

# Neoadjuvant immune checkpoint inhibitor treatment + chemotherapy (vs. chemotherapy alone) for locally advanced non-small cell lung cancer: A retrospective cohort study

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**Abstract.** Neoadjuvant immune checkpoint inhibitor (ICI) treatment + chemotherapy has been used for locally advanced non-small cell lung cancer (NSCLC); however, evidence regarding the efficacy of this treatment is insufficient, particularly in Chinese patients. Therefore, the aim of the present study was to evaluate the efficacy and safety of neoadjuvant ICI treatment + chemotherapy compared with neoadjuvant chemotherapy alone for locally advanced NSCLC. For this, 50 patients with locally advanced NSCLC were retrospectively analyzed; of these, 23 patients received pre-operative camrelizumab or sintilimab + chemotherapy (ICI + chemo group) and 27 patients received pre-operative chemotherapy alone (chemo group). The objective response rate (73.9 vs. 44.4%,  $P=0.035$ ) was superior in the ICI + chemo group compared with the chemo group. Nevertheless, surgical resection rate (100.0 vs. 88.9%,  $P=0.240$ ), major pathological response (60.9 vs. 41.7%,  $P=0.188$ ) and complete pathological response (CPR; 30.4 vs. 8.3%,  $P=0.072$ ) were not significantly different in the ICI + chemo group compared with the chemo group. Following adjustment, ICI + chemo was independently associated with an elevated CPR ( $P=0.029$ ). Disease-free survival (DFS) was prolonged in the ICI + chemo group compared with the chemo group (1-year DFS, 94.1 vs. 81.6%; 2-year DFS, 80.7 vs. 42.9%;  $P=0.047$ ), while no significant differences were observed in overall survival (OS; 1-year OS, 100.0 vs. 95.7%; 2-year OS, 90.0 vs. 64.9%;  $P=0.187$ ). Additionally, the majority of adverse event incidences (apart from leukopenia) did not differ significantly between the ICI + chemo and chemo groups (all  $P>0.050$ ). On the whole, the present study demonstrated that neoadjuvant ICI treatment + chemotherapy exhibited adequate

efficacy and acceptable toxicity compared with chemotherapy alone in patients with locally advanced NSCLC.

## Introduction

Non-small cell lung cancer (NSCLC) is a major type of lung cancer, accounting for ~85% of all lung cancer cases (1,2). To date, NSCLC remains the second most common malignancy and the leading cause of cancer-associated mortality worldwide (3,4). For NSCLC management, surgery is the cornerstone treatment option for patients with early- and intermediate-stage NSCLC; nonetheless, for patients with locally advanced NSCLC, resection is not always feasible (5,6). Consequently, to increase the feasibility of surgery and improve survival, neoadjuvant therapy has been adopted for patients with locally advanced NSCLC (7,8).

Immune checkpoint inhibitors (ICIs) are a class of immune-oncology drugs that inhibit immune escape of tumor cells and enhance T cell antitumor responses (9,10). The Pacific study demonstrated that durvalumab (vs. placebo) after chemoradiotherapy leads to prolonged estimated 5-year progression-free survival (33.1 vs. 19.0%) and overall survival (OS; 42.9 vs. 33.4%) in patients with stage III NSCLC (11). Recently, ICI in combination with chemotherapy as a neoadjuvant treatment has been used for patients with locally advanced NSCLC (12,13). For example, a previous study demonstrated that complete pathological response (CPR) and major pathological response (MPR) are 41.67 and 33.33% in patients with locally advanced NSCLC treated with neoadjuvant ICI + chemotherapy (12). Another study reported that following treatment with neoadjuvant nivolumab + paclitaxel and carboplatin, 43 (95.6%) patients with locally advanced NSCLC achieve R0 resection; moreover, the 1-year disease-free survival (DFS) and OS rates are 45.8 and 79.9%, respectively (13). Nevertheless, the application of neoadjuvant ICI treatment + chemotherapy for patients with locally advanced NSCLC requires more clinical evidence.

Therefore, the present retrospective cohort study retrieved data of clinical and pathological response, survival and adverse events (AEs) of 50 patients with locally advanced NSCLC who received neoadjuvant ICI + chemotherapy or neoadjuvant chemotherapy alone, aiming to evaluate the efficacy and safety of neoadjuvant ICI treatment (camrelizumab or sintilimab) + chemotherapy for patients with locally advanced NSCLC,

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which would provide evidence for novel treatment of clinical NSCLC management.

## Patients and methods

**Patients.** The present study was a retrospective cohort study that analyzed 50 patients with locally advanced NSCLC [15 (30.0%) females and 35 (70.0%) males] with a mean age of  $59.2 \pm 7.6$  years, who received neoadjuvant therapy in The Third People's Hospital of Chengdu (Chengdu, China) from April 2019 to December 2021. Of these patients, 23 received ICI + chemotherapy (ICI + chemo), while 27 patients received chemotherapy alone (chemo group). The criteria for inclusion were as follows: i) Diagnosis of NSCLC; ii) age >18 years; iii) patients with locally advanced NSCLC with tumor-node-metastasis (TNM) stage of IIIA-IIIB (T1-T4N2M0, T3-T4N1M0 and T4N0M0) (14); iv) Eastern Cooperative Oncology Group Performance Status (ECOG PS) scores ranging from 0 to 1; v) patients who underwent ICI + chemotherapy or chemotherapy alone as neoadjuvant therapy. The exclusion criteria were as follows: i) Diagnosis of metastatic NSCLC and ii) lack of clinical, pathological or follow-up information. Moreover, at the initiation of the study, all the surviving patients provided written informed consent; for the deceased patients, informed consent forms were signed by their family members. The protocol for the present study was approved by the Ethics Committee of The Third People's Hospital of Chengdu [Chengdu, China; ethics approval no. (2021) S-199].

**Treatment.** Patients who received camrelizumab or sintilimab + chemotherapy (carboplatin combined with nab-paclitaxel or paclitaxel) were defined as the ICI + chemo group; patients who received carboplatin combined with nab-paclitaxel or paclitaxel were defined as the chemo group. Camrelizumab or sintilimab were administered at 200 mg for a 3-week cycle; paclitaxel was administered at 200 mg/m<sup>2</sup> for a 3-week cycle; nab-paclitaxel was administered at 100 mg/m<sup>2</sup> on the 1st, 8th and 15th days of a 3-week cycle. Carboplatin was administered with an area under the concentration-time curve of 5 mg/ml on the first day of a 3-week cycle. Following neoadjuvant therapy, resectability was evaluated (two senior clinicians independently evaluated the possibility of complete resection according to the preoperative computed tomography CT results; in case of disagreement, the two doctors discussed and decided on the best results) (15).

**Assessment.** The clinical response rate [complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD)] was evaluated in all patients; moreover, Response Evaluation Criteria In Solid Tumours (RECIST, version 1.1) was used as a reference (16). MPR and CPR were also evaluated in patients who underwent surgical resection. Definition of MPR was as follows: Viable carcinoma cells did not comprise >10% on the tumor cut side; the definition of CPR was: 0% tumor tissue observed on the surgical margin, as described in previous studies (17,18). The follow-up data were collected on the last follow-up time point in June 2022. DFS was evaluated in patients who underwent surgery and was determined as the duration from the surgical resection to

disease relapse, mortality for any reason or the last follow-up; OS was assessed in all patients and calculated from the date of neoadjuvant therapy or mortality or the last follow-up. In addition, AEs were documented and graded using Common Toxicity Criteria for AEs, version 4.0 (19). Additionally, programmed death-ligand 1 (PD-L1) expression data, assessed by immunohistochemistry (IHC) using Anti-PD-L1 antibody (Abcam) and evaluated based on the percentage of the stained positive cells, was obtained.

**Statistical analysis.** SPSS 26.0 software (IBM Corp.) was utilized for statistical analysis. GraphPad Prism 9.0 software (GraphPad Software Inc.) was used to draw graphs. Mean  $\pm$  standard deviation (SD) was used to present continuous variables, while number (percentage) was used to present categorical variables. Comparisons between the ICI + chemo group and the chemo group were performed using an un-paired Student's *t*,  $\chi^2$ , Mann-Whitney U and Fisher's exact test. Kaplan-Meier curves and log-rank test were used to compare the cumulative DFS and OS of patients between the two groups. Logistic and Cox regression analyses were used to analyze the superiority of ICI + chemotherapy over chemotherapy alone, as well as other independent prognostic factors for patients with locally advanced NSCLC (all factors analyzed in the univariate analysis were subsequently input in multivariate analysis with the entering mode). *P*<0.05 was considered to indicate a statistically significant difference.

## Results

**Study flow and basic characteristics of patients in the ICI + chemo group and chemo group.** The study process is displayed in Fig. S1. The mean age of the patients in the ICI + chemo group (*n*=23) was  $57.8 \pm 6.3$  years; the group comprised 7 (30.4%) females and 16 (69.6%) males; the mean age of the patients in the chemo group (*n*=27) was  $60.4 \pm 8.6$  years; the chemo group comprised 8 (29.6%) females and 19 (70.4%) males (Table I). No significant differences were found in the basic characteristics the ICI + chemo and chemo group, including age, sex, smoking status, ECOG PS score, histological type, cT, cN and cTNM stage (all *P*>0.05). Moreover, 10 (43.5%) patients in the ICI + chemo group were assessed as having a high PD-L1 expression ( $\geq 50\%$ ), while the other 13 (56.5%) patients were evaluated as having a low PD-L1 expression (<50%). The detailed basic characteristics of all subjects are presented in Table I.

**Treatment information and pathological (p)N2 stage at time of surgery.** In the ICI + chemo group, 10 (43.5%), 4 (17.4%), 7 (30.4%) and 2 (8.7%) patients received sintilimab + paclitaxel + carboplatin, sintilimab + nab-paclitaxel + carboplatin, camrelizumab + paclitaxel + carboplatin and camrelizumab + nab-paclitaxel + carboplatin, respectively. In the chemo group, 17 (63.0%) patients were treated with paclitaxel + carboplatin, while the other 10 (37.0%) patients received nab-paclitaxel + carboplatin (Table II). A total of 4 (17.4%) patients in the ICI + chemo group and 9 (33.3%) patients in the chemo group were evaluated as pN2 stage at the time of surgery (*P*=0.200).

Table I. Basic characteristics of patients in the ICI + chemo group and chemo group.

Characteristic	ICI + chemo (n=23)	Chemo (n=27)	Statistical value (t/ $\chi^2$ /Z)	P-value
Mean age $\pm$ SD, years	57.783 $\pm$ 6.310	60.370 $\pm$ 8.607	1.194	0.239 <sup>a</sup>
Sex, n (%)			0.004	0.951 <sup>b</sup>
Female	7 (30.400)	8 (29.600)		
Male	16 (69.600)	19 (70.400)		
Smoking status, n (%)			2.820	0.244 <sup>c</sup>
Never	5 (21.739)	3 (11.111)		
Former	12 (52.174)	11 (40.741)		
Current	6 (26.087)	13 (48.148)		
ECOG PS score, n (%)			0.119	0.730 <sup>b</sup>
0	18 (78.300)	20 (74.100)		
1	5 (21.700)	7 (25.900)		
Histological type, n (%)			0.557	0.757 <sup>c</sup>
ADC	8 (34.783)	7 (25.926)		
SCC	13 (56.522)	18 (66.667)		
Others	2 (8.696)	2 (7.407)		
cT stage, n (%)			-0.305	0.761 <sup>d</sup>
cT2	11 (47.826)	10 (37.037)		
cT3	9 (39.130)	16 (59.259)		
cT4	3 (13.043)	1 (3.704)		
cN stage, n (%)			2.339	0.126 <sup>b</sup>
cN1	7 (30.435)	14 (51.852)		
cN2	16 (69.565)	13 (48.148)		
cTNM stage, n (%)			-0.259	0.796 <sup>d</sup>
cT2N2M0	11 (47.826)	10 (37.037)		
cT3N1M0	4 (17.391)	13 (48.148)		
cT3N2M0	5 (21.739)	3 (11.111)		
cT4N1M0	3 (13.043)	1 (3.704)		
PD-L1 expression, n (%)			-	-
<50%	10 (43.478)	0 (0.000)		
$\geq$ 50%	13 (56.522)	0 (0.000)		
Not assessed	0 (0.000)	27 (100.000)		

Calculated using <sup>a</sup>Student's t, <sup>b</sup> $\chi^2$ , <sup>c</sup>Fisher's exact and <sup>d</sup>Mann-Whitney U test. ICI, immune checkpoint inhibitor; SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group performance status; ADC, adenocarcinoma; SCC, squamous scarcinoma; PD-L1, programmed cell death ligand 1; -, the comparison was not performed as PD-L1 expression was not evaluated in the chemo group.

*ICI + chemo realized better treatment response compared with chemo alone.* The treatment response was superior in the ICI + chemo group than in the chemo group (P=0.021, Fig. 1A). Specifically, the CR, PR, SD and PD of patients treated with ICI + chemotherapy were 0.0, 73.9, 26.1 and 0.0%, respectively; while these were 0.0, 44.4, 40.7 and 14.8% in the patients who received chemotherapy alone. The objective response rate (ORR) was elevated in the ICI + chemo group compared with the chemo group (73.9 vs. 44.4%, P=0.035, Fig. 1B). Nevertheless, surgical resection rate (100.0 vs. 88.9%, P=0.240, Fig. 1C) and MPR (60.9 vs. 41.7%, P=0.188, Fig. 1D) did not differ significantly between the ICI + chemo and chemo group. CPR was higher but not significantly so in the ICI + chemo group compared with the chemo group (30.4% vs. 8.3%, P=0.072, Fig. 1E).

To eliminate the potential confounding factors influencing the comparison of the pathological response between the ICI + chemo and chemo alone groups, multivariate logistic regression analysis was applied. ICI + chemo (vs. chemo) was independently associated with an elevated CPR in patients with NSCLC [odds ratio (OR), 19.920; 95% confidence interval (CI), 1.363-291.038, P=0.029; Table III].

*ICI + chemo led to an improving survival profile compared with chemo alone.* DFS was prolonged in patients who received ICI + chemotherapy compared with those who received chemotherapy alone (P=0.047, Fig. 2A). The 1-year and 2-year DFS rates were 94.1 and 80.7 in the ICI + chemo group but only 81.6 and 42.9% in the chemo group, respectively. However, OS

Table II. Treatment and pN2 at the time of surgery.

Characteristic	ICI + chemo, n=23 (%)	Chemo n=27 (%)	$\chi^2$ value	P-value
Treatment			-	-
Sintilimab + paclitaxel + carboplatin	10 (43.478)	-		
Sintilimab + nab-paclitaxel + carboplatin	4 (17.391)	-		
Camrelizumab + paclitaxel + carboplatin	7 (30.435)	-		
Camrelizumab + nab-paclitaxel + carboplatin	2 (8.700)	-		
Paclitaxel + carboplatin	-	17 (63.000)		
Nab-paclitaxel + carboplatin	-	10 (37.000)		
pN2 at time of surgery	4 (17.391)	9 (33.333)	1.641	0.200 <sup>a</sup>

<sup>a</sup>Calculated using Fisher's exact test. ICI, immune checkpoint inhibitor; pN2, pathological node stage 2; -, the treatment therapy was different between the two groups, and therefore the comparison of treatment could not be performed.

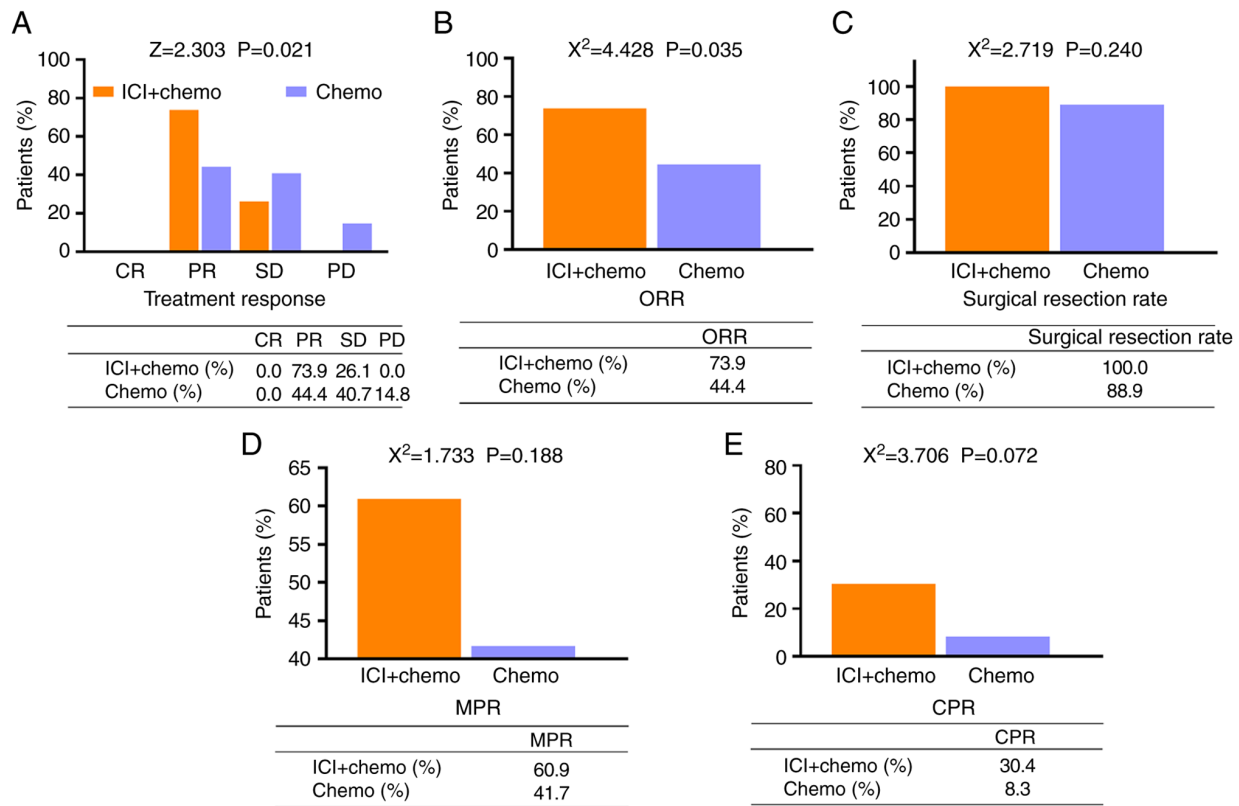


Figure 1. Treatment response and ORR are elevated in the ICI + chemo group (vs. chemo group). Comparison of (A) treatment response, (B) ORR, (C) surgical resection rate, (D) MPR and (E) CPR of patients with locally advanced non-small cell lung cancer between the ICI + chemo and the chemo group. ORR, objective response rate; ICI, immune checkpoint inhibitor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; MPR, major pathological response; CPR, complete pathological response.

did not differ significantly between the ICI + chemo group and chemo group (P=0.187, Fig. 2B). Specifically, the 1-year and 2-year OS rates were 100.0 and 90.0 in the ICI + chemo and 95.7 and 64.9% in the chemo group, respectively.

Furthermore, multivariate Cox proportional hazards regression analysis revealed that the ICI + chemo group had a non-inferior DFS [hazard ratio (HR), 1.893; 95% CI, 0.100-35.704; P=0.670] and OS (HR, 0.189; 95% CI, 0.012-3.05; P=0.241) compared with the chemo group (Table IV).

*Non-significant differences in tolerance between ICI + chemo and chemo alone.* The incidence of AEs did not differ significantly between the ICI + chemo and the chemo group (all P>0.05), apart from the increased leukopenia incidence in the ICI + chemo group (47.8 vs. 18.5%; P=0.036). The incidences of all grade 3-4 AEs were not different between the two groups, including leukopenia, anemia, neutropenia, thrombocytopenia, fatigue, nausea and vomiting and constipation (all P>0.050). Furthermore, the majority of AEs in the

Table III. Factors associated with CPR by multivariate logistic regression analysis.

Variable	P-value	OR	95% CI	
			Lower	Upper
Therapy (ICI + chemo vs. Chemo)	0.029	19.920	1.363	291.038
Age ( $\geq 60$ vs. $<60$ years)	0.617	1.630	0.240	11.077
Sex (male vs. female)	0.421	2.657	0.246	28.749
Smoking status (current vs. former + never)	0.181	6.172	0.428	89.014
ECOG PS score (1 vs. 0)	0.475	0.392	0.030	5.123
Histological type (SCC vs. ADC + other)	0.060	14.741	0.890	244.222
Higher cT stage	0.894	0.857	0.089	8.231
Higher cN stage	0.602	2.145	0.122	37.651

All statistical values were calculated using multivariate logistic regression analysis. CPR, complete pathological response; OR, odds ratio; CI, confidence interval; ICI, immune checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; SCC, squamous carcinoma; ADC, adenocarcinoma.

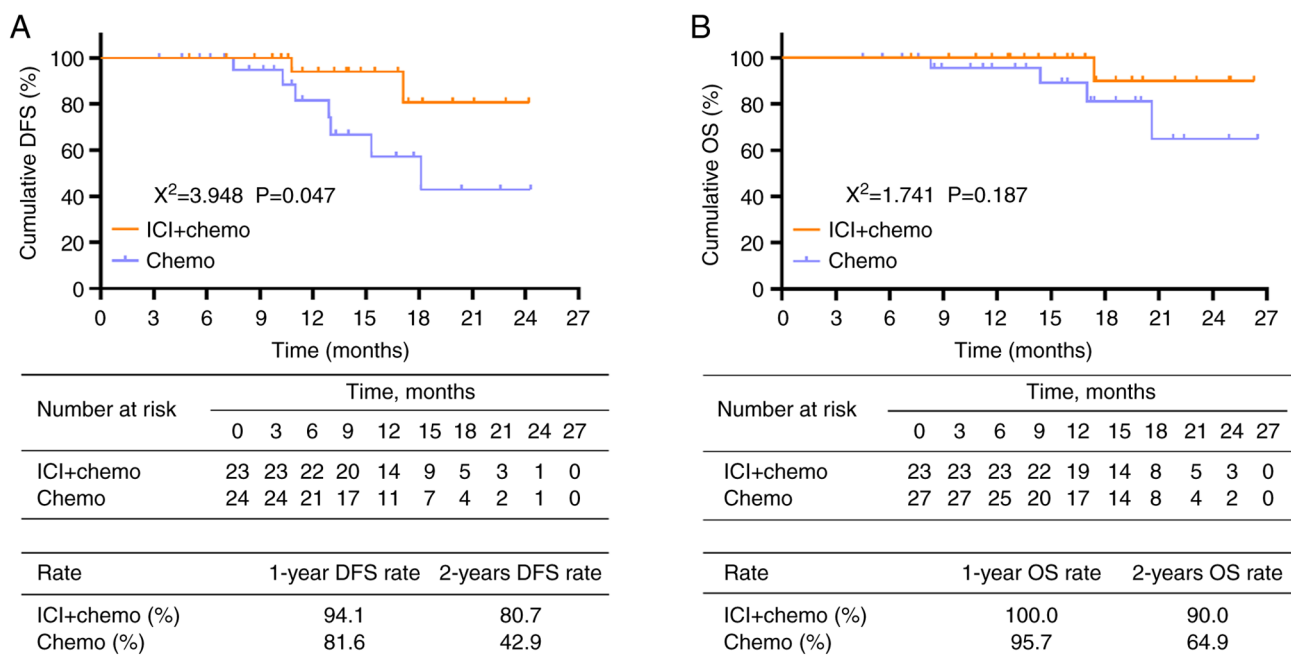


Figure 2. DFS is prolonged in the ICI + chemo group (vs. chemo group). Comparison of (A) DFS and (B) OS of patients with locally advanced non-small cell lung cancer between the ICI + chemo group and the chemo group. DFS, disease-free survival; ICI, immune checkpoint inhibitor; OS, overall survival.

ICI + chemo group were moderate and controllable. The most frequent hematological AEs in the ICI + chemo group were leukopenia (47.8%), anemia (39.1%) and neutropenia (34.8%), while the most common non-hematological AEs were alopecia (43.5%), fatigue (43.5%) and nausea and vomiting (39.1%). Grade 3-4 AEs in the ICI + chemo group included three cases (13.0%) of neutropenia and one case (4.3%) each of leukopenia, anemia and thrombocytopenia (Table V).

## Discussion

The efficacy of ICI-based neoadjuvant treatment for early-to-intermediate stage NSCLC has already been demonstrated in previous studies (17,20,21). Nevertheless, a limited

number of studies have applied the combination of ICI + chemotherapy as neoadjuvant therapy for treatment of patients with locally advanced NSCLC (12,22). For example, a previous study observed that the CPR (25.8 vs. 8.3%) and MPR (61.3 vs. 37.5%) are higher in patients treated with neoadjuvant camrelizumab + chemotherapy compared with patients who received chemotherapy alone (22). In line with the findings of previous studies (12,22), the present study also demonstrated that neoadjuvant ICI treatment + chemotherapy led to a superior treatment response and ORR (73.9 vs. 44.4%) compared with chemotherapy alone in patients with locally advanced NSCLC. Furthermore, ICI + chemotherapy (vs. chemotherapy alone) was independently associated with elevated CPR in patients with NSCLC. The reasons for this may be that ICI directly enhanced

Table IV. Factors associated with DFS and OS by multivariate Cox's proportional hazards regression analysis.

Variable	P-value	HR	95% CI	
			Lower	Upper
Therapy (ICI + chemo vs. Chemo)	0.670	1.893	0.100	35.704
Age ( $\geq 60$ vs. $< 60$ years)	0.164	4.942	0.521	46.913
Sex (male vs. female)	0.051	0.031	0.001	1.016
Smoking status (current vs. former + never)	0.039	51.637	1.219	2,187.218
ECOG PS score (1 vs. 0)	0.055	17.194	0.944	313.078
Histological type (SCC vs. ADC + other)	0.661	1.760	0.141	21.959
Higher cT stage	0.092	0.018	0.000	1.928
Higher cN stage	0.145	0.029	0.000	3.361

## B, OS

Variable	P-value	HR	95% CI	
			Lower	Upper
Therapy (ICI + chemo vs. Chemo)	0.241	0.189	0.012	3.055
Age ( $\geq 60$ vs. $< 60$ years)	0.331	5.623	0.172	183.294
Sex (male vs. female)	0.534	0.407	0.024	6.902
Smoking status (current vs. former + never)	0.519	2.508	0.153	41.146
ECOG PS score (1 vs. 0)	0.485	0.312	0.012	8.200
Histological type (SCC vs. ADC + other)	0.197	8.906	0.320	247.496
Higher cT stage	0.525	2.583	0.139	48.099
Higher cN stage	0.281	8.748	0.170	450.532

All statistical values were calculated using multivariate Cox's proportional hazards regression analysis. DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ICI, immune checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; SCC, squamous carcinoma; ADC, adenocarcinoma.

the antitumor immune response in the tumor microenvironment by targeting PD-1 or PD-L1 (17,23) or there was a potential synergy between ICI and chemotherapy, which enhanced the treatment efficacy (24,25). ICI + chemotherapy achieved better treatment response compared with chemotherapy alone.

Neoadjuvant ICI treatment + chemotherapy also leads to a satisfactory survival profile in patients with locally advanced NSCLC, according to previous studies (13,26). For example, in the neoadjuvant nivolumab plus chemotherapy in operable stage IIIA NSCLC trial, the 2-year DFS and OS rates were 77.1 and 89.9% in patients with locally advanced NSCLC who received neoadjuvant nivolumab + paclitaxel-carboplatin therapy, respectively (26). Another study demonstrated 2-year DFS and OS rates of 45.8 and 79.9% in patients treated with the neoadjuvant ICI + chemotherapy regimen (13). However, the majority of previous studies are single-arm studies (13,26). In the present study, neoadjuvant ICI + chemotherapy prolonged the DFS of patients with NSCLC compared with chemotherapy alone; however, no significant difference was observed in OS. The 2-year DFS rate was 80.7% in the ICI + chemo group and 42.9% in the chemo group. These findings revealed that ICI +

chemotherapy led to an improved survival profile compared with chemotherapy alone; additionally, the survival outcome of the patients in the ICI + chemo group in the present study was similar to that of previous studies (13,26). A possible explanation for this may be that combination of ICI + chemotherapy improved the pathological response, which further suppressed disease progression and recurrence of NSCLC (27). Therefore, DFS was prolonged in patients who received ICI + chemotherapy compared with those who received chemotherapy alone. Multivariate Cox proportional hazards regression analysis suggested that the therapy (ICI + chemo vs. chemo) was not an independent factor of DFS or OS. This may be because mutual interference between the therapy and the cT stage weakened the effects on DFS and were not independent factors of DFS or the small number of deaths weakened the statistical power and no factor was independently associated with OS.

Moreover, the Pacific study found ORR and 1-year DFS rate of 28.4 and 55.9%, respectively, in patients with stage III NSCLC who received durvalumab after chemoradiotherapy, which indicated the potency of ICI + chemoradiotherapy treatment pattern in patients with NSCLC (28). To the best of our knowledge,



Table V. AEs.

AE	ICI + chemo, n=23 (%)			Chemo, n=27 (%)			P-value <sup>a</sup>	P-value <sup>b</sup>
	Total	Grade 1-2	Grade 3-4	Total	Grade 1-2	Grade 3-4		
Hematological								
Leukopenia	11 (47.8)	10 (43.5)	1 (4.3)	5 (18.5)	5 (18.5)	0 (0.0)	0.036	0.460
Anemia	9 (39.1)	8 (34.8)	1 (4.3)	9 (33.3)	8 (29.6)	1 (3.7)	0.771	1.000
Neutropenia	8 (34.8)	5 (21.7)	3 (13.0)	9 (33.3)	8 (29.6)	1 (3.7)	0.914	0.322
Thrombocytopenia	5 (21.7)	4 (17.4)	1 (4.3)	9 (33.3)	9 (33.3)	0 (0.0)	0.529	0.460
Non-hematological								
Alopecia	10 (43.5)	10 (43.5)	0 (0.0)	13 (48.1)	13 (48.1)	0 (0.0)	0.782	-
Fatigue	10 (43.5)	10 (43.5)	0 (0.0)	7 (25.9)	6 (22.2)	1 (3.7)	0.239	1.000
Nausea and vomiting	9 (39.1)	9 (39.1)	0 (0.0)	7 (25.9)	6 (22.2)	1 (3.7)	0.373	1.000
Constipation	6 (26.1)	6 (26.1)	0 (0.0)	6 (22.2)	5 (18.5)	1 (3.7)	1.000	1.000
Elevated transaminase	6 (26.1)	6 (26.1)	0 (0.0)	5 (18.5)	5 (18.5)	0 (0.0)	0.733	-
Anorexia	6 (26.1)	6 (26.1)	0 (0.0)	5 (18.5)	5 (18.5)	0 (0.0)	0.733	-
Rash	5 (21.7)	5 (21.7)	0 (0.0)	7 (25.9)	7 (25.9)	0 (0.0)	1.000	-
Diarrhea	3 (13.0)	3 (13.0)	0 (0.0)	4 (14.8)	4 (14.8)	0 (0.0)	1.000	-
Elevated bilirubin	3 (13.0)	3 (13.0)	0 (0.0)	4 (14.8)	4 (14.8)	0 (0.0)	1.000	-
Hypothyroidism	2 (8.7)	2 (8.7)	0 (0.0)	2 (7.4)	2 (7.4)	0 (0.0)	1.000	-
Peripheral neuropathy	2 (8.7)	2 (8.7)	0 (0.0)	1 (3.7)	1 (3.7)	0 (0.0)	0.588	-

<sup>a</sup>Total incidence; <sup>b</sup>Grade 3-4 AEs. All statistical values were calculated using Fisher's exact test. AE, adverse event; ICI, immune checkpoint inhibitor; -, the comparison could not be performed due to the lack of corresponding grade 3-4 AEs in the two groups.

application of ICI + chemoradiotherapy as neoadjuvant treatment in NSCLC patients is rarely reported (29,30). Therefore, the comparison of treatment efficacy between neoadjuvant ICI + chemotherapy and neoadjuvant ICI + chemoradiotherapy in patients with NSCLC requires further investigation.

Previous studies have reported the non-inferior tolerance between neoadjuvant ICI + chemotherapy and neoadjuvant chemotherapy alone in patients with locally advanced NSCLC; here, the most common AEs in the ICI + chemo group included alopecia, nausea and vomiting, anemia and fatigue (22,31,32). Consistent with the aforementioned studies, the present study revealed that the incidence of most AEs did not differ significantly between the ICI + chemo and the chemo group, apart from the increased leukopenia incidence in the ICI + chemo group. Notably, the majority of AEs in the ICI + chemo group were moderate and controllable, with a low incidence of grade 3-4 AEs, which implied the reliable safety profile of neoadjuvant ICI + chemotherapy for patients with locally advanced NSCLC.

There were limitations to the present study. Firstly, the present study was a retrospective study and the selection bias was difficult to avoid. Secondly, due to the small number of patients in our department, it was hard to enroll more eligible patients within the study period; thus, the sample size (n=50) was small and further large-scale studies were warranted to enhance the statistical power. Thirdly, the follow-up duration was relatively short; hence, further studies with a long-term follow up are required. Fourthly, pathological N staging before neoadjuvant therapy was a reference for patients whose surgical feasibility was hard to decide. However, due to the fact that this was a retrospective study and most patients were

originally assessed as operable patients, pathological staging before neoadjuvant therapy and surgery was not conducted in most patients. Consequently, most patients only had the clinical TNM stage before neoadjuvant treatment and CT images for surgical-feasibility reassessment before surgery.

In conclusion, the present study demonstrated that neoadjuvant ICI + chemotherapy provided an encouraging pathological response, survival benefits and acceptable safety profiles compared with chemotherapy alone in patients with locally advanced NSCLC.

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#### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

#### Authors' contributions

ZL contributed to the conception and the design of the study. YY and ZL were responsible for the acquisition, analysis and interpretation of the data. ZL and YY confirm the authenticity of all the raw data. Both have read and approved the final manuscript.

## Ethics approval and consent to participate

The present study was permitted by the ethical committee of The Third People's Hospital of Chengdu [ethics approval no. (2021) S-199]. All surviving patients provided written informed consent; for the deceased patients, informed consent was signed by their family members.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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