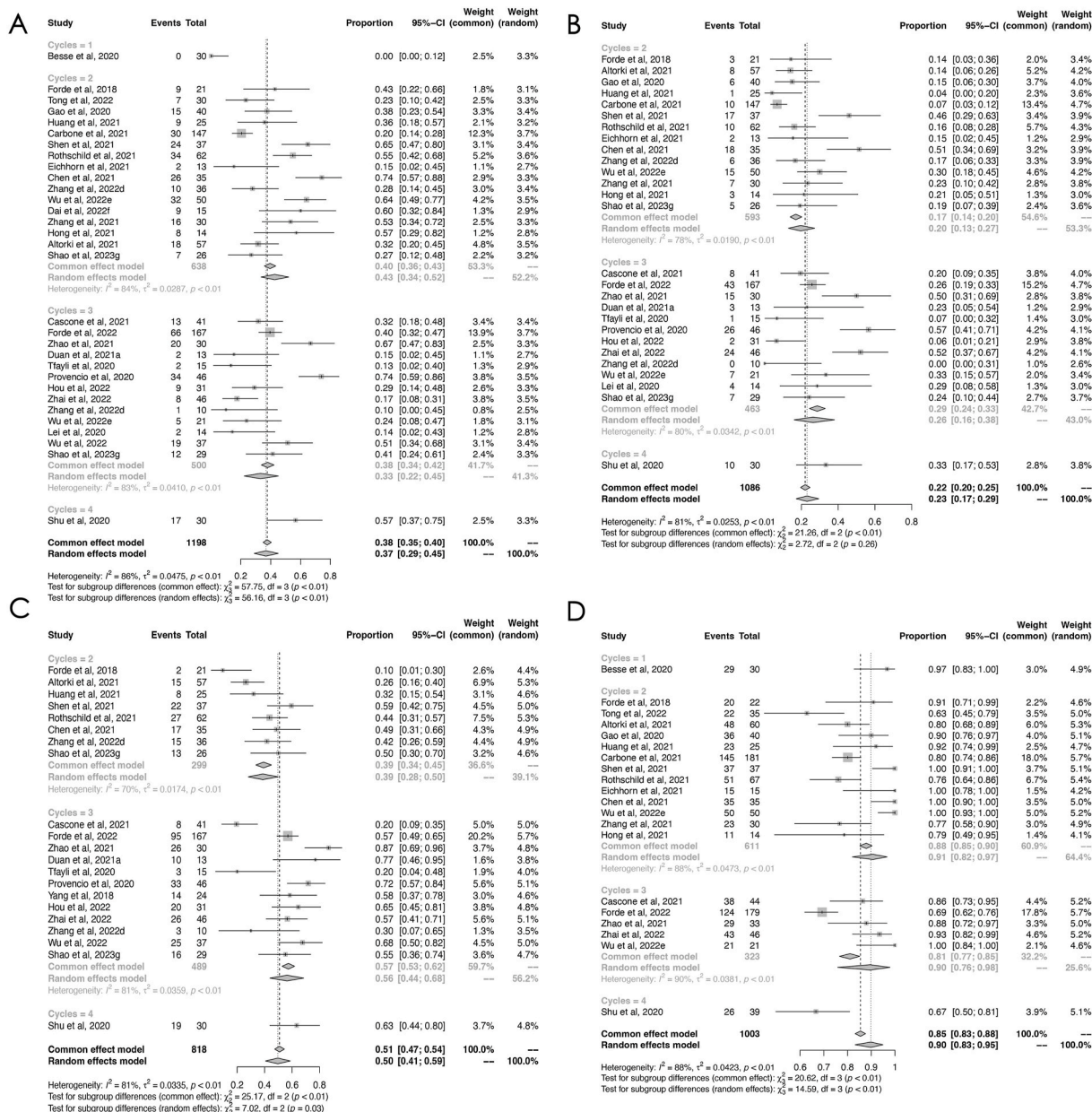
Fig. 2. Forest plot of the efficacy of different cycles of neoadjuvant immunotherapy.
(A) MPR rates; (B) pCR rates; (C) PR rates; (D) R0 resection rates. Total in A to C, the total number of patients who completed neoadjuvant immunotherapy in the study; Total in D, the total number of patients included in the study. CI, confidence interval.

for evaluating the efficacy of neoadjuvant immunotherapy [16,17]. Major pathological response (MPR) and pathological complete response (pCR) are two specific endpoints used to assess the extent of tumor regression. MPR was defined as having no more than 10 % viable tumor cells in the tumors and lymph nodes upon postoperative pathological review, while pCR was defined as having no viable tumor cells upon postoperative pathological review. As shown in Fig. 2A and B, the rates of MPR and pCR were not improved when the number of cycles of neoadjuvant immunotherapy was increased. Specifically, the pooled rates of MPR were 43 % (95 % CI, 34–52 %) and 33 % (95 % CI, 22–45 %) in the two cycles group and three cycles group, respectively (Fig. 2A). The pooled pCR rates for two cycles and three cycles of treatment were 20 % (95 % CI, 13–27 %) and 26 % (95 % CI, 16–38 %), respectively (Fig. 2B).

The data are consistent with findings from the neoSCORE trial [12], which was the only randomized trial assessing different cycles of neoadjuvant immunotherapy. In the neoSCORE trial, the MPR rate was 26.9 % (7/26; 95 % CI, 11.6–47.8 %) in the two-cycle arm and 41.4 % (12/29; 95 % CI, 23.5–61.1 %; p = 0.260) in the three-cycle arm, whereas the pCR rate was 19.2 % (95 % CI, 6.6–39.4 %) and 24.1 % (7/29; 95 % CI, 10.3–43.5 %; p = 0.660) with two and three cycles, respectively [12]. Despite higher rates of MPR and pCR
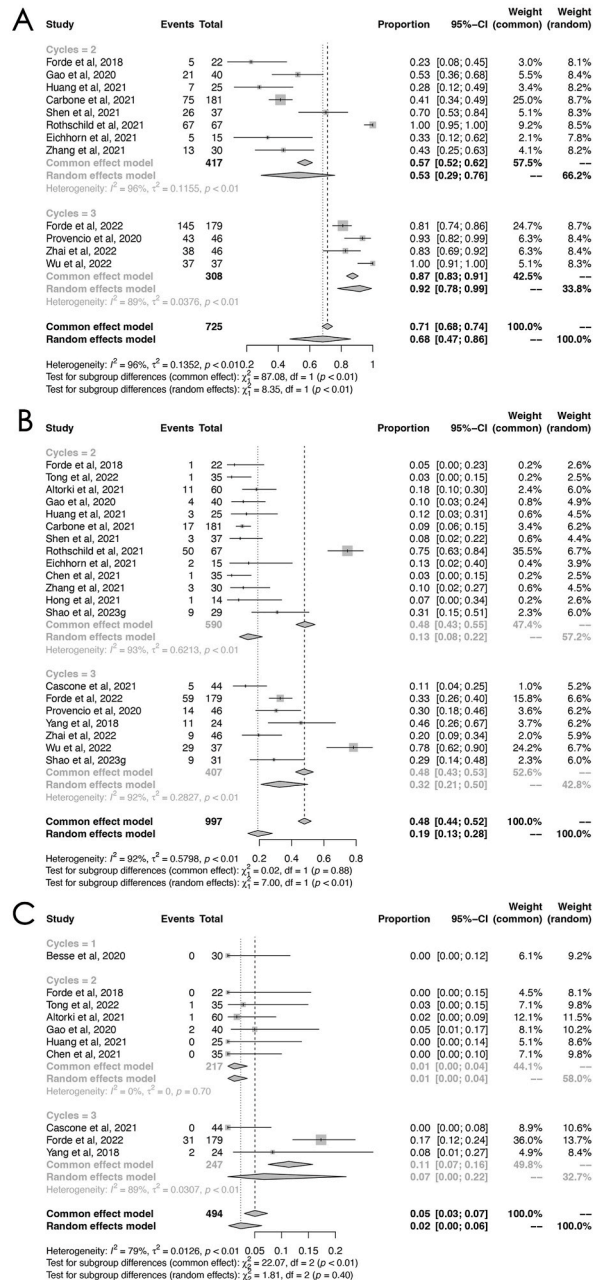

Fig. 3. Forest plot of the safety of different cycles of neoadjuvant immunotherapy.
(A) TRAE rates; (B) SAE rates; (C) Surgical delay rates; Total, the total number of patients included in the study. CI, confidence interval.

with three cycles, the differences were not statistically significant [12]. Our findings consistently suggest that increasing the treatment cycles of neoadjuvant immunotherapy may not improve the pathological responses.

Radiological response involves assessing the changes in tumor size and characteristics using imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) scans. Response Evaluation Criteria in Solid Tumors (RECIST) [18] is a commonly used guideline to categorize responses as complete response (CR, disappearance of all target lesions), partial response (PR, significant reduction in tumor size), stable disease (SD, no significant changes), or progressive disease (PD, increase in tumor size). The rates of CR and PR are considered essential indicators for evaluating the efficacy of treatment. However, the pooled rates of CR were not calculated because the number of patients who had achieved CR were too small. It should be noted that the PR rates significantly improved with the increase in the number of cycles of neoadjuvant immunotherapy (Fig. 2C). The overall PR rates of patients who received two and three cycles of treatment were 39 % (95 % CI, 28–50 %) and 56 % (95 % CI, 44–68 %), respectively (Fig. 2C), indicating that the addition of treatment cycles of neoadjuvant immunotherapy might improve the radiological response for patients with resectable NSCLC.

R0 resection means that no residual tumor cells are detected at the edges of the excised tissue, which is considered as the optimal outcome of surgery for cancer. Achieving an R0 resection is generally associated with a better prognosis, as it indicates a more complete removal of the tumor and reduces the likelihood of local recurrence. Notably, the rates of R0 resection were similar in patients who received two cycles of neoadjuvant immunotherapy (91 %; 95 % CI, 82%–97 %) and those who received three cycles (90 %; 95 % CI, 76–98 %) (Fig. 2D).

Except for the observed increase in the rate of PR, our analysis indicated that the rates of MPR, pCR, and R0 resection did not show a significant increase when the number of cycles of neoadjuvant immunotherapy was increased from two to three. This suggests that additional treatment cycles may primarily improve the radiological response rather than the pathological responses. However, it is important to note that only pathological assessments after neoadjuvant therapies have demonstrated correlation with patient prognosis [16,17]. This implies that additional treatment cycles may not substantially improve the overall efficacy of neoadjuvant immunotherapy. However, it is crucial to consider that the conclusion regarding the outcomes of four cycles of neoadjuvant immunotherapy should be reevaluated in light of further studies, as the current analysis only included one study with four treatment cycles. Gathering more comprehensive evidence through additional research will enable more precise conclusions to be drawn regarding the optimal number of cycles of neoadjuvant immunotherapy.

3.2. Evaluation of safety outcomes

Treatment-related adverse events (TRAEs), assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) [19], version 4.0., are associated with safety of neoadjuvant immunotherapy. The incidence of TRAEs in patients who received three cycles of neoadjuvant immunotherapy was 92 % (95 % CI, 78%–99 %), which tended to be significantly higher than that in patients who received two cycles of treatment (53 %; 95 % CI, 29–76 %) (Fig. 3A). Furthermore, grade 3 or higher TRAEs are considered as severe adverse events (SAEs). The rates of SAEs significantly increased as the number of treatment cycles varied from two to three (Fig. 3B). The rate of SAEs significantly increased from 13 % (95 % CI, 8–22 %) in patients who received two cycles of neoadjuvant immunotherapy to 32 % (95 % CI, 21–50 %) in patients who received three cycles. This indicates that both the severity and incidence of adverse events substantially increase with increasing the number of treatment cycles.

The surgical delay rate, which measures the ratio of patients with surgical delays due to adverse events caused by neoadjuvant immunotherapy to all patients scheduled for surgery, is valuable in assessing the safety of neoadjuvant therapy. The surgical delay rate was 1 % (95 % CI, 0–4%) in patients who received two cycles of neoadjuvant immunotherapy and 7 % (95 % CI, 0–22 %) in patients who received three cycles (Fig. 3C). These data imply that there is a trend towards a higher likelihood of experiencing TRAEs that may cause delays in scheduled surgeries when the number of treatment cycles is increased.

To date, numerous clinical trials have assessed the efficacy and safety of neoadjuvant immunotherapy [8,10,20–23]. According to publicly available clinical trial data, most patients receive either two or three cycles of neoadjuvant immunotherapy before surgery, yielding promising outcomes in terms of improving pathological responses, radiological response, and R0 resection rates [8,10,20–23]. Furthermore, as noted in neoSCORE trial, the median overall survival (OS) and disease-free survival (DFS) were not reached at the time of data cutoff, indicating the long-term effectiveness of neoadjuvant treatment to some extent [12]. In line with the previous study, our data also confirmed the efficacy of neoadjuvant immunotherapy, regardless of whether patients received two or three treatment cycles. (Fig. 2). However, in patients with resctable NSCLC, a longer duration of neoadjuvant immunotherapy may carry the risk of tumor progression, potentially missing the window of opportunity for surgery. In neoSCORE trial, although three cycles of treatment presented a 14.5 % increase in the MPR rate and a 5 % increase in the pCR rate relative to two cycles, the difference did not achieve statistical significance, suggesting that increasing the number of treatment cycles may not substantially improve the efficacy while potentially increasing the risk of adverse events, which aligned with our current analysis. These findings underscore the need for a judicious balance between benefits and risks. Further research and clinical trials are necessary to provide more comprehensive and reliable conclusions regarding the optimal number of cycles for neoadjuvant immunotherapy.

3.3. Subgroup analysis

Subgroup analysis did not reveal that any specific immune checkpoint inhibitor (ICI) agent was superior to another (Fig. S1). Moreover, study design (Fig. S2) did not significantly influence the primary endpoints of neoadjuvant immunotherapy. In other words, the evidence gathered from observational studies, which observe patients in real-world settings and clinical trials, yielded similar

results regarding the impact of neoadjuvant immunotherapy on the safety and efficacy outcomes. Hence, study design did not introduce significant bias or confounding factors that would affect the overall conclusions regarding the safety and efficacy of neo-adjuvant immunotherapy. In contrast, neoadjuvant treatment modes were closely associated with the outcomes of neoadjuvant immunotherapy (Fig. S3). Specifically, the combination of neoadjuvant immunotherapy with chemotherapy was more effective in improving the pathological response and radiological response compared with immunotherapy alone (Figs. S3A–C). However, the combination of immunotherapy and chemotherapy also resulted in higher rates of TRAEs compared with immunotherapy alone (83 % vs. 38 %, Fig. S3E), but the incidence of SAEs (grade $\geq$3 TRAEs) in patients receiving the combination therapy remained within an acceptable range (23 %; 95%CI, 15–35 %, Fig. S3F).

To ensure a rigorous evaluation of the objective of the current study, which focused on examining the relationships between the number of cycles of neoadjuvant immunotherapy and the endpoints, we aggregated the outcomes with different numbers of cycles of neoadjuvant therapy from patients who received either immunotherapy alone or in combination with chemotherapy. Consistent with our previous data, the findings indicated that regardless of the treatment mode administered, an increase in the number of treatment cycles did not substantially improve the overall efficacy of neoadjuvant immunotherapy (Fig. 4A–D; Fig. 5A–D), but raised the risk of adverse events (Fig. 4E–G; Fig. 5E–G).
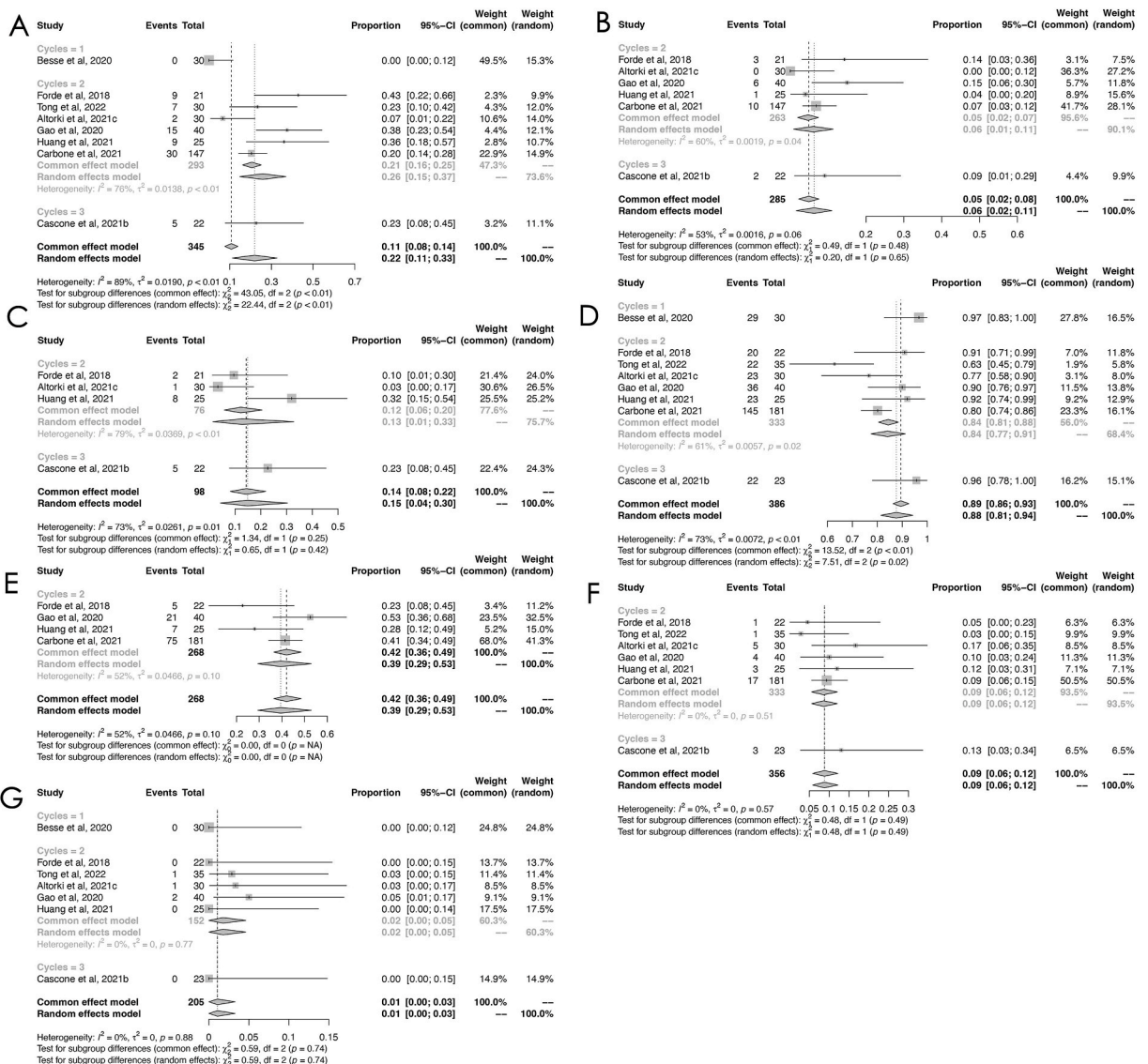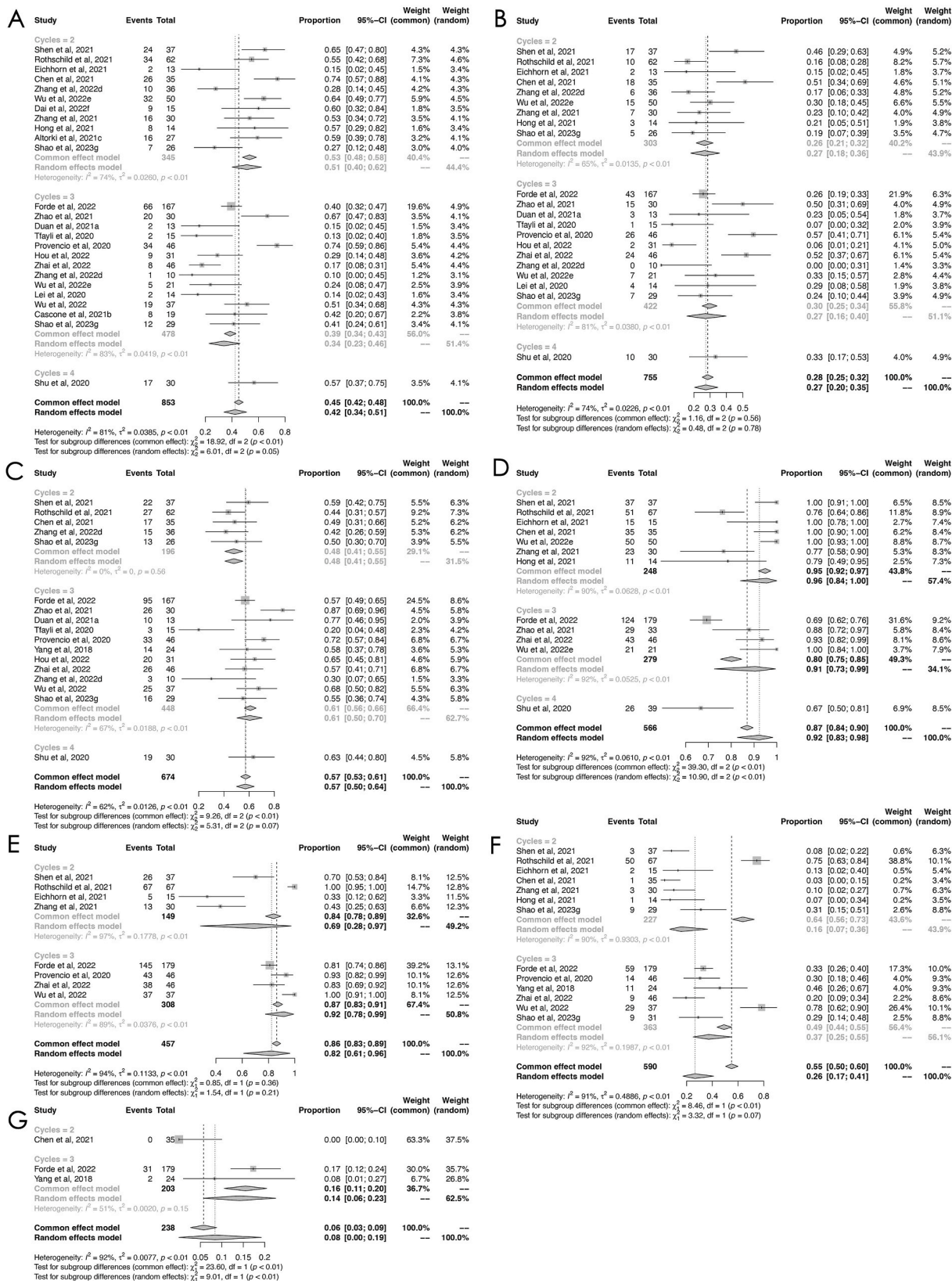

Fig. 4. Forest plot of the outcomes of different cycles of neoadjuvant treatment in patients who receiving immunotherapy alone.
(A) MPR rates; (B) pCR rates; (C) PR rates; (D) R0 resection rates; (E) incidence of TRAEs; (F) incidence of SAEs; (G) surgical delay rates. Total in A to C, the total number of patients who completed neoadjuvant immunotherapy in the study; Total in D to G, the total number of patients included in the study. CI, confidence interval.

Fig. 5. Forest plot of the outcomes of different cycles of neoadjuvant treatment in patients who receiving immunotherapy in combination with chemotherapy.
(A) MPR rates; (B) pCR rates; (C) PR rates; (D) R0 resection rates; (E) incidence of TRAEs; (F) incidence of SAEs; (G) surgical delay rates. Total in A to C, the total number of patients who completed neoadjuvant immunotherapy in the study; Total in D to G, the total number of patients included in the study. CI, confidence interval.
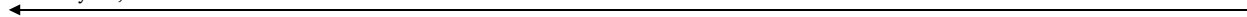
4. Discussion

The primary goal of neoadjuvant immunotherapy is to decrease the surgical stage, enhance the resection rate, and promptly treat subclinical micrometastases [11,24,25]. It is crucial to find the optimal duration for neoadjuvant immunotherapy given that a shorter cycle may not provide adequate time for the treatment to exert its full effects, while a longer cycle may carry the risk of tumor progression and potentially miss the window of opportunity for surgery. Therefore, it is of utmost importance to determine the optimal duration for neoadjuvant immunotherapy. However, there is a lack of standardized guidelines and reference criteria for determining the optimal cycles of neoadjuvant immunotherapy. In this context, we categorized the published studies to evaluate the efficacy and safety of different cycles of neoadjuvant immunotherapy in patients with resectable NSCLC.

In this analysis, a total of 29 studies with 1331 patients were included, and the majority of these studies performed two to three cycles of neoadjuvant immunotherapy. The data showed that increasing the number of cycles of neoadjuvant immunotherapy from two to three did not lead to substantial improvements in pathological responses, while potentially increasing the risk of adverse events. In contrast, a higher number of treatment cycles improved the radiological response of neoadjuvant immunotherapy. Radiological response is an important measure in assessing the effectiveness of treatment, given that it provides valuable information regarding tumor size reduction, regression, or stabilization [18]. The positive effect observed in the radiological response may support the potential benefits of extending the treatment duration. However, it is essential to consider that radiological response may have a poorer correlation with the overall survival in comparison with pathological response [16,17]. Therefore, the relationship between the efficacy of neoadjuvant immunotherapy and the number of additional treatment cycles remains a topic of controversy.

In this context, it is of great importance to standardize the treatment modes of neoadjuvant immunotherapy, so as to ensure uniformity in treatment protocols, allowing for more accurate comparisons and evaluations of its efficacy and safety across different patient populations. Currently, numerous phase II/III clinical trials are being conducted to investigate the optimal treatment mode in the neoadjuvant setting, including mono-ICI, dual-ICIs, ICI combination with chemotherapy, and ICI combination with radiotherapy. One such trial is CheckMate-816 [8], which is the first phase III trial comparing the addition of nivolumab to neoadjuvant platinum-doublet chemotherapy. The results from this trial showed that neoadjuvant immune-chemotherapy combinations appeared to achieve higher radiological and pathological responses than chemotherapy approaches alone. Another important trial is NEOSTAR [10], which is the first reported, randomized, phase II trial testing neoadjuvant nivolumab and nivolumab + ipilimumab in patients with resectable NSCLC. The combination therapy produced higher MPR and pCR rates compared with nivolumab monotherapy. Furthermore, the data from a randomized phase II trial that investigated the outcomes of immunotherapy combined with radiotherapy have also provided promising results [21]. The trial evaluated the preoperative combination of immune checkpoint blockade and radiotherapy to the primary tumor, and found that it was well-tolerated, safe, and associated with significant improvements in MPR and pCR. In the current study, our subgroup analysis also demonstrated more favorable outcomes of the administration of neoadjuvant immuno-chemotherapy compared with immunotherapy alone, without significantly increasing the incidence of SAEs in patients with resectable NSCLC. Overall, the findings from these trials highlight the potential synergistic effects of combination therapy based on ICIs in the neoadjuvant setting. However, it is important to note that these trials have relatively small sample sizes, which may limit the generalizability of the results. Therefore, future efforts should focus on conducting larger-scale trials to validate these findings and establish more precise guidelines for neoadjuvant immunotherapy in various patient populations.

In terms of neoadjuvant immunotherapy in combination with chemotherapy, the neoSCORE trial was the only randomized controlled trial that focused on assessing the efficacy and safety of different cycles of immuno-chemotherapy in the neoadjuvant setting [12]. The results from the neoSCORE trial showed that although three cycles of treatment presented a 14.5 % increase in the MPR rate relative to two cycles of treatment, the difference did not achieve statistical significance, which aligned with our current analysis [12]. Furthermore, at the time of data cutoff, the median OS and DFS were not reached, which identified the long-term effectiveness of neoadjuvant treatment to some extent. Nonetheless, there was no clear advantage in terms of 12-month OS and DFS rates when comparing two cycles to three cycles of neoadjuvant immunotherapy. It is important to note that these rates represent a specific time point and longer-term follow-up is necessary to determine the impact of treatment cycles on survival outcomes. Overall, further research with larger sample sizes and longer-term follow-up is necessary to validate these findings and provide more conclusive evidence regarding the optimal number of treatment cycles in neoadjuvant immunotherapy.

Since the 1990s, most clinical studies have taken OS as the main endpoint to evaluate the efficacy of tumor therapy. The definition of OS is very clear, and it is also the gold standard reflecting the long-term survival of patients [9]. With the continuous enrichment of treatment methods, the OS of lung cancer patients is also improving. However, clinical trials of resectable NSCLC with the OS as the primary endpoint require 5 years or even longer to complete, which greatly increases the difficulty of clinical practice [9]. Therefore, the outcomes such as pathological responses and radiological response are commonly considered as alternative endpoints to evaluate the efficacy of neoadjuvant therapy. However, the inconsistency between radiological and pathological assessments has raised formidable challenge for the evaluation [25]. In the NADIM study, 33 % and 73 % of patients radiologically assessed as SD and PR, respectively, were confirmed to have pCR after surgery [10]. This has highlighted the need for a comprehensive and multidimensional

approach to treatment evaluation. Combining multiple assessment modalities, considering clinical parameters, and exploring novel imaging techniques can help improve the accuracy of evaluating treatment effectiveness in the neoadjuvant setting.

There are several limitations to this analysis. First, most of the included studies were non-randomized single-arm clinical trials with a small sample size. Second, not all the included studies provided data on all key endpoints. Third, the follow-up periods of these studies were relatively short. Therefore, long-term outcomes such as DFS and OS, which better indicate treatment efficacy, have not yet been provided. Fourth, only one of the 29 included studies reported the outcomes of four cycles of neoadjuvant immunotherapy in patients with resectable NSCLC. Hence, we did not compare the outcomes of efficacy and safety of four cycles to other treatment cycles. Fifth, the majority of the included studies were single-arm trials, and the issue of publication bias may not be applicable. Lastly, we have to acknowledge the presence of significant heterogeneity among the included studies, which could not be effectively mitigated by removing any specific study from the analysis. However, based on the data of the sensitivity analysis, removal of any study did not significantly change the overall conclusion.

5. Conclusion

In the current study, we conducted the first comprehensive analysis comprising a wide range of studies with large sample sizes. Our analysis emphasizes the significant differences in the efficacy and safety of various treatment modes of neoadjuvant immunotherapy and confirms the clear advantages of immuno-chemotherapy in terms of both efficacy and safety in neoadjuvant settings. Increasing the number of cycles of neoadjuvant immunotherapy from two to three primarily improves the radiological response rather than the pathological responses, while potentially increasing the risk of adverse events. Therefore, it remains a topic of controversy whether increasing the number of cycles of neoadjuvant immunotherapy is beneficial for patients with resectable NSCLC. Given these findings, it is imperative to gather more research data focusing on investigating four cycles of neoadjuvant immunotherapy and explore more comprehensive and multidimensional approaches to treatment evaluation. This will allow for more accurate conclusions regarding the optimal number of cycles of neoadjuvant immunotherapy to be drawn. Nevertheless, the data presented in our study may provide valuable reference information for further clinical trial design and clinical decision-making processes regarding neoadjuvant therapy.

6. Ethics declarations

Not applicable.

Funding

7. Data availability statement

All data relevant to the study are included in the article or uploaded as online supplemental information.

CRediT authorship contribution statement

Linlin Ye: Writing – original draft, Funding acquisition, Formal analysis, Conceptualization. **Yao Liu:** Validation, Data curation. **Xuan Xiang:** Investigation, Data curation. **Zihao Wang:** Software. **Wenbei Peng:** Investigation. **Xiaoshan Wei:** Funding acquisition. **Siyu Zhang:** Visualization. **Qianqian Xue:** Data curation. **Qiong Zhou:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31549.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, CA Cancer J Clin 69 (1) (2019) 7–34, 2019, http://10.3322/caac.21551.

[2] R. Masarwy, et al., Neoadjuvant PD-1/PD-L1 inhibitors for resectable head and neck cancer: a systematic review and meta-analysis, JAMA Otolaryngol Head Neck Surg 147 (10) (2021) 871–878. http://10.1001/jamaoto.2021.2191.

[3] J.R. Molina, et al., Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship, Mayo Clin. Proc. 83 (5) (2008) 584, 94, http://10.4065/83.5.584.

[4] B.W. Carter, et al., Immunotherapy in non-small cell lung cancer treatment: current status and the role of imaging, J. Thorac. Imag. 32 (5) (2017) 300–312. http://10.1097/rti.0000000000000291.

[5] E. Ahern, et al., Neoadjuvant immunotherapy for non-small cell lung cancer: right drugs, right patient, right time? J Immunother Cancer 9 (6) (2021). http://10.1136/jitc-2020-002248.

[6] C. Aguado, et al., Neoadjuvant treatment in non-small cell lung cancer: new perspectives with the incorporation of immunotherapy, World J. Clin. Oncol. 13 (5) (2022) 314–322. http://10.5306/wjco.v13.i5.314.

[7] T. Cascone, et al., Tumor immunology and immunotherapy of non-small-cell lung cancer, Cold Spring Harb Perspect Med 12 (5) (2022). http://10.1101/cshperspect.a037895.

[8] P.M. Forde, et al., Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer, N. Engl. J. Med. 386 (21) (2022) 1973–1985. http://10.1056/NEJMoa2202170.

[9] H. Xie, X. Shi, G. Wang, Neoadjuvant immunotherapy for resectable non-small cell lung cancer, Am. J. Cancer Res. 11 (6) (2021) 2521–2536.

[10] T. Cascone, et al., Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: the phase 2 randomized NEOSTAR trial, Nat Med 27 (3) (2021) 504–514. http://10.1038/s41591-020-01224-2.

[11] J. Kang, C. Zhang, W.Z. Zhong, Neoadjuvant immunotherapy for non-small cell lung cancer: state of the art, Cancer Commun. 41 (4) (2021) 287–302. http://10.1002/cac2.12153.

[12] M. Shao, et al., Two vs three cycles of neoadjuvant sintilimab plus chemotherapy for resectable non-small-cell lung cancer: neoSCORE trial, Signal Transduct Target Ther 8 (1) (2023) 146. http://10.1038/s41392-023-01355-1.

[13] D. Moher, et al., Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, PLoS Med. 6 (7) (2009) e1000097, https://doi.org/10.1371/journal.pmed.1000097.

[14] D.F. Stroup, et al., Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group, JAMA 283 (15) (2000) 2008, 12, http://10.1001/jama.283.15.2008.

[15] R.P. Manning, et al., A systematic review of adult attachment and social anxiety, J. Affect. Disord. 211 (2017) 44–59. http://10.1016/j.jad.2016.12.020.

[16] L.C. Villaruz, M.A. Socinski, The clinical viewpoint: definitions, limitations of RECIST, practical considerations of measurement, Clin. Cancer Res. 19 (10) (2013) 2629, 36, http://10.1158/1078-0432.Ccr-12-2935.

[17] K. Tanaka, et al., Prospective comparison of various radiological response criteria and pathological response to preoperative chemotherapy and survival in operable high-grade soft tissue sarcomas in the Japan Clinical Oncology Group study JCOG0304, World J. Surg. Oncol. 16 (1) (2018) 162. http://10.1186/s12957-018-1462-y.

[18] L. Seymour, et al., iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics, Lancet Oncol. 18 (3) (2017) e143–e152. http://10.1016/s1470-2045(17)30074-8.

[19] A. Freites-Martinez, et al., Using the Common Terminology criteria for adverse events (CTCAE - version 5.0) to evaluate the severity of adverse events of anticancer therapies, Actas Dermosifiliogr (Engl Ed) 112 (1) (2021) 90–92. http://10.1016/j.ad.2019.05.009.

[20] Z.R. Zhao, et al., Phase 2 trial of neoadjuvant toripalimab with chemotherapy for resectable stage III non-small-cell lung cancer, OncoImmunology 10 (1) (2021) 1996000. http://10.1080/2162402X.2021.1996000.

[21] N.K. Altorki, et al., Neoadjuvant durvalumab with or without stereotactic body radiotherapy in patients with early-stage non-small-cell lung cancer: a single-centre, randomised phase 2 trial, Lancet Oncol. 22 (6) (2021) 824–835. http://10.1016/s1470-2045(21)00149-2.

[22] S.I. Rothschild, et al., Sakk 16/14: durvalumab in addition to neoadjuvant chemotherapy in patients with stage IIIA(N2) non–small-cell lung cancer—a multicenter single-arm phase II trial, J. Clin. Oncol. 39 (26) (2021) 2872–2880. http://10.1200/JCO.21.00276.

[23] P.M. Forde, et al., Neoadjuvant PD-1 blockade in resectable lung cancer, N. Engl. J. Med. 378 (21) (2018) 1976–1986. http://10.1056/NEJMoa1716078.

[24] A. Friedlaender, et al., Role and impact of immune checkpoint inhibitors in neoadjuvant treatment for NSCLC, Cancer Treat Rev. 104 (2022) 102350. http://10.1016/j.ctrv.2022.102350.

[25] B. Zhang, H. Zhong, B. Han, Neoadjuvant immunotherapy for patients with non-small cell lung cancer-is a new era coming? JAMA Oncol. 9 (3) (2023) 301–302. http://10.1001/jamaoncol.2022.6898.

[26] B. Besse, et al., 1215O-Neoadjuvant atezolizumab (A) for resectable non-small cell lung cancer (NSCLC): results from the phase II PRINCEPS trial, Ann. Oncol. 31 (Supplement 4) (2020) S794–S795.

[27] B.C. Tong, et al., Perioperative outcomes of pulmonary resection after neoadjuvant pembrolizumab in patients with non-small cell lung cancer, J. Thorac. Cardiovasc. Surg. 163 (2) (2022) 427–436. http://10.1016/j.jtcvs.2021.02.099.

[28] S. Gao, et al., Neoadjuvant PD-1 inhibitor (sintilimab) in NSCLC, J. Thorac. Oncol. 15 (5) (2020) 816–826. http://10.1016/j.jtho.2020.01.017.

[29] Z. Huang, et al., Perioperative safety and feasibility outcomes of stage IIIA-N2 non-small cell lung cancer following neoadjuvant immunotherapy or neoadjuvant chemotherapy: a retrospective study, Ann. Transl. Med. 9 (8) (2021) 685. http://10.21037/atm-21-1141.

[30] D. Shen, et al., Neoadjuvant pembrolizumab with chemotherapy for the treatment of stage IIB-IIIB resectable lung squamous cell carcinoma, J. Thorac. Dis. 13 (3) (2021) 1760–1768. http://10.21037/jtd-21-103.

[31] F. Eichhorn, et al., Neoadjuvant anti-programmed death-1 immunotherapy by pembrolizumab in resectable non-small cell lung cancer: first clinical experience, Lung Cancer 153 (2021) 150–157. http://10.1016/j.lungcan.2021.01.018.

[32] Y. Chen, et al., Neoadjuvant chemoimmunotherapy in resectable stage IIIA/IIIB non-small cell lung cancer, Transl. Lung Cancer Res. 10 (5) (2021) 2193–2204. http://10.21037/tlcr-21-329.

[33] F. Zhang, et al., Comparison of surgical difficulty in patients with resectable non-small cell lung cancer under different neoadjuvant treatment modes: a retrospective cohort study, J. Thorac. Dis. 13 (10) (2021) 5604–5616, https://doi.org/10.21037/jtd-21-1007.

[34] T. Hong, et al., Surgical perspective in neoadjuvant chemoimmunotherapy for stage II-III non-small cell lung cancer, Thorac Cancer 12 (20) (2021) 2796–2802. http://10.1111/1759-7714.14127.

[35] A. Tfayli, et al., Neoadjuvant chemotherapy and Avelumab in early stage resectable nonsmall cell lung cancer, Cancer Med. 9 (22) (2020) 8406–8411. http://10.1002/cam4.3456.

[36] J. Lei, et al., 62MO A randomised, controlled, multicenter phase II trial of camrelizumab combined with albumin-bound paclitaxel and cisplatin as neoadjuvant treatment in locally advanced NSCLC, Ann. Oncol. 31 (Supplement 7) (2020) S1441–S1442.

[37] J. Wu, et al., Real-world clinical outcomes of neoadjuvant immunotherapy combined with chemotherapy in resectable non-small cell lung cancer, Lung Cancer 165 (2022) 115–123. http://10.1016/j.lungcan.2022.01.019.

[38] M. Provencio, et al., Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial, Lancet Oncol. 21 (11) (2020) 1413–1422. http://10.1016/s1470-2045(20)30453-8.

[39] C.J. Yang, et al., Surgical outcomes after neoadjuvant chemotherapy and ipilimumab for non-small cell lung cancer, Ann. Thorac. Surg. 105 (3) (2018) 924–929. http://10.1016/j.athoracsur.2017.09.030.

[40] X. Hou, X. Shi, J. Luo, Efficacy and safety of camrelizumab (a PD-1 inhibitor) combined with chemotherapy as a neoadjuvant regimen in patients with locally advanced non-small cell lung cancer, Oncol. Lett. 24 (1) (2022) 215. http://10.3892/ol.2022.13336.

[41] H. Zhai, et al., Neoadjuvant nivolumab and chemotherapy in patients with locally advanced non-small cell lung cancer: a retrospective study, Cancer Manag. Res. 14 (2022) 515–524. http://10.2147/cmar.S344343.

[42] C.A. Shu, et al., Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: an open-label, multicentre, single-arm, phase 2 trial, Lancet Oncol. 21 (6) (2020) 786–795. http://10.1016/s1470-2045(20)30140-6.

[43] H. Duan, et al., Neoadjuvant programmed cell death protein 1 inhibitors combined with chemotherapy in resectable non-small cell lung cancer: an open-label, multicenter, single-arm study, Transl. Lung Cancer Res. 10 (2) (2021) 1020–1028, https://doi.org/10.21037/tlcr-21-130.

[44] P. Zhang, et al., Neoadjuvant sintilimab and chemotherapy for resectable stage IIIA non-small cell lung cancer, Ann. Thorac. Surg. 114 (3) (2022) 949–958. http://10.1016/j.athoracsur.2022.01.039.

[45] J. Dai, et al., Sleeve resection after neoadjuvant chemoimmunotherapy in the treatment of locally advanced non-small cell lung cancer, Transl. Lung Cancer Res. 11 (2) (2022) 188–200. http://10.21037/tlcr-22-56.