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

XINLEI HOU[1*], XUELIANG SHI[1*] and JIE LUO[2]

Departments of [1]Thoracic Surgery and [2]Ophthalmology, Daqing Oil Field General Hospital, Daqing, Heilongjiang 163001, P.R. China

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Abstract. Camrelizumab is a novel programmed cell death protein 1 (PD-1) inhibitor developed in China that exhibits good efficacy in several advanced cancer types, including non-small cell lung cancer (NSCLC); however, its utility as a neoadjuvant regimen in NSCLC remains unclear. Thus, the present study aimed to explore the efficacy and safety of neoadjuvant camrelizumab plus chemotherapy in patients with locally advanced NSCLC. A total of 56 patients with stage IIIA/IIIB resectable NSCLC were analyzed in the present prospective observational study. Amongst the cohort, 31 patients underwent neoadjuvant camrelizumab (200 mg every 2 weeks) plus paclitaxel and carboplatin (PC) chemotherapy, while another 25 cases underwent neoadjuvant PC chemotherapy alone. The pathological response, disease-free survival (DFS) time, overall survival (OS) time and adverse events (AEs) were analyzed. The complete pathological response (25.8 vs. 8.3%; P=0.159) and major pathological response (MPR) (61.3 vs. 37.5%; P=0.080) rates were higher in the camrelizumab plus PC group compared with the findings in the PC group, although the results were not statistically significant. DFS time was significantly prolonged in the camrelizumab plus PC group compared with that in the PC group (P=0.030); however, there was no difference in OS time between these two groups (P=0.251). Following adjustment by multivariate analysis, the camrelizumab plus PC regimen versus the PC regimen alone was independently associated with higher MPR [odds ratio, 5.216; 95% confidence interval (CI), 1.178-23.086; P=0.030], and favorable DFS [hazard ratio (HR), 0.055; 95% CI, 0.007-0.442; P=0.006] and OS (HR, 0.025; 95% CI, 0.002-0.416; P=0.010) times. The most common AEs of the neoadjuvant camrelizumab plus PC regimen were alopecia (51.6%), nausea and vomiting (45.2%), anemia (41.9%) and fatigue (41.9%), the majority of which occurred in patients with grade 1-2 disease. The present results indicated that neoadjuvant camrelizumab plus PC chemotherapy exhibited a superior pathological response and survival profile to PC chemotherapy alone, and was well tolerated in patients with locally advanced NSCLC.

Correspondence to: Dr Jie Luo, Department of Ophthalmology, Daqing Oil Field General Hospital, 9 Zhongkang Road, Daqing, Heilongjiang 163001, P.R. China
E-mail: lanjie475738@163.com

*Contributed equally

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Introduction

Lung cancer was ranked as the second most prevalent type of cancer in 2020 and as the cancer with the highest mortality worldwide according to Global Cancer Statistics for that year; of these lung cancer cases, ~85% correspond to non-small cell lung cancer (NSCLC) (1,2). Surgical resection with or without adjuvant therapy is currently the optimal choice for patients with NSCLC and achieves relatively favorable outcomes; however, the majority of patients with NSCLC are diagnosed at the advanced stage, and therefore are not suitable for surgery (3,4). In order to give patients the opportunity of undergoing surgery, neoadjuvant chemotherapy has been proposed, particularly in patients with locally advanced NSCLC (5-8). Notably, in patients with locally advanced NSCLC exhibiting sensitive gene mutations [such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and proto-oncogene tyrosine-protein kinase ROS (ROS1) alterations], the addition of a tyrosine kinase inhibitor to chemotherapy as the neoadjuvant regimen could further improve the patient prognosis; however, in patients without sensitive gene alterations, these novel drugs are not applicable (9-11).

Camrelizumab, as a programmed cell death protein 1 (PD-1) inhibitor, affects antitumor activity by inhibiting the binding of PD-1 to programmed cell death 1 ligand 1 (PD-L1) to prevent the immune escape of tumor cells (12). Although camrelizumab has been only been commercially available since 2019, it has been applied in numerous cancer types, including esophageal, hepatocellular and renal cell carcinoma, as well as NSCLC, and exhibits good efficacy and an acceptable tolerance (12-16). Regarding NSCLC treatment, camrelizumab plus chemotherapy or anti-angiogenic drugs has improved the outcomes of

patients with unresectable advanced NSCLC (16-18). However, to the best of our knowledge, the application of camrelizumab as neoadjuvant treatment bridging to tumor resection in patients with NSCLC has not been reported to date.

Therefore, the present cohort study aimed to investigate the efficacy and safety of camrelizumab plus chemotherapy versus chemotherapy alone as a neoadjuvant regimen in patients with locally advanced NSCLC.

Materials and methods

Patients. Between July 2019 and February 2021, the present prospective, cohort, observational study consecutively enrolled 31 patients with locally advanced NSCLC who received neoadjuvant therapy consisting of camrelizumab plus a paclitaxel and carboplatin (PC) regimen in Daqing Oil Field General Hospital (Daqing, China). The inclusion criteria were: i) Pathologically confirmed NSCLC; ii) age >18 years; iii) TNM stage IIIA-IIIB (T1-T4N2M0, T3-T4N1M0 and T4N0M0) (19) and suitable for surgical resection; iv) Eastern Cooperative Oncology Group performance status (ECOG PS) score from 0 to 1 (20); v) no EGFR, ALK or ROS1 sensitizing alterations; and vi) choice of receiving neoadjuvant therapy of camrelizumab plus PC. The exclusion criteria were as follows: i) Patients with contraindications to the treatment or allergy to the drugs used in the study; ii) patients with NSCLC accompanied by other malignancies; iii) patients who had difficulty in attending regular follow-ups; and iv) pregnant or lactating women. In addition to the aforementioned 31 patients, the present study concurrently analyzed 25 patients with locally advanced NSCLC who only received a PC regimen as a neoadjuvant therapy during the same period. These 25 patients also met the aforementioned criteria with the exception that they chose to receive neoadjuvant therapy of PC, and therefore served as controls in the present study.

The current study did not intervene in the treatment of the patients. The patients received the corresponding treatment regimen according to their willingness and disease conditions, but such treatment regimens were not assigned by the researchers. Patients who received camrelizumab combined with the PC regimen were considered as the camrelizumab plus PC group (n=31), while patients who only received the PC regimen were considered as the PC group (n=25). The present study was approved by the Ethics Committee of Daqing Oil Field General Hospital (Daqing, China; approval no. KS1952). Written informed consent for participation and data use was provided by all the patients included in the study.

Treatment procedures. Patients in the camrelizumab plus PC group received camrelizumab combined with the PC regimen for 3 cycles prior to surgery. Camrelizumab was administered every 2 weeks by intravenous drip at a dose of 200 mg for 30 min, while paclitaxel was provided intravenously at a dose of 200 mg/m^2 on day 1 and carboplatin was administered with an area under the curve of 6 (6 mg/ml per min) on day 1. Both paclitaxel and carboplatin were administered every 21 days (which was the duration of a treatment cycle). Approximately 4 weeks after the completion of neoadjuvant treatment, patients underwent surgical resection. Following recovery from the surgery, patients received ≥2 cycles of adjuvant therapy with camrelizumab monotherapy or camrelizumab plus the PC regimen.

Patients in the PC group received neoadjuvant treatment with 3 cycles of the PC regimen prior to surgery and underwent surgery ~4 weeks after completion of the neoadjuvant treatment. Upon recovery from surgery, the patients also received ≥2 cycles of PC regimen as adjuvant therapy. The administration of the PC regimen was performed in the same manner in both groups.

Outcome evaluation. An enhanced chest computed tomography (CT) scan was performed to evaluate the clinical response of the tumor ~4 weeks after the last dose of neoadjuvant treatment, according to the Response Evaluation Criteria In Solid Tumors (RECIST) (21). The clinical response outcomes were classified as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The objective response rate (ORR) was also calculated as the sum of the CR and PR rates. At the time of surgery, the resected primary tumors of the patients were examined by pathologists to assess their pathological response according to a previously reported methodology (22). Major pathological response (MPR) was defined as ≤10% residual viable tumor in the surgically removed tumor and lymph node tissues (23), while complete pathological response (CPR) was defined as lack of any viable tumor cells in the surgically removed tumor and lymph node tissues (23). Adverse events (AEs) during the administration of camrelizumab were documented and graded based on the Common Terminology Criteria for Adverse Events (version 4.0) (24). Since the AEs of patients in the PC group were not recorded in detail, they were not included in the analysis. Patients were followed up by outpatient visits or telephone conversations. The last follow-up was completed on August 31, 2021. Disease-free survival (DFS) and overall survival (OS) times were calculated from the date of surgery until disease recurrence or mortality, respectively (25). Tumor PD-L1 expression was detected by immunohistochemistry with a human anti-PD-L1 antibody (cat. no. MAB1561; R&D Systems Europe, Ltd.; UK) and was calculated as the percentage of tumor cells with positive membranous staining, according to a previous study (26). In brief, tumor tissues were fixed using formalin (10%) at room temperature for 24 h and embedded in paraffin, and then cut into 4-μm slices. The slices were deparaffinized using xylene, rehydrated using gradient ethanol, and then antigen retrieval was performed. The slice was blocked with 5% goat serum (Beyotime Institute of Biotechnology) at room temperature for 1 h. Subsequently, the slices were incubated with PD-L1 antibody (1:200 dilution; cat. no. MAB1561; R&D Systems Europe, Ltd.) at 4˚C overnight, and then incubated with anti-rabbit IgG H&L (HRP) antibody (1:1,000 dilution; cat. no. ab6721; Abcam). Finally, the staining image was obtained via a light microscope (Nikon Corporation) and evaluated using ImageJ software Version 1.8.0 (National Institutes of Health). The detection of PD-L1 was not specifically performed for this study but was a routine test at Daqing Oil Field General Hospital.

Statistical analysis. Comparison of clinical characteristics between two groups was conducted with an unpaired Student's t-test, Wilcoxon rank sum test or χ^2 test. Comparison of the clinical and pathological responses between two groups was performed with Wilcoxon's rank sum test, the χ^2 test or Fisher's exact test as appropriate. Notably, in the PC group, there was a patient with PD who exhibited contralateral lymph

Table I. Clinical characteristics.

Characteristic	PC group (n=25)	Camrelizumab plus PC group (n=31)	P-value
Mean age ± SD, years	62.3±7.3	59.4±7.2	0.134
Sex, n (%)			0.446
Female	7 (28.0)	6 (19.4)	
Male	18 (72.0)	25 (80.6)	
Smoke status, n (%)			0.360
Never	5 (20.0)	5 (16.1)	
Former	9 (36.0)	17 (54.9)	
Current	11 (44.0)	9 (29.0)	
Histological type, n (%)			0.359
ADC	10 (40.0)	14 (45.2)	
SCC	15 (60.0)	15 (48.3)	
Others	0 (0.0)	2 (6.5)	
ECOG PS score, n (%)			0.514
0	19 (76.0)	26 (83.9)	
1	6 (24.0)	5 (16.1)	
Tumor PD-L1 expression, n (%)			-
≤50%	-	11 (35.5)	
>50%	-	20 (64.5)	
cT stage, n (%)			0.978
cT1	0 (0.0)	1 (3.2)	
cT2	9 (36.0)	10 (32.3)	
cT3	14 (56.0)	17 (54.8)	
cT4	2 (8.0)	3 (9.7)	
cN stage, n (%)			0.359
cN0	1 (4.0)	1 (3.2)	
cN1	11 (44.0)	10 (32.3)	
cN2	13 (52.0)	20 (64.5)	
cTNM stage, n (%)			0.593
cT1N2M0	0 (0.0)	1 (3.2)	
cT2N2M0	9 (36.0)	10 (32.3)	
cT3N1M0	10 (40.0)	8 (25.8)	
cT3N2M0	4 (16.0)	9 (29.0)	
cT4N0M0	1 (4.0)	1 (3.2)	
cT4N1M0	1 (4.0)	2 (6.5)	

PC, paclitaxel plus carboplatin; SD, standard deviation; ADC, adenocarcinoma; SCC, squamous cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; cT, clinical tumor; cN, clinical node; cTNM, clinical Tumor-Node-Metastasis.

node metastasis (as revealed by CT) after neoadjuvant treatment; based on a comprehensive evaluation conducted by the physician, it was decided that the patient was no longer suitable for surgery. Therefore, this patient only had clinical response data documented and was not included in the analysis of pathological response or survival. DFS and OS were calculated using the Kaplan-Meier method, and the comparison of DFS and OS between two groups was conducted using the log-rank test. The factors associated with MPR were analyzed with a multivariable logistic regression model, while the factors associated with DFS or OS were analyzed with the multivariable Cox's proportional hazards regression model. SPSS 22.0 (IBM Corp.) and GraphPad Prism 7.02 (GraphPad Software, Inc.) were applied for analysis and graphical representation of the data, respectively. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. The mean age (± SD) of the 31 patients in the camrelizumab plus PC group was 59.4±7.2 years, and 80.6% of them were male, while 19.4% were female. The mean age (± SD) of the 25 patients in the PC group was 62.3±7.3 years, and 72.0% were male, while 28.0% were female. No difference was observed in terms of age, sex, smoking status, histological type, ECOG PS or TNM stage between the camrelizumab plus PC group and the PC group (all $P>0.05$; Table I). In addition,

Table II. Clinical response in the PC (n=25) and camrelizumab plus PC (n=31) groups.

Response	PC group, n (%)	Camrelizumab plus PC group, n (%)	P-value
Clinical response			0.046[a]
CR	0 (0.0)	0 (0.0)	
PR	10 (40.0)	20 (64.5)	
SD	13 (52.0)	11 (35.5)	
PD	2 (8.0)	0 (0.0)	
ORR (CR+PR)	10 (40.0)	20 (64.5)	0.067

[a]P<0.05. PC, paclitaxel + carboplatin; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate.

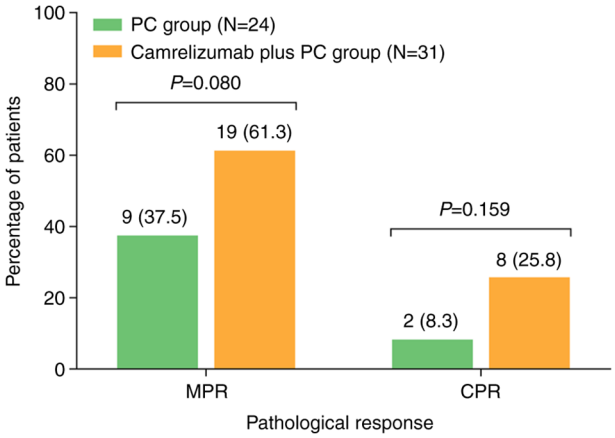

Figure 1. Comparison of the pathological response between the camrelizumab plus PC and PC groups. Values above the bars show n (%). PC, paclitaxel and carboplatin; MPR, major pathological response; CPR, complete pathological response.

20 (64.5%) patients had tumor PD-L1 expression >50%, while 11 (35.5%) patients had tumor PD-L1 expression ≤50% in the camrelizumab plus PC group.

Clinical response. Following neoadjuvant therapy, the clinical response was assessed according to RECIST, which revealed that 0.0, 64.5, 35.5 and 0.0% of patients exhibited CR, PR, SD and PD, respectively, in the camrelizumab plus PC group, while 0.0, 40.0, 52.0 and 8.0% of patients had CR, PR, SD and PD, respectively, in the PC group. The camrelizumab plus PC group achieved a better clinical response than the PC group (P=0.046). Furthermore, the camrelizumab plus PC group exhibited a higher ORR than the PC group, although this was not statistically significant (64.5 vs. 40.0%; P=0.067) (Table II).

Pathological response. The resected tumor was evaluated by pathological examination to assess the pathological response, which revealed that MPR exhibited a higher trend in the camrelizumab plus PC group than in the PC group, although the difference was not statistically significant (61.3 vs. 37.5%; P=0.080). In addition, CPR also exhibited an elevated trend in the camrelizumab plus PC group compared with that of the PC group, but again the result was not statistically significant (25.8 vs. 8.3%; P=0.159) (Fig. 1).

Survival outcome. During a median follow-up time of 11.8 months, DFS time was prolonged in the camrelizumab plus PC group compared with that in the PC group (P=0.030; Fig. 2A). In addition, the 1-year DFS rate was 91.6% in the camrelizumab plus PC group and 57.0% in the PC group. In terms of OS, there was no significant difference between the camrelizumab plus PC and PC groups (P=0.251; Fig. 2B). The 1-year OS was 95.0% in the camrelizumab plus PC group and 83.2% in the PC group. In the camrelizumab plus PC group, it was observed that patients with PD-L1 expression >50% tended to have a longer DFS time compared with that of patients with PD-L1 expression ≤50%, although the difference was not statistically significant (P=0.233; Fig. S1A). The OS time also did not differ significantly between the two groups (P=0.542; Fig. S1B).

Adjustment by multivariate analyses. Upon adjustment by multivariate logistic regression analysis, the camrelizumab plus PC regimen versus the PC regimen were independently associated, with higher MPR [odds ratio (OR), 5.216; 95% confidence interval (CI), 1.178-23.086; P=0.030; Fig. 3]. Furthermore, higher T and N stages were independently associated with a lower MPR.

Following adjustment by multivariate Cox's proportional hazards regression analysis, the camrelizumab plus PC regimen was superior to the PC regimen regarding both DFS [hazard ratio (HR), 0.055; 95% CI, 0.007-0.442; P=0.006] and OS (HR, 0.025; 95% CI, 0.002-0.416; P=0.010) (Table III) times. Furthermore, a higher TNM stage was independently associated with poor DFS and OS (both P=0.002).

AEs. The most common AEs of the neoadjuvant camrelizumab plus PC regimen were alopecia (51.6%), nausea and vomiting (45.2%), anemia (41.9%), fatigue (41.9%), neutropenia (38.7%), reactive cutaneous capillary endothelial proliferation (RCCEP) (35.5%), leukopenia (29.0%), peripheral neuropathy (25.8%), thrombopenia (22.6%) and anorexia (22.6%) (Table IV). The majority of AEs associated with the camrelizumab plus PC regimen were at grade 1-2, and only a few AEs were observed at grade 3-4, including neutropenia (9.7%), nausea and vomiting (6.5%), fatigue (6.5%), anemia (3.2%), leukopenia (3.2%), anorexia (3.2%) and elevated transaminase (3.2%).

Discussion

Camrelizumab is a PD-1 inhibitor, which was recently developed in China and is currently widely used for the treatment of advanced tumors (12-18,27). For instance, in one study, camrelizumab plus lenvatinib increased the ORR and disease control rate, and also prolonged the progression-free survival (PFS) time, compared with lenvatinib alone when treating advanced hepatocellular carcinoma (27). In terms of NSCLC, treatment with camrelizumab plus carboplatin and pemetrexed led to a favorable PFS compared with treatment with

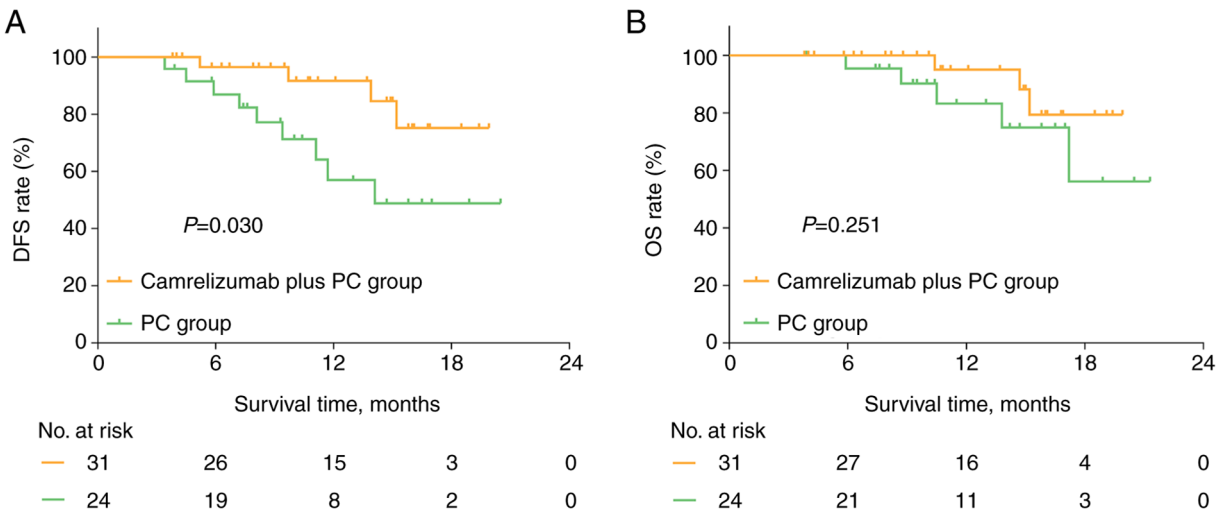

Figure 2. Comparison of the survival profile between the camrelizumab plus PC and PC groups. Comparison of (A) DFS and (B) OS between the camrelizumab plus PC and PC groups. PC, paclitaxel and carboplatin; DFS, disease-free survival; OS, overall survival.

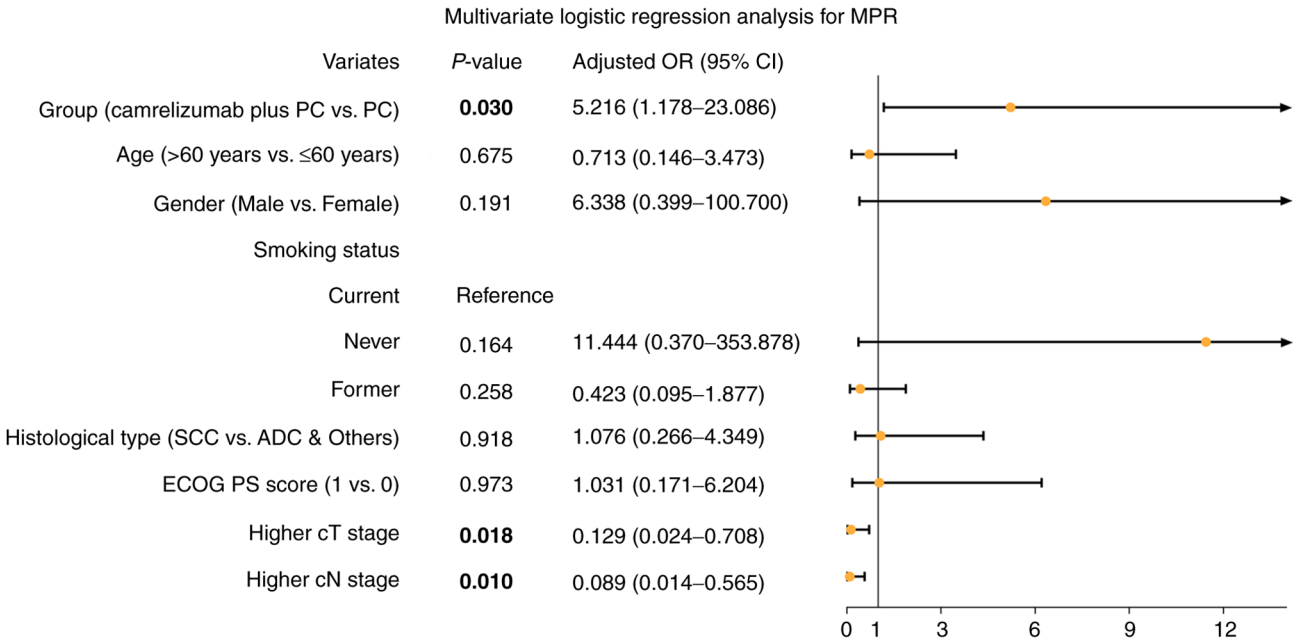

Figure 3. Multivariate logistic regression analysis for the MPR. MPR, major pathological response; SCC, squamous cell carcinoma; ADC, adenocarcinoma; cT, clinical tumor; cN, clinical node; ECOG PS, Eastern Cooperative Oncology Group performance status.

carboplatin and pemetrexed chemotherapy alone in patients with advanced non-squamous NSCLC without EGFR or ALK mutations (16). Furthermore, camrelizumab plus anlotinib achieved a median PFS time of 8.2 months and a median OS time of 12.7 months in patients with advanced NSCLC who had been subjected to multiple failed lines of treatment (17). However, the use of camrelizumab as a neoadjuvant therapy in cancer lacks sufficient evidence, and only a limited number of reports have been published, including two studies on neoadjuvant camrelizumab plus chemotherapy with or without apatinib in locally advanced esophageal squamous cell carcinoma and gastroesophageal junction adenocarcinoma (28,29), and one study on neoadjuvant camrelizumab plus lenvatinib in patients with hepatocellular carcinoma (HCC) who underwent a liver transplant (30). In detail, neoadjuvant camrelizumab plus nab-paclitaxel and S1 achieved a 33% CPR and 75% MPR in locally advanced esophageal squamous cell carcinoma (28), while another study reported the use of neoadjuvant immunotherapy involving camrelizumab plus chemotherapy, realizing a 34% CPR and 76% MPR in locally advanced esophageal squamous cell carcinoma and gastroesophageal junction adenocarcinoma (29). For HCC, neoadjuvant camrelizumab plus lenvatinib achieved a 71% ORR and 85% DCR, and the patients successfully underwent liver transplantation (30).

In terms of locally advanced NSCLC, various studies have reported the advantages of PD-1 inhibitors as neoadjuvant therapy (31-33). For instance, the neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM) trial indicated that neoadjuvant nivolumab plus PC chemotherapy achieved a clinical response (according

Table III. Multivariable Cox's proportional hazards regression analysis for DFS and OS.

	DFS		OS	
Variable	P-value	HR (95% CI)	P-value	HR (95% CI)
Group (camrelizumab plus PC vs. PC)	0.006[a]	0.055 (0.007-0.442)	0.010[a]	0.025 (0.002-0.416)
Age (>60 vs. ≤60 years)	0.624	0.681 (0.146-3.166)	0.116	0.096 (0.005-1.781)
Sex (male vs. female)	0.403	0.421 (0.055-3.200)	0.456	48.644 (0.002-1336754.889)
Smoke status				
Current	Reference	-	Reference	-
Never	0.189	0.155 (0.010-2.506)	0.660	9.603 (0.000-231266.344)
Former	0.991	1.008 (0.256-3.969)	0.853	0.782 (0.058-10.557)
Histological type (SCC vs. ADC & others)	0.900	0.910 (0.207-3.999)	0.746	1.462 (0.146-14.602)
ECOG PS score (1 vs. 0)	0.901	1.114 (0.206-6.020)	0.194	7.002 (0.372-131.960)
cTNM stage (IIIB vs. IIIA)	0.002[a]	29.007 (3.488-241.219)	0.002[a]	110.594 (5.863-2085.989)

[a]P<0.05. DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; PC, paclitaxel + carboplatin; SCC, squamous cell carcinoma; ADC, adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; cTNM, clinical Tumor-Node-Metastasis.

Table IV. Adverse events in the camrelizumab plus paclitaxel and carboplatin group.

Adverse event	Total, n (%)	Grade 1-2, n (%)	Grade 3-4, n (%)
Alopecia	16 (51.6)	16 (51.6)	0 (0.0)
Nausea and vomiting	14 (45.2)	12 (38.7)	2 (6.5)
Anemia	13 (41.9)	12 (38.7)	1 (3.2)
Fatigue	13 (41.9)	11 (35.5)	2 (6.5)
Neutropenia	12 (38.7)	9 (29.0)	3 (9.7)
RCCEP	11 (35.5)	11 (35.5)	0 (0.0)
Leukopenia	9 (29.0)	8 (25.8)	1 (3.2)
Peripheral neuropathy	8 (25.8)	8 (25.8)	0 (0.0)
Thrombopenia	7 (22.6)	7 (22.6)	0 (0.0)
Anorexia	7 (22.6)	6 (19.4)	1 (3.2)
Constipation	6 (19.4)	6 (19.4)	0 (0.0)
Elevated bilirubin	6 (19.4)	6 (19.4)	0 (0.0)
Elevated transaminase	6 (19.4)	5 (16.1)	1 (3.2)
Diarrhea	5 (16.1)	5 (16.1)	0 (0.0)
Rash	4 (12.9)	4 (12.9)	0 (0.0)
Hypothyroidism	3 (9.7)	3 (9.7)	0 (0.0)

RCCEP, reactive cutaneous capillary endothelial proliferation.

to RECIST criteria) of a 4% CR and 76% ORR, and a pathological response (according to pathological examination) of an 83% MPR and 63% CPR in patients with TNM stage IIIA NSCLC (31). A recent retrospective cohort study revealed that nivolumab or pembrolizumab plus PC chemotherapy led to a 41.7% CPR and 75.0% MPR in patients with TNM stage IIIA/IIIB NSCLC (32). In addition, a prospective cohort study indicated that PD-1 inhibitors (including multiple products) plus albumin paclitaxel and carboplatin produced a CPR of 29.1% in patients with TNM stage IIIA NSCLC (33). However, the previous studies lacked a control group or cohort, and the sample size was relatively small. Furthermore, to the bets of our knowledge, in patients with locally advanced NSCLC, no reports have been published to date on the application of neoadjuvant camrelizumab for the treatment of these patients.

The present study revealed that neoadjuvant camrelizumab plus PC led to a 0.0% CR, 64.5% PR, 35.5% SD, 0.0% PD and 64.5% ORR according to the RECIST criteria, and achieved a 25.8% CPR and 61.3% MPR according to the pathological examination in patients with locally advanced NSCLC. These results were partially in line with those from previous studies on other PD-1 inhibitors (31-33), although the CPR seemed relatively low compared with that of the aforementioned studies, which may be due to the following reasons: i) Patients with TNM stage IIIB were also enrolled in the present study; ii) the duration of adjuvant therapy differed among studies; and iii) different drugs were used. Notably, the present study revealed that neoadjuvant camrelizumab plus PC chemotherapy achieved a better clinical response than neoadjuvant PC chemotherapy, and exhibited a higher ORR, CPR and MRP compared with those of neoadjuvant PC chemotherapy in patients with locally advanced NSCLC. A possible explanation could be that camrelizumab synergized with PC chemotherapy by blocking immune escape and enhancing chemosensitivity, therefore improving the neoadjuvant treatment response (34,35).

The NADIM trial found that neoadjuvant nivolumab plus PC chemotherapy achieved a 1-year PFS rate of 95.7%, a 2-year PFS rate of 77.1%, a 1-year OS rate of 97.8% and a 2-year OS rate of 89.9% in patients with TNM stage IIIA NSCLC (31). However, no relevant data on neoadjuvant camrelizumab therapy in patients with locally advanced NSCLC has been published to date. Although the follow-up duration was relatively short, the present study revealed that neoadjuvant camrelizumab plus PC chemotherapy led to a 1-year DFS rate

of 91.6% and a 1-year OS rate of 95.0% in patients with locally advanced NSCLC, which was in accordance with previous studies on other PD-1 inhibitors (31,32). Importantly, a control cohort was included in the current study, and it was observed that neoadjuvant camrelizumab plus PC chemotherapy led to a prolonged DFS time compared with that of neoadjuvant PC chemotherapy in patients with locally advanced NSCLC, with a benefit from the synergy between camrelizumab and chemotherapy (34,35).

In addition, since compounding factors may exist due to the cohort study design, the present study further performed multivariate logistic regression analysis and multivariate Cox's proportional hazards regression analysis for adjustment, which revealed that neoadjuvant camrelizumab plus PC chemotherapy versus PC chemotherapy were independently associated with a higher MPR, as well as prolonged DFS and OS times. This provided evidence of the advantages of neoadjuvant camrelizumab plus PC chemotherapy for the treatment of patients with locally advanced NSCLC.

Regarding safety, a previous study reported that the most common AEs were hypertension, fatigue, transaminitis, diarrhea, headache/dizziness and neutropenia in patients with advanced NSCLC who underwent camrelizumab plus anlotinib treatment (18). Another study revealed that the most prevalent AEs were RECCP, decreased neutrophil, platelet and white blood cell counts, anemia, and increased aspartate and alanine aminotransferases in patients with advanced NSCLC who underwent camrelizumab plus carboplatin and pemetrexed chemotherapy (16). However, the safety profile of neoadjuvant camrelizumab in locally advanced NSCLC remains unclear. The current study revealed that the most common AEs were alopecia, nausea, vomiting, anemia, fatigue, neutropenia, RCCEP, leukopenia, peripheral neuropathy, thrombopenia and anorexia in patients with locally advanced NSCLC who underwent neoadjuvant camrelizumab plus PC chemotherapy. In addition, the majority of AEs of neoadjuvant camrelizumab plus PC chemotherapy were at grade 1-2, while only a few AEs were at grade 3-4. This suggested an acceptable tolerance to neoadjuvant camrelizumab plus PC chemotherapy in these patients. However, since PD-1 inhibitors directly affect T cells, which can increase the risk of hematological AEs, this issue needs to be monitored during its application (16).

The present study has several limitations: i) Due to the present cohort study design, a further randomized, controlled study to validate the findings would be useful; ii) the current study was a single-center-based study, and therefore patient selection bias and physician assessment bias may exist; thus, a multiple center-based study should be conducted in the future; and iii) the follow-up duration was relatively short in the present study due to the limited time that camrelizumab had been available on the market (the camrelizumab was on the market for ~2.2 years at the last follow-up date; therefore, the follow-up duration for each patient was within 2.2 years), and therefore the follow-up time should be prolonged in future studies.

In conclusion, the present study revealed that neoadjuvant camrelizumab plus PC chemotherapy exhibited a superior pathological response and survival profile over neoadjuvant PC chemotherapy, and was tolerable in patients with locally advanced NSCLC.

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Availability of data and materials

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

Authors' contributions

JL conceived and designed the study. XH and XS collected and analyzed the data. JL prepared the figures and tables. XH and XS wrote the manuscript. XH and XS confirm the authenticity of all the raw data. JL revised the manuscript. All authors read and approved the submitted version.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Daqing Oil Field General Hospital (Daqing, China; approval no. KS1952). Written informed consent for participation and data use was provided by all the patients included in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
2. Clark SB and Alsubait S: Non Small Cell Lung Cancer. StatPearls. Treasure Island, FL, 2021.
3. Ikeda N: Updates on minimally invasive surgery in non-small cell lung cancer. Curr Treat Options Oncol 20: 16, 2019.
4. Alexander M, Kim SY and Cheng H: Update 2020: Management of non-small cell lung cancer. Lung 198: 897-907, 2020.
5. Jazieh AR, Zeitouni M, Alghamdi M, Alrujaib M, Lotfi S, Daff SA, Alomair A, Alshehri S, Alhusaini H, Allehebi A, *et al*: Management guidelines for stage III non-small cell lung cancer. Crit Rev Oncol Hematol 157: 103144, 2021.
6. Patane AK: Minimal invasive surgery in locally advanced N2 non-small cell lung cancer. Transl Lung Cancer Res 10: 519-528, 2021.
7. Passiglia F, Bertolaccini L, Del Re M, Facchinetti F, Ferrara R, Franchina T, Malapelle U, Menis J, Passaro A, Pilotto S, *et al*: Diagnosis and treatment of early and locally advanced non-small-cell lung cancer: The 2019 AIOM (Italian Association of Medical Oncology) clinical practice guidelines. Crit Rev Oncol Hematol 148: 102862, 2020.
8. Ren S, Xu A, Lin Y, Camidge DR, Maio MD, Califano R, Hida T, Rossi A, Guibert N, Zhu C and Shen J: A narrative review of primary research endpoints of neoadjuvant therapy for lung cancer: Past, present and future. Transl Lung Cancer Res 10: 3264-3275, 2021.

9. Xiong L, Lou Y, Bai H, Li R, Xia J, Fang W, Zhang J, Zhang HH, Lizaso A, Li B, *et al*: Efficacy of erlotinib as neoadjuvant regimen in EGFR-mutant locally advanced non-small cell lung cancer patients. J Int Med Res 48: 300060519887275, 2020.
10. Zhang C, Li SL, Nie Q, Dong S, Shao Y, Yang XN, Wu YL, Yang Y and Zhong WZ: Neoadjuvant crizotinib in resectable locally advanced non-small cell lung cancer with ALK rearrangement. J Thorac Oncol 14: 726-731, 2019.
11. Zhao S, Zhu S, Lei X, Xu D, Shi T, Chen Q, Ren F, Chen G, Huang D and Xu S: Use of crizotinib as neoadjuvant therapy for non-small cell lung cancers patient with ROS1 rearrangement: A case report. Thorac Cancer 12: 2815-2818, 2021.
12. Markham A and Keam SJ: Camrelizumab: First global approval. Drugs 79: 1355-1361, 2019.
13. Luo H, Lu J, Bai Y, Mao T, Wang J, Fan Q, Zhang Y, Zhao K, Chen Z, Gao S, *et al*: Effect of camrelizumab vs placebo added to chemotherapy on survival and progression-free survival in patients with advanced or metastatic esophageal squamous cell carcinoma: The ESCORT-1st randomized clinical trial. JAMA 326: 916-925, 2021.
14. Huang Y, Zhang Z, Liao W, Hu K and Wang Z: Combination of sorafenib, camrelizumab, transcatheter arterial chemoembolization, and stereotactic body radiation therapy as a novel downstaging strategy in advanced hepatocellular carcinoma with portal vein tumor thrombus: A case series study. Front Oncol 11: 650394, 2021.
15. Qu YY, Zhang HL, Guo H, Luo H, Zou Q, Xing N, Xia S, Sun Z, Zhang X, He C, *et al*: Camrelizumab plus famitinib in patients with advanced or metastatic renal cell carcinoma: Data from an open-label, multicenter phase II basket study. Clin Cancer Res 27: 5838-5846, 2021.
16. Zhou C, Chen G, Huang Y, Zhou J, Lin L, Feng J, Wang Z, Shu Y, Shi J, Hu Y, *et al*: Camrelizumab plus carboplatin and pemetrexed versus chemotherapy alone in chemotherapy-naive patients with advanced non-squamous non-small-cell lung cancer (CameL): A randomised, open-label, multicentre, phase 3 trial. Lancet Respir Med 9: 305-314, 2021.
17. Zhou N, Jiang M, Li T, Zhu J, Liu K, Hou H and Zhang X: Anlotinib combined with anti-PD-1 antibody, camrelizumab for advanced NSCLCs after multiple lines treatment: An open-label, dose escalation and expansion study. Lung Cancer 160: 111-117, 2021.
18. Wang P, Fang X, Yin T, Tian H, Yu J and Teng F: Efficacy and safety of anti-pd-1 plus anlotinib in patients with advanced non-small-cell lung cancer after previous systemic treatment failure-a retrospective study. Front Oncol 11: 628124, 2021.
19. Chansky K, Detterbeck FC, Nicholson AG, Rusch VW, Vallières E, Groome P, Kennedy C, Krasnik M, Peake M, Shemanski L, *et al*: The IASLC lung cancer staging project: External validation of the revision of the TNM stage groupings in the eighth edition of the TNM classification of lung cancer. J Thorac Oncol 12: 1109-1121, 2017.
20. Mischel AM and Rosielle DA: Eastern cooperative oncology group performance status #434. J Palliat Med 25: 508-510, 2022.
21. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al*: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009.
22. Pataer A, Kalhor N, Correa AM, Raso MG, Erasmus JJ, Kim ES, Behrens C, Lee JJ, Roth JA, Stewart DJ, *et al*: Histopathologic response criteria predict survival of patients with resected lung cancer after neoadjuvant chemotherapy. J Thorac Oncol 7: 825-832, 2012.
23. Travis WD, Dacic S, Wistuba I, Sholl L, Adusumilli P, Bubendorf L, Bunn P, Cascone T, Chaft J, Chen G, *et al*: IASLC multidisciplinary recommendations for pathologic assessment of lung cancer resection specimens after neoadjuvant therapy. J Thorac Oncol 15: 709-740, 2020.
24. Chen AP, Setser A, Anadkat MJ, Cotliar J, Olsen EA, Garden BC and Lacouture ME: Grading dermatologic adverse events of cancer treatments: The common terminology criteria for adverse events version 4.0. J Am Acad Dermatol 67: 1025-1039, 2012.
25. Shu CA, Gainor JF, Awad MM, Chiuzan C, Grigg CM, Pabani A, Garofano RF, Stoopler MB, Cheng SK, White A, *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: 786-795, 2020.
26. Aguilar EJ, Ricciuti B, Gainor JF, Kehl KL, Kravets S, Dahlberg S, Nishino M, Sholl LM, Adeni A, Subegdjo S, *et al*: Outcomes to first-line pembrolizumab in patients with non-small-cell lung cancer and very high PD-L1 expression. Ann Oncol 30: 1653-1659, 2019.
27. Wei F, Huang Q, He J, Luo L and Zeng Y: Lenvatinib plus camrelizumab versus lenvatinib monotherapy as post-progression treatment for advanced hepatocellular carcinoma: A short-term prognostic study. Cancer Manag Res 13: 4233-4240, 2021.
28. Yang G, Su X, Yang H, Luo G, Gao C, Zheng Y, Xie W, Huang M, Bei T, Bai Y, *et al*: Neoadjuvant programmed death-1 blockade plus chemotherapy in locally advanced esophageal squamous cell carcinoma. Ann Transl Med 9: 1254, 2021.
29. Wu Z, Zheng Q, Chen H, Xiang J, Hu H, Li H, Pan Y, Peng Y, Yao X, Liu P, *et al*: Efficacy and safety of neoadjuvant chemotherapy and immunotherapy in locally resectable advanced esophageal squamous cell carcinoma. J Thorac Dis 13: 3518-3528, 2021.
30. Qiao ZY, Zhang ZJ, Lv ZC, Tong H, Xi ZF, Wu HX, Chen XS, Xia L, Feng H, Zhang JJ and Xia Q: Neoadjuvant programmed cell death 1 (PD-1) inhibitor treatment in patients with hepatocellular carcinoma before liver transplant: A cohort study and literature review. Front Immunol 12: 653437, 2021.
31. Provencio M, Nadal E, Insa A, García-Campelo MR, Casal-Rubio J, Dómine M, Majem M, Rodríguez-Abreu D, Martínez-Martí A, Carpeño JD, *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: 1413-1422, 2020.
32. Chen T, Ning J, Campisi A, Dell'Amore A, Ciarrocchi AP, Li Z, Song L, Huang J, Yang Y, Stella F and Luo Q: Neoadjuvant PD-1 inhibitors and chemotherapy for locally advanced NSCLC: A retrospective study. Ann Thorac Surg 113: 993-999, 2021.
33. Wang J, Li J, Cai L, Chen S and Jiang Y: The safety and efficacy of neoadjuvant programmed death 1 inhibitor therapy with surgical resection in stage IIIA non-small cell lung cancer. Ann Transl Med 9: 486, 2021.
34. Chen Z, Lu X and Koral K: The clinical application of camrelizumab on advanced hepatocellular carcinoma. Expert Rev Gastroenterol Hepatol 14: 1017-1024, 2020.
35. Yang C, Xu C, Li X, Zhang Y, Zhang S, Zhang T and Zhang Y: Could camrelizumab plus chemotherapy improve clinical outcomes in advanced malignancy? A systematic review and network meta-analysis. Front Oncol 11: 700165, 2021.