Camrelizumab combined with apatinib and nanoparticle albumin-bound paclitaxel in lung adenocarcinoma (CAPAP-lung): a single-arm phase II study

Xingxiang Pu,[a,g] Gen Lin,[b,g] Maoliang Xiao,[c] Jie Lin,[d] Qianzhi Wang,[a] Yi Kong,[a] Xuejun Yan,[c] Fang Xu,[a] Yan Xu,[a] Jia Li,[a] Kang Li,[a] Bolin Chen,[a] Xiaoping Wen,[a] Yali Tan,[c] Fengzhuo Cheng,[e] Kangle Zhu,[e] Na Li,[f] and Lin Wu[a,*]

[a]Department of Thoracic Medical Oncology, Hunan Cancer Hospital, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha 410000, China
[b]Department of Thoracic Medical Oncology, Fujian Cancer Hospital, Fuzhou 350014, China
[c]Department of Medical Oncology, Hunan Province Directly Affiliated TCM Hospital, Zhuzhou 412000, China
[d]Department of Oncology, The Second Affiliated Hospital of Kunming Medical University, Yunnan 650108, China
[e]Medical Affairs, Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai, China
[f]Shenzhen Engineering Center for Translational Medicine of Precision Cancer Immunodiagnosis and Therapy, Shenzhen YuceBio Technology Co., Ltd, Shenzhen 518000, China

eClinicalMedicine 2024;67: 102403
Published Online xxx https://doi.org/10.1016/j.eclinm.2023.102403

Summary

Background Platinum-doublet chemotherapy plus immunotherapy has been the standard of care for the first-line treatment of advanced non-small cell lung cancer lacking actional driver mutations. However, optimization of drug combinations is still needed to find a better balance between therapeutic efficacy and safety in the immunotherapy era. We aimed to investigate the efficacy and safety of platinum-free albumin bound paclitaxel (nab-paclitaxel) combined with camrelizumab and apatinib as first-line treatment for patients with advanced lung adenocarcinoma.

Methods In this multicenter open-label, single-arm phase II trial, patients with systemic treatment-naïve advanced lung adenocarcinoma without epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations received a rational-based combination of camrelizumab (200 mg intravenously, day one), apatinib (250 mg, q.d., five continuous days per week), and nab-paclitaxel (135 mg/m^2 intravenously, days one and eight) every three weeks for four to six cycles in China. Patients with controlled disease were maintained with camrelizumab and apatinib. The primary end point was progression-free survival (PFS). This trial is registered with ClinicalTrials.gov (No. NCT04459078).

Findings Between August 26, 2020 and May 20, 2022, 64 patients were enrolled. The median PFS was 14.3 (95% CI: 9.9, not reached) months. The confirmed objective response rate was 64.1% (95% CI: 51.1, 75.7). The grade 3–4 hematologic treatment-related adverse events (TRAEs) were decreased neutrophil count (14.1%), decreased white blood cell count (7.8%), and anemia (3.1%). The most common non-hematologic TRAEs of grade 3–4 were increased alanine transaminase (18.8%) and aspartate transaminase (15.6%). No treatment-related death occurred. The quality of life was on average not clinically meaningful worse through treatment cycle 14.

Interpretation Nab-paclitaxel plus camrelizumab and apatinib showed clinically meaningful anti-tumor activity and manageable safety, with few hematologic toxicities, and might be a potential treatment option in patients with advanced lung adenocarcinoma lacking EGFR/ALK mutations.

Funding Heath Research Foundation of Chinese Society of Clinical Oncology, Hunan Provincial Natural Science Foundation of China, Hunan Cancer Hospital Climb Plan, Sister Institution Network Fund of The University of Texas MD Anderson Cancer Center, The Science and Technology Innovation Program of Hunan Province, and Suzhou Sheng Diya Biomedical Co., Ltd, a subsidiary of Jiangsu Hengrui Pharmaceuticals Co., Ltd. (Shanghai, China).

*Corresponding author. The Department of Thoracic Medical Oncology, Hunan Cancer Hospital, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, 283 Tongzipo Road, Yuelu District, Changsha, Hunan 410013, China.
E-mail address: wulin-calf@vip.163.com (L. Wu).
[g]Contributed equally to this work.

Keywords: Advanced non-small cell lung cancer (NSCLC); Platinum-free chemotherapy; Immunotherapy; Antiangiogenic therapy; Efficacy; Safety

Research in context

Evidence before this study

Platinum-doublet chemotherapy plus immunotherapy has been the standard of care for the first-line treatment of advanced non-small cell lung cancer lacking actional driver mutations. However, optimization of drug combination is still needed to find a better balance between therapeutic efficacy and safety in the immunotherapy era. Platinum agents have been reported to attenuate, rather than enhance, the immunomodulatory effects of pemetrexed or paclitaxel *in vitro*.

We searched PubMed up to August 2023 using the terms ("single-agent chemotherapy" OR "platinum-free chemotherapy" OR "Paclitaxel") AND ("Immunotherapy" OR "immune checkpoint inhibitor" OR "Anti-PD-1" OR "Camrelizumab") AND ("Antiangiogenic therapy" OR "Antiangiogenic agents" OR "VEGFR2 inhibitor" OR "Apatinib") AND ("Non-small cell lung cancer" OR "NSCLC" OR "Lung adenocarcinoma"). No previous studies have investigated platinum-free single-agent chemotherapy in combination with immunotherapy and antiangiogenic therapy in patients with systemic treatment-naïve advanced lung adenocarcinoma lacking actional driven mutations.

Added value of this study

We conducted a multicenter single-arm phase II study to investigate the efficacy and safety of platinum-free chemotherapy combined with immunotherapy and antiangiogenic therapy as the first-line treatment for patients with advanced lung adenocarcinoma without actional mutations. Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) plus camrelizumab and apatinib show clinically meaningful anti-tumor activity and manageable safety, with few hematologic toxicities, in patients with advanced lung adenocarcinoma lacking actional driver mutations.

Implications of all the available evidence

The findings of this study may shed light on platinum-free nab-paclitaxel in combination with camrelizumab and apatinib as an optional treatment strategy in advanced lung adenocarcinoma with no actional driver mutations. Acknowledging the limitations of cross-trial comparisons, these results require confirmation in a randomized controlled trial.

Introduction

Lung cancer remains the leading cause of cancer-related death worldwide, with an estimated 1.8 million deaths in 2020.[1] Approximately 85% of lung cancers are non-small cell lung cancer (NSCLC), of which lung adenocarcinoma is one of the most common subtypes and accounts for almost 40% of all lung cancers.[2] Patients with lung adenocarcinoma harboring genotype-driven mutations can benefit from targeted therapy.[3] For those lacking actional driver mutations, platinum-doublet chemotherapy plus immunotherapy has been the cornerstone of first-line treatment, irrespective of programmed death ligand-1 (PD-L1) status.[4]

Strategical drug combination in the immunotherapy era is critical to finding a better balance between therapeutic efficacy and safety. Combination of immunotherapy with the existing platinum-doublet chemotherapy has been preferentially investigated and demonstrated their synergistic antitumor effects in advanced NSCLC. However, whether these empirical regimens are ideal in the immunotherapy era remains unknown.[5] Besides, platinum-based therapy has historically been reported to be associated with higher nausea/vomiting and hematologic toxicity when compared with non-platinum therapy.[6] Even though in most cases, these side effects can be managed, patient compliance and treatment adherence may be compromised.

Different chemotherapeutic agents or their combinations may exert different immunomodulatory effects in the combination settings. Paclitaxel, an antimitotic agent, exhibited an immunomodulating effect via inducing maturation of dendritic cells and enhancing T cell function, as well as inducing apoptosis of regulatory T cells.[7–10] However, platinum agents (cisplatin and carboplatin) exerted a negative immunomodulating effect via upregulating PD-L1 expression in tumor tissue.[11] What's more, platinum agents have been reported to attenuate, rather than enhance, the immunomodulatory effects of pemetrexed or paclitaxel *in vitro*.[12] These results suggest the combinatorial potential of platinum-free chemotherapy and immunotherapy.

Antiangiogenic therapy also shows immunomodulatory effects in the combination settings.[13] Antiangiogenic therapy and immunotherapy combinations have been explored in advanced NSCLC.[14,15] Importantly, antiangiogenic therapy and chemotherapy act synergistically with immunotherapy in NSCLC. Combinations of immunotherapy with platinum-doublet

chemotherapy plus antiangiogenic therapy demonstrated significant survival benefits in advanced non-squamous NSCLC.[16,17] These lead us to consider the feasibility of platinum-free chemotherapy in combination with immunotherapy and antiangiogenic therapy.

Camrelizumab, a humanized monoclonal antibody against programmed cell death 1 (PD-1), has been approved in China as the first-line treatment for patients with advanced non-squamous and squamous NSCLC when in combination with platinum-doublet chemotherapies.[18,19] Low-dose apatinib (an oral receptor tyrosine kinase inhibitor selectively targeting vascular endothelial growth factor receptor 2 [VEGFR2]) optimized the immunosuppressive tumor microenvironment and enhanced the therapeutic response to immunotherapy with camrelizumab in both the preclinical and clinical data of NSCLC.[20] In phase II studies, camrelizumab in combination with apatinib showed promising antitumor activity and an acceptable safety profile in patients with treatment-naïve advanced non-squamous NSCLC or those previously treated with chemotherapy.[21,22]

Here in this single-arm study, we investigated the efficacy and safety of platinum-free albumin-bound paclitaxel (nab-paclitaxel) combined with camrelizumab and apatinib as the first-line treatment for patients with advanced lung adenocarcinoma lacking epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) alternations.

Methods

Study design and participants

This multicenter, open-label, single-arm, phase II trial was conducted at four tertiary hospitals in China. Eligible patients were aged 18 years or older and had histologically confirmed locally advanced, recurrent, or metastatic lung adenocarcinoma who were ineligible for curative surgery or radiotherapy and had not received prior systemic treatment. Other eligible criteria were Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, at least one measurable lesion as per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1),[23] no EGFR or ALK aberrations, adequate organ function, and an expected survival of ≥12 weeks. All consecutive patients who presented at all participating centers were screened for potential participation. Patients who had previously received neoadjuvant and/or adjuvant therapy were eligible if their diseases progressed at least six months after completion of treatment. Methods used for the determination of EGFR and ALK alternations were not specified in the study protocol. All patients were screened using next-generation sequencing in local laboratories.

Key exclusion criteria were an active autoimmune disease requiring systemic treatment within two-year before enrollment, untreated or active central nervous system metastases, clinically significant hemoptysis, tumor bleeding or thrombus, radiographic evidence of macrovascular invasion or infiltration, other malignancies within five years, corticosteroid treatment within 28 days before enrollment, uncontrollable pleural effusion or ascites, or previous immunotherapy (e.g., anti-PD-1/PD-L1/Cytotoxic T lymphocyte antigen 4 [CTLA4] inhibitors) or anti-angiogenetic therapy.

Ethics statement

The study protocol and all amendments were approved by the Institutional Review Boards of all participating centers. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients signed the written informed consent before participation. The trial is registered with ClinicalTrials.gov (No. NCT04459078). This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Treatments

All patients received camrelizumab, apatinib, and nab-paclitaxel every three weeks for four to six cycles. Camrelizumab was administered intravenously at a dose of 200 mg on day one of every three weeks. Nab-paclitaxel of 135 mg/m^2 was then administered intravenously on days one and eight of each cycle. Apatinib (250 mg) was taken orally once daily for five continuous days per week. Patients with the controlled diseases (complete response, partial response, or stable disease according to the RECIST v1.1 criterion) were then maintained with camrelizumab and apatinib until disease progression, intolerable toxicity, withdrawal of consent, or death. The treatment could be suspended or discontinued if significant hematological or non-hematological toxicity occurred as specified in the study protocol. Dose reduction was allowed for nab-paclitaxel and apatinib but not for camrelizumab.

End points and assessments

The primary endpoint was progression-free survival (PFS) defined as the time from the date of treatment initiation to the date of disease progression or death from any cause. The secondary endpoints included objective response rate (ORR), disease control rate, duration of response, overall survival (OS), safety, and quality of life (QOL) of patients. The ORR was defined as the percentage of patients achieving complete response or partial response, while the disease control rate was the percentage of patients with complete response, partial response, or stable disease according to the RECIST v1.1. The duration of response was calculated as the time from the date of the first confirmed complete or partial response to the date of the first documented disease progression. The OS was defined as the time from the date of treatment initiation to the date of death from any cause. Exploratory end points

were biomarker analyses of PD-L1 expression and peripheral blood protein levels.

Tumor assessment was performed with computed tomography and/or magnetic resonance imaging scanning at baseline (within 28 days before treatment initiation), every six weeks for the first 12 months, and every 12 weeks thereafter. The responses must be confirmed on the next assessment. Safety was assessed by evaluating the incidence, nature, and severity of treatment-related adverse events and immune-related adverse events. All adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.[24]

The QOL data were collected at the same time points as the tumor assessments, namely, at baseline, every six weeks for the first 12 months, and then every 12 weeks, with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)[25] and Lung Cancer 13 (EORTC-QLQ-LC-13).[26]

Biomarker analyses

A post-hoc PD-L1 expression analysis was performed in patients with archived or fresh tissues available at baseline. A tumor proportion score of 1% or greater was defined as PD-L1 positive.

In addition, plasma levels of 92 protein biomarkers were determined using the Olink proximity extension assay with the Target 96 Immuno-Oncology panel (Olink Proteomics AB, Uppsala, Sweden) according to the manufacturer's instructions (Supplementary Table S1). The assay employed two matched DNA oligonucleotides-labelled antibodies, enabling simultaneous quantification of 92 protein biomarkers using real-time quantitative polymerase chain reaction (qPCR). The qPCR readouts were normalized and presented as Normalized Protein eXpression (NPX), which is an arbitrary unit in the Log2 scale. A high NPX value indicates a high protein concentration.

Statistical analysis

Assuming a median PFS of 6 months with platinum-doublet chemotherapy, we calculated a sample size of 57 to obtain a median PFS of 9 months, with a power of 80% using the two-sided Log-rank test at an alpha value of 0.05. A total of 63 patients were needed when considering a drop-out rate of 10%. Efficacy and safety analyses were based on the final patients who received at least one dose of study treatment. Median follow-up was estimated using the reversed Kaplan–Meier method. The PFS and OS were estimated using the Kaplan–Meier method and expressed as median and 95%

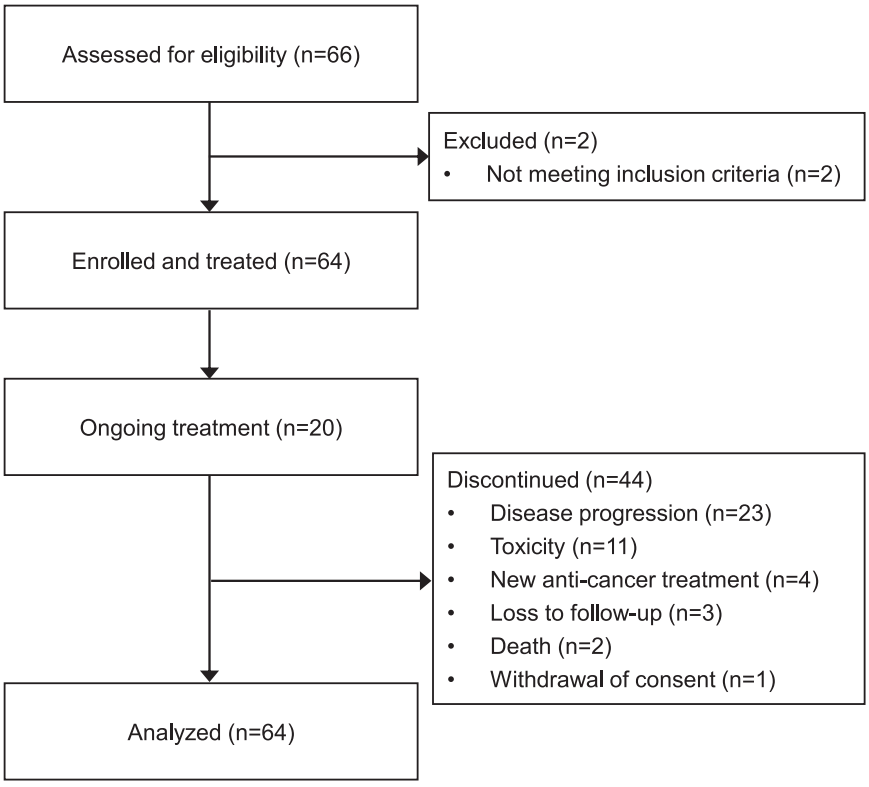

Fig. 1: Trial profile.

confidence interval (CI). The 95% CI of ORR was estimated using the Clopper-Pearson method, which could provide a conservative estimate, ensuring that the true value with a specified level of confidence is included, though the confidence interval can be wider than other methods. Besides, the sample size and data distribution were taken into consideration when selecting a method to compute confidence intervals for binomial data. A mean change in the QOL scores of ten points or greater from baseline was considered clinically meaningful.[27]

Associations between plasma protein levels and clinical outcomes were analyzed using the Welch Two Sample t-test for AEs, and the Log-rank test for PFS and OS with the median NPX value as cutoff for each protein. Univariate and multivariate Cox regression models were established to identify potential factors associated with PFS. The proportional hazards assumption was checked by including time-dependent covariates in the univariate Cox regression model. All clinical variables in the univariate analysis and plasma protein biomarkers with a p-value of less than 0.05 in the univariate analysis were considered in the multivariate Cox regression model. The fitted Cox regression model was established using the stepwise method. All analyses were performed with SAS version 9.4 (SAS Institute Inc.).

Role of the funding source

Jiangsu Hengrui Pharmaceuticals Co., Ltd. provided the study drugs, and had a role in data collection, data analysis, and data interpretation. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Patient characteristics

Between August 26, 2020, and May 20, 2022, a total of 64 patients were enrolled. All patients received at least one dose of study treatment and were included in the efficacy and safety analyses. On the data cutoff date of March 20, 2023, 20 patients were still on study treatment, while the other 44 patients discontinued the treatment. The main reasons for treatment discontinuation were disease progression (n = 23) and toxicity (n = 11) (Fig. 1).

Most patients were men (85.9%), had a smoking history (70.3%) and present with stage IV disease (82.8%). All patients had ECOG performance status of 1. Seven (10.9%) patients had brain metastases at baseline. Baseline patient characteristics are summarized in Table 1.

Characteristics	Total (n = 64)
Median age (range), years	62 (33, 75)
Sex, n (%)	
Male	55 (85.9)
Female	9 (14.1)
Smoking status, n (%)	
Former/current	45 (70.3)
Never	17 (26.6)
Unknown	2 (3.1)
ECOG performance status, n (%)	
0	0
1	64 (100.0)
TNM stage, n (%)	
III	11 (17.2)
IV	53 (82.8)
Lymph node metastases, n (%)	
Yes	20 (31.2)
No	44 (68.8)
Distant metastases, n (%)	
Bone	23 (35.9)
Brain	7 (10.9)
Liver	3 (4.7)
PD-L1 TPS, n (%)	
≥1%	21 (32.8)
<1%	18 (28.1)
Unknown	25 (39.1)

Note: ECOG, Eastern Cooperative Oncology Group; TNM, Tumor-lymph node-metastasis; PD-L1, programmed death ligand-1; TPS, Tumor proportion score.

Table 1: **Baseline patient characteristics.**

Efficacy

At the data cutoff, the median follow-up time was 15.7 (95% CI: 13.3, 18.8) months. Overall, 25 patients developed disease progression and 11 patients died. The estimated median PFS was 14.3 (95% CI: 9.9, not reached [NR]) (Fig. 2A). The median OS was not reached, and the estimated 12-month OS rate was 88.2% (95% CI: 76.8, 94.2) (Fig. 2B).

Among the 64 patients, 58 (90.6%) were evaluable for tumor response, with 41 (70.7%) partial responses, 16 (27.6%) stable diseases, and one (1.7%) progressive disease (Fig. 3A). The confirmed ORR was 64.1% (95% CI: 51.1, 75.7) and the confirmed disease control rate was 89.1% (95% CI: 78.8, 95.5) in overall patients. The median time to response was 1.6 (95% CI: 1.4, 2.8) months. Most patients achieved partial responses at the time of the first or second radiologic assessment. Two patients showed a delayed response at the time of the third or fourth radiologic assessment (Supplementary Fig. S1). One patient developed brain metastases at the time of the first radiologic assessment despite a >20% reduction in the target lesions (Fig. 3B). The median duration of response among patients with partial responses was 12.7 (95% CI: 10.3, 16.3) months (Table 2).

Safety

The median number of cycles of study treatment was 14 (Interquartile range [IQR]: 6, 21). The median duration

of treatment was 8.2 (IQR: 3.7, 14.3) months. Almost all (61/64, 95.3%) patients experienced at least one treatment-related adverse event. Grade 3 or 4 treatment-related adverse events occurred in 33 (51.6%) patients. The treatment-related hematologic adverse events of grade 3 or 4 occurred in 12 (18.8%) patients, including nine (14.1%) decreased neutrophil count, five (7.8%) decreased white blood cell count, and two (3.1%) anemia. The most common grade 3 or 4 treatment-related non-hematologic adverse events were increased alanine transaminase (18.8%) and aspartate transaminase (15.6%) (Table 3). Treatment-related serious adverse events occurred in 40.6% (26/64) of patients. Adverse events leading to treatment discontinuation occurred in 15 (23.4%) patients. No treatment-related death occurred. Immune-related adverse events occurred in 57.8% (37/64) of patients, most commonly reactive cutaneous capillary endothelial proliferation (RCCEP) (17.2%) and hypothyroidism (17.2%). Treatment-related adverse events occurring in ≥10% of patients and immune-related adverse events are summarized in Table 3.

Patient-reported quality of life (QOL)

All except one (98.4%) patients completed the EORTC QLQ-C30 and QLQ-LC questionnaires at baseline. The

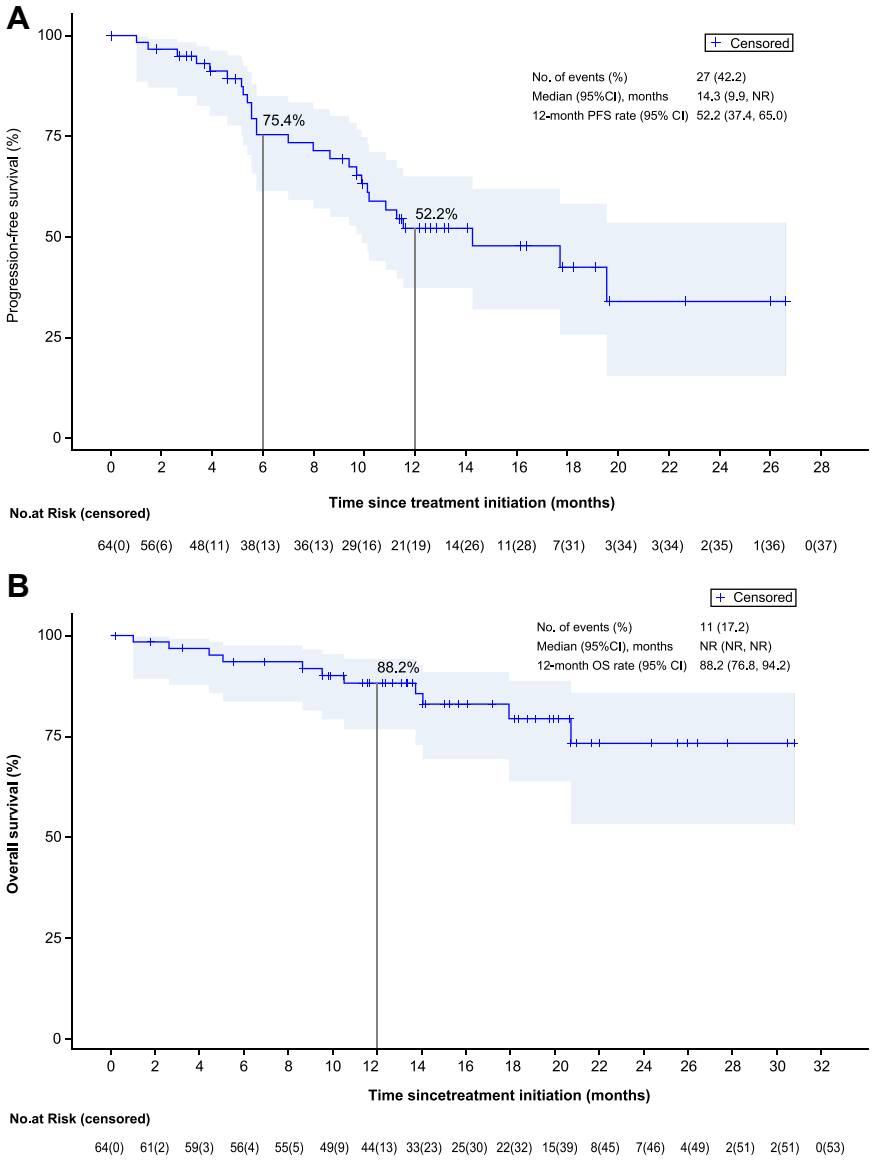

Fig. 2: Kaplan–Meier curves for progression-free survival (A) and overall survival (B). PFS, Progression-free survival; OS, Overall survival; No., Number; CI, Confidence interval; NR, Not reached.

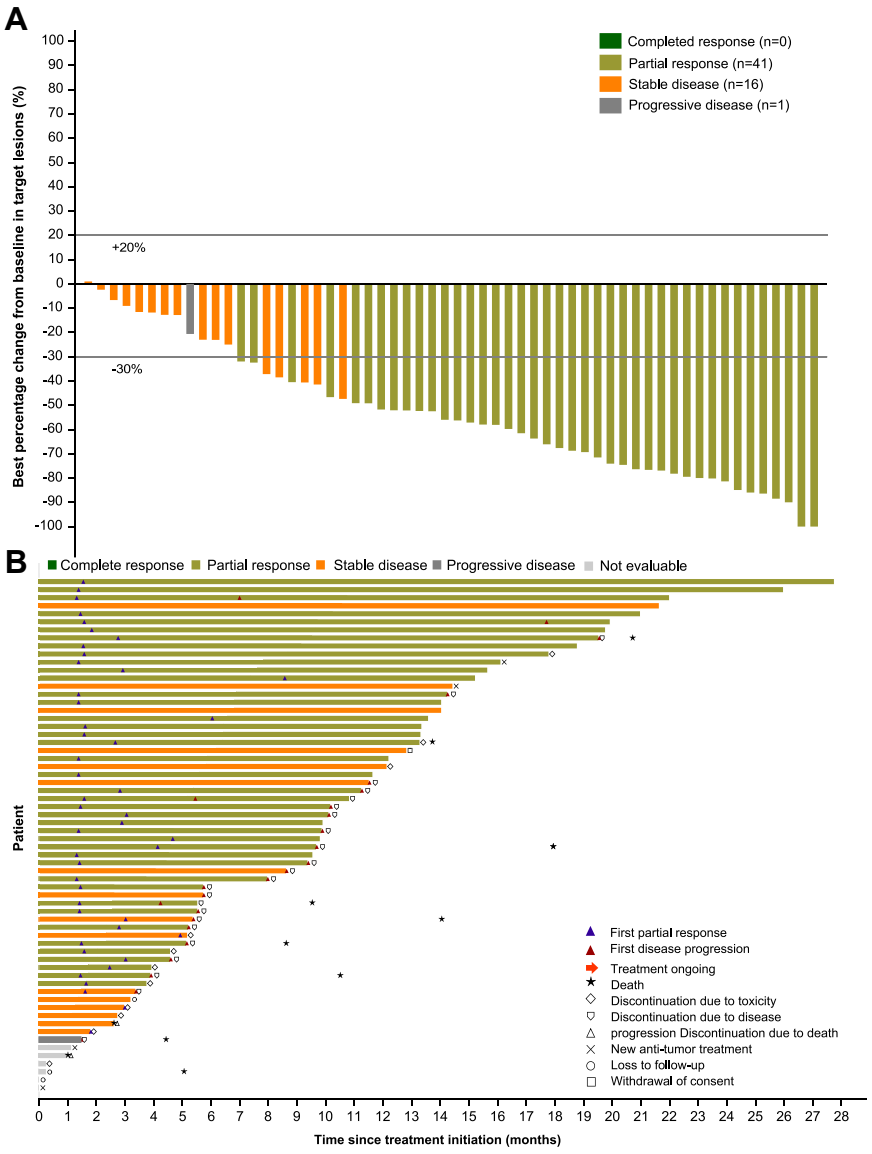

Fig. 3: Tumor response to albumin bound paclitaxel (nab-paclitaxel) plus camrelizumab and apatinib in patients with advanced lung adenocarcinoma. (A) Waterfall plot. Each bar indicates the best percentage change in the sum of targeted lesions from baseline as per RECIST v1.1 criterion; (B) Swimmer plot. Each bar indicates the duration of therapy, time to response, and duration of response. Six patients have no measurable lesions at baseline and are not evaluable for tumor response. CR: Complete response; PR: Partial response; PD: Progressive disease; AE: Adverse events. RECIST V1.1, Response Evaluation Criteria In Solid Tumors version 1.1.

completion rate of the active patients at each time point remained ≥80% through the 14 cycles of treatment. The data were not interpreted after cycle 14 since less than 30% of patients were active.

Patients generally reported moderate-to-high functioning scores and low symptom scores at baseline. The QOL of patients on average was not clinically meaningfully worse at any time point through cycle 14 regarding global health status and five functional scales. Mean changes in treatment-related symptom scores from baseline are shown in Fig. 4. A clinically meaningful improvement in symptom severity of peripheral neuropathy was observed through 14 cycles of treatment. Also, the severity of alopecia was improved, particularly at early treatment cycles (two to four).

Associations of PD-L1 expression and plasma protein levels with efficacy and safety

Of the 64 patients, 39 (60.9%) were tested for PD-L1 expression and 21 (32.8%) had a tumor proportion

	Total (n = 64)
Best overall response, n (%)	
Complete response	0
Partial response	41 (64.1)
Stable disease	16 (25.0)
Progressive disease	1 (1.6)
Not evaluable	6 (9.4)
Objective response rate, %	64.1
95% CI	51.1, 75.7
Disease control rate, %	89.1
95% CI	78.8, 95.5
Duration of response, months	
Median (95% CI)	12.7 (10.3, 16.3)

Note: CI, Confidence interval.

Table 2: **Tumor response.**

score of 1% or greater. There were no significant associations between PD-L1 expression status and PFS, OS, or ORR. The median PFS was 14.3 months (95% CI: 9.9, NR) in the PD-L1-positive population and 11.3 months (95% CI: 5.4, NR) in the PD-L1-negative population (Supplementary Fig. S2A). The median OS was not reached, and the 12-month OS rate was 90.5% (95% CI: 67.0, 97.5) and 80.8% (95% CI: 51.4, 93.4) in the PD-L1-positive and PD-L1-negative populations, respectively (Supplementary Fig. S2B). Accordingly, the corresponding confirmed ORR was 76.2% (95% CI: 52.8, 91.8) and 55.6% (95% CI: 30.8, 78.5), while the confirmed disease control rate was 85.7% (95% CI: 63.7, 97.0) and 83.3% (95% CI: 58.6, 96.4).

Blood samples were obtained from 53 patients at baseline. After quality control, 51 samples were used for plasma biomarker analyses of 92 proteins. The median NPX value was adopted as the cutoff for each protein to differentiate high and low protein levels. Low protein levels of carbonic anhydrase 9 (CAIX), C–C motif chemokine 20 (CCL20), cluster of differentiation 70 (CD70), C-X-C motif chemokine 10 (CXCL10), C-X-C motif chemokine 11 (CXCL11), interleukin 6 (IL6), interleukin 8 (IL8), or a high interleukin 4 (IL4) level at baseline were associated with better PFS (Supplementary Fig. S3 and Tables S2 and S3). After adjustment for baseline patient characteristics in a multivariate Cox regression model, IL8 (hazard ratio [HR]: 0.26, 95% CI: 0.10, 0.70, p = 0.01), CXCL10 (HR: 0.31, 95% CI: 0.12, 0.82, p = 0.02), CD70 (HR: 0.38, 95% CI: 0.16, 0.92, p = 0.03), and IL4 (HR: 2.61, 95% CI: 1.05, 6.47, p = 0.04) were associated with PFS (Table 4).

Associations between the plasma levels of 92 proteins and major tissue/system-specific toxicity were also analyzed, as shown in Supplementary Fig. S4A. Angiopoietin 1 (ANGPT1) was associated with gastrointestinal and hematological adverse events. Angiopoietin 2 (ANGPT2) was associated with liver and skin adverse events. CD40 ligand (CD40-L) was associated with gastrointestinal and skin adverse events (Supplementary Fig. S4B). In addition, the correlation between the 92 proteins and immune-related adverse events was analyzed. Patients with low levels of CD70, CXCL11, interferon-gamma (IFN-gamma), interleukin-12 receptor subunit beta-1 (IR12RB1), tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), or tumor necrosis factor ligand superfamily member 12 (TWEAK) were more likely to develop immune-related adverse events (Supplementary Fig. S4C).

Discussion

In this single-arm phase II study, the rational-based combination of platinum-free nab-paclitaxel plus camrelizumab and apatinib provided clinically meaningful anti-tumor activity and a manageable safety profile, with few hematologic toxicities, in patients with advanced lung adenocarcinoma lacking EGFR or ALK mutations. The median PFS was 14.3 months and the confirmed ORR was 64.1%. The grade 3 or greater treatment-related adverse events, especially those related to hematological toxicity, were less commonly reported. Our study may shed light on platinum-free chemotherapy in combination with PD-1-based immunotherapy and antiangiogenic therapy as a potential treatment option for patients with advanced lung adenocarcinoma.

In terms of efficacy, the findings of the present study were generally comparable to those with platinum-doublet chemotherapy plus immunotherapy with or without bevacizumab in patients with advanced non-squamous NSCLC lacking actional driver mutations (Supplementary Table S4). In the Impower-150 trial, a median PFS was 8.3 months and an ORR was 63.5% with platinum-doublet chemotherapy plus atezolizumab and bevacizumab.[16] A median PFS of 12.1 months and an ORR of 61.5% were obtained in a phase III trial of platinum-doublet chemotherapy plus nivolumab and bevacizumab.[17] Meanwhile, first-line platinum-doublet chemotherapy plus camrelizumab demonstrated a median PFS of 11.3 months and an ORR of 60.5% in the CameL trial.[19] Additionally, in the recent single-arm phase II trial of camrelizumab plus apatinib, a median PFS was 9.6 months and an ORR was 40% in treatment-naïve advanced non-squamous NSCLC patients with no sensitizing EGFR or ALK alterations and a high tumor mutational burden.[21] A small number of patients with stage III disease were included in this study, and the results were generally not affected given the limited number of patients (Supplementary Fig. S5). Additionally, nab-paclitaxel which needs no steroid premedication may be a promising therapeutic option when in combination with immunotherapy. Acknowledging the limitations of cross-trial comparisons, these results require confirmation in a randomized controlled trial.

	Grade 3	Grade 4	Any grade
Treatment-related adverse events, n (%)	23 (35.9)	10 (15.6)	**61 (95.3)**
Hematologic events			
Neutrophil count decreased	6 (9.4)	3 (4.7)	35 (54.7)
White blood cell decreased	4 (6.3)	1 (1.6)	30 (46.9)
Anemia	1 (1.6)	1 (1.6)	14 (21.9)
Platelet count decreased	0	0	11 (17.2)
Non-hematologic events			
ALT increased	7 (10.9)	5 (7.8)	36 (56.3)
AST increased	9 (14.1)	1 (1.6)	34 (53.1)
Blood bilirubin increased	2 (3.1)	0	28 (43.8)
Hypertension	4 (6.3)	0	24 (37.5)
Proteinuria	0	0	17 (26.6)
Alopecia	0	0	16 (25.0)
GGT increased	3 (4.7)	0	14 (21.9)
Hand-foot syndrome	1 (1.6)	0	14 (21.9)
Peripheral neuritis	0	0	13 (20.3)
RCCEP	0	0	11 (17.2)
Hypothyroidism	0	0	11 (17.2)
Fatigue	0	0	10 (15.6)
Hypertriglyceridemia	0	0	10 (15.6)
Rash	1 (1.6)	0	10 (15.6)
Diarrhea	0	0	9 (14.1)
Oral ulcer	0	0	9 (14.1)
Loss of appetite	0	0	9 (14.1)
Blood creatinine increased	0	0	9 (14.1)
Hyperthyroidism	0	0	7 (10.9)
Pruritus	0	0	7 (10.9)
Immune-related adverse events, n (%)			**37 (57.8)**
RCCEP	0	0	11 (17.2)
Hypothyroidism	0	0	11 (17.2)
Hyperthyroidism	0	0	7 (10.9)
Immune-related rash	2 (3.1)	0	6 (9.4)
Immune-related hepatitis	4 (6.3)	0	4 (6.3)
Immune-related pneumonia	1 (1.6)	2 (3.1)	4 (6.3)
ALT increased	1 (1.6)	2 (3.1)	3 (4.7)
AST increased	3 (4.7)	0	3 (4.7)
Pruritus	0	0	3 (4.7)
Immune-related colitis	1 (1.6)	0	2 (3.1)
Immune-related myocarditis	1 (1.6)	0	2 (3.1)
Immune-related arthritis	0	0	1 (1.6)

Note: ALT, Alanine transaminase; AST, Aspartate transaminase; GGT: Gamma-glutamyl transferase; RCCEP, Reactive cutaneous capillary endothelial proliferation.

Table 3: **Treatment-related adverse events (≥10% of patients) and immune-related adverse events.**

Of note, the grade 3 or greater treatment-related adverse events, especially hematological toxicities that typically occurred with chemotherapy or platinum agents, were less commonly reported (Supplementary Table S5). The grade 3 or 4 treatment-related hematologic adverse events occurring in this study were decreased neutrophil count (14.1%), decreased white blood cell count (7.8%), and anemia (3.1%). These data were numerically lower than those previously reported for platinum-doublet chemotherapy plus immunotherapy with or without bevacizumab, with decreased neutrophil count being most common (30.8%–55%), followed by decreased white blood cell count (14.7%–30%), anemia (5.5%–19%), and decreased platelet count (5.9%–17%).[17–19,28] By contrast, the incidence of treatment-related adverse events of any grade was generally similar to that of platinum-doublet chemotherapy plus camrelizumab[18,19] or plus bevacizumab and atezolizumab[16]/nivolumab.[17] The safety profile observed in this study

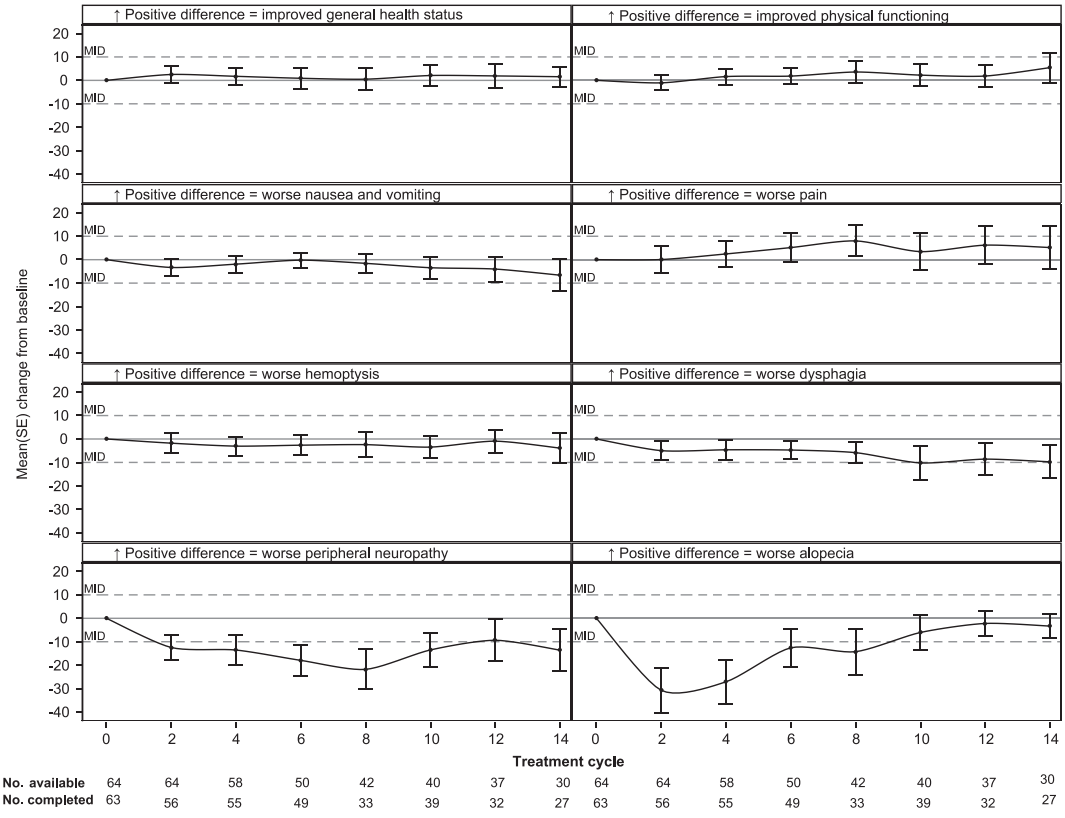

Fig. 4: Mean change in health-related quality of life scores from baseline, including global health status, physical functioning, and patient-reported symptom severity of nausea and vomiting, pain, hemoptysis, dysphagia, peripheral neuropathy, and alopecia. The line graphs are smoothed using a smooth curve to connect the evenly spaced data points by SMOOTHCONNECT option in SAS 9.4. SE, Standard error; MID, Minimum importance difference.

	Univariate analysis		Multivariate analysis[a]	
	HR (95% CI)	p value	HR (95% CI)	p value
Age ≥ 65 years	1.11 (0.50, 2.45)	0.80		
Male	0.50 (0.22, 1.15)	0.10		
Smoking	1.17 (0.51, 2.67)	0.72		
TNM stage III	0.77 (0.23, 2.60)	0.99		
Lymph node metastases	2.69 (1.23, 5.89)	**0.01**		
Bone metastases	0.99 (0.44, 2.22)	0.68		
PD-L1 ≥ 1%	0.52 (0.19, 1.48)	0.22		
IL8 low	0.35 (0.14, 0.84)	**0.02**	0.26 (0.10, 0.70)	**0.01**
IL6 low	0.33 (0.14, 0.79)	**0.01**		
CXCL11 low	0.39 (0.16, 0.92)	**0.03**		
CAIX low	0.40 (0.16, 0.98)	**0.04**		
CXCL10 low	0.39 (0.16, 0.95)	**0.04**	0.31 (0.12, 0.82)	**0.02**
CD70 low	0.31 (0.13, 0.74)	**0.01**	0.38 (0.16, 0.92)	**0.03**
IL4 low	2.66 (1.11, 6.34)	**0.03**	2.61 (1.05, 6.47)	**0.04**
CCL20 low	0.32 (0.13, 0.78)	**0.01**		

The IL8, CXCL10, CD70, and IL4 were retained in the model after a stepwise selection. Proportional Hazards Assumption was checked and valid (Supplementary Tables 6–8). The significance of bold is p value < 0.05. TNM, Tumor-lymph node-metastasis; PD-L1, programmed death ligand-1; IL8, Interleukin 8; IL6, Interleukin 6; CXCL11, C-X-C motif chemokine 11; CAIX, Carbonic anhydrase 9; CXCL10, C-X-C motif chemokine 10; CD70, Cluster of differentiation 70; IL4, Interleukin 4; CCL20, C-C motif chemokine 20. [a]All variables were considered in the multivariate analysis.

Table 4: **Cox regression analysis for progression-free survival.**

was generally consistent with that of each study drug previously reported,[18,19,21,22,29,30] with no new safety signals noted.

Interestingly, RCCEP was less commonly reported in this study. One possible explanation is the introduction of anti-angiogenic agents like apatinib that may prevent and alleviate this camrelizumab-induced unique adverse event. Camrelizumab may drive the development of RCCEP via indirectly upregulating the expression of vascular endothelial growth factor-A (VEGF-A). Previous studies showed a lower incidence of RCCEP in patients receiving camrelizumab plus anti-angiogenic agents than in patients receiving camrelizumab alone.[31,32] Apatinib was suggested as a salvage therapy that can cause the rapid regression of RCCEP, thus limiting the impairment on the QOL.[33] However, the increased alanine transaminase and aspartate transaminase were more common in our patients, consistent with the previous studies of camrelizumab plus apatinib.[21,22] Nevertheless, the treatment-related adverse events were generally manageable and no treatment-related death occurred.

The EORTC QLQ-C30 and QLQ-LC13 are commonly used for measuring the QOL of lung cancer patients. The QOL of patients was generally stable throughout the treatment in this study. Intriguingly, nab-paclitaxel plus camrelizumab and apatinib resulted in a clinically meaningful improvement in the symptom severity of peripheral neutropenia. In the IMpower-150 study, platinum-doublet chemotherapy plus atezolizumab and bevacizumab resulted in a clinically meaningful worsening in peripheral neuropathy symptom score.[17] However, due to the reduced number of patients considered evaluable and potential bias introduced due to missing data, QOL data were only interpreted up to treatment cycle 14. The long-term QOL of patients is still unclear.

The potential biomarkers associated with survival and safety outcomes were also explored. Baseline PD-L1 expression was not found to be significantly associated with PFS or OS, consistent with the previous study of camrelizumab plus apatinib.[21] PD-L1 expression status might not be a reliable biomarker for prognostic prediction of camrelizumab plus apatinib and nab-paclitaxel in advanced lung adenocarcinoma. Despite that, whether PD-L1 expression status is a potential predictive biomarker in immunotherapy combination setting still need further investigation. To explore potential biomarkers associated with prognosis and risk of adverse events, we further analyzed plasma levels of 92 immuno-oncology proteins. Our results showed that patients with a low level of CAIX, CCL20, CD70, CXCL10, CXCL11, IL6, or IL8, or a high IL4 level at baseline were associated with better PFS. These results were broadly consistent with previous studies, which indicated that CCL20, CXCL10, IL6, and IL8 were negatively associated with clinical outcomes of immune checkpoint blockade.[34–37] The multivariate Cox regression showed that low plasma levels of IL8, CXCL10, and CD70, while a high IL4 level, were associated with better PFS in this study. Given the post-hoc exploratory nature and the limited number of patients with available and qualified tissue and/or blood samples for analysis, as well as the large number of variables included for analysis, these results should be interpreted with caution. Future studies using a large sample size are indispensable to clarify their prognostic predictive values.

The main limitation of this study was its inherent single-arm design; thus, data need to be interpreted in the context of historical comparison that may introduce bias. The preliminary results observed in this study should be further investigated and verified in a randomized controlled trial (platinum-doublet chemotherapy plus immunotherapy as a control), also the underlying mechanisms need to be explored. Additionally, the median OS was not reached at the data cutoff, long-term follow-up is necessary to understand the survival outcomes of platinum-free chemotherapy in the immunotherapy combination setting.

In conclusion, the findings of this study suggest that platinum-free nab-paclitaxel plus camrelizumab and apatinib is effective and well-tolerated, with few hematologic toxicities, in patients with advanced lung adenocarcinoma lacking EGFR/ALK mutations and may serve as a potential treatment option.

Contributors

W.L., L.G., P.X.X, and L.J. contributed to the study conception and design. L.G., P.X.X, and C.F.Z. contributed to the statistical analysis. L.G. and P.X.X. drafted the manuscript. W.L., L.G., P.X.X, X.M.L., and L.J. contributed to administrative, technical, and material support, as well as study supervision. W.L., L.G., P.X.X, Z.K.L., and C.F.Z. contributed to the critical revision of the manuscript for important intellectual content. W.L. and P.X.X obtained funding. All authors contributed to the acquisition, analysis, or interpretation of data.

Data sharing statement

The deidentified individual patient data underlying the results reported in this article will be available upon reasonable request from the corresponding authors (Prof. Wu, wulin-calf@vip.163.com).

Declaration of interests

FC and KZ are employees of Jiangsu Hengrui Pharmaceuticals co. Ltd. NL is an employee of Shenzhen YuceBio Technology Co., Ltd. Prof. Wu declares support (study drugs) from Jiangsu Hengrui Pharmaceuticals Co., Ltd. All the other authors declare no conflicting of interest.

Acknowledgements

This work was supported by Heath Research Foundation of Chinese Society of Clinical Oncology (Y-2019Genecast-024), Hunan Provincial Natural Science Foundation of China (No. 2021JJ30430), Hunan Cancer Hospital Climb Plan (No. YF2020005 and No. ZX2020005-5), Sister Institution Network Fund of The University of Texas MD Anderson Cancer Center, The Science and Technology Innovation Program of Hunan Province (No. 2021SK51121 and No. 2023SK4024), and Suzhou Sheng Diya Biomedical Co., Ltd. The study drugs were provided by Suzhou Sheng Diya Biomedical Co., Ltd, a subsidiary of Jiangsu Hengrui Pharmaceuticals Co., Ltd. (Shanghai, China).

We thank all patients, their families, and the site investigators who made the study possible. We also thank Prof. Qian Chu (Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology), Prof. Zhijie Wang (Cancer Hospital of Chinese Academy of Medical Sciences), and Dr. Wenying Peng (Yunnan Cancer Hospital & The Third Affiliated Hospital of Kunming Medical University & Yunnan Cancer Center) for their input in study design, Zijin Zhang (a statistical programmer at Jiangsu Hengrui Pharmaceuticals Co., Ltd) for her input in data analysis, and Jinyun Sun (Jiangsu Hengrui Pharmaceuticals Co., Ltd) for her input in medical writing assistance according to Good Publication Practice Guidelines.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102403.

References

1 Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. https://doi.org/10.3322/caac.21660.
2 Denisenko TV, Budkevich IN, Zhivotovsky B. Cell death-based treatment of lung adenocarcinoma. *Cell Death Dis*. 2018;9(2):117. https://doi.org/10.1038/s41419-017-0063-y.
3 Barlesi F, Mazieres J, Merlio JP, et al. Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT). *Lancet*. 2016;387(10026):1415–1426. https://doi.org/10.1016/s0140-6736(16)00004-0.
4 *NCCN clinical Practice guidelines in oncology (NCCN guidelines). Non–Small cell lung cancer;* 2023. Version 5.
5 Heinhuis KM, Ros W, Kok M, Steeghs N, Beijnen JH, Schellens JHM. Enhancing antitumor response by combining immune checkpoint inhibitors with chemotherapy in solid tumors. *Ann Oncol*. 2019;30(2):219–235. https://doi.org/10.1093/annonc/mdy551.
6 D'Addario G, Pintilie M, Leighl NB, Feld R, Cerny T, Shepherd FA. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. *J Clin Oncol*. 2005;23(13):2926–2936. https://doi.org/10.1200/JCO.2005.03.045.
7 Leonetti A, Wever B, Mazzaschi G, et al. Molecular basis and rationale for combining immune checkpoint inhibitors with chemotherapy in non-small cell lung cancer. *Drug Resist Updat*. 2019;46:100644. https://doi.org/10.1016/j.drup.2019.100644.
8 Zitvogel L, Apetoh L, Ghiringhelli F, Kroemer G. Immunological aspects of cancer chemotherapy. *Nat Rev Immunol*. 2008;8(1):59–73. https://doi.org/10.1038/nri2216.
9 John J, Ismail M, Riley C, et al. Differential effects of Paclitaxel on dendritic cell function. *BMC Immunol*. 2010;11:14. https://doi.org/10.1186/1471-2172-11-14.
10 Zhang L, Dermawan K, Jin M, et al. Differential impairment of regulatory T cells rather than effector T cells by paclitaxel-based chemotherapy. *Clin Immunol*. 2008;129(2):219–229. https://doi.org/10.1016/j.clim.2008.07.013.
11 Xue Y, Gao S, Gou J, et al. Platinum-based chemotherapy in combination with PD-1/PD-L1 inhibitors: preclinical and clinical studies and mechanism of action. *Expert Opin Drug Deliv*. 2021;18(2):187–203. https://doi.org/10.1080/17425247.2021.1825376.
12 Schaer DA, Geeganage S, Amaladas N, et al. The folate pathway inhibitor pemetrexed pleiotropically enhances effects of cancer immunotherapy. *Clin Cancer Res*. 2019;25(23):7175–7188. https://doi.org/10.1158/1078-0432.CCR-19-0433.
13 Hegde PS, Wallin JJ, Mancao C. Predictive markers of anti-VEGF and emerging role of angiogenesis inhibitors as immunotherapeutics. *Semin Cancer Biol*. 2018;52(Pt 2):117–124. https://doi.org/10.1016/j.semcancer.2017.12.002.
14 Provencio M, Ortega AL, Coves-Sarto J, et al. Atezolizumab plus bevacizumab as first-line treatment for patients with metastatic nonsquamous non-small cell lung cancer with high tumor mutation burden: a nonrandomized controlled trial. *JAMA Oncol*. 2022;9(3):344–353. https://doi.org/10.1001/jamaoncol.2022.5959.
15 Chu T, Zhong R, Zhong H, et al. Phase 1b study of sintilimab plus anlotinib as first-line therapy in patients with advanced NSCLC. *J Thorac Oncol*. 2021;16(4):643–652. https://doi.org/10.1016/j.jtho.2020.11.026.
16 Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378(24):2288–2301. https://doi.org/10.1056/NEJMoa1716948.
17 Sugawara S, Lee JS, Kang JH, et al. Nivolumab with carboplatin, paclitaxel, and bevacizumab for first-line treatment of advanced nonsquamous non-small-cell lung cancer. *Ann Oncol*. 2021;32(9):1137–1147. https://doi.org/10.1016/j.annonc.2021.06.004.
18 Ren S, Chen J, Xu X, et al. Camrelizumab plus carboplatin and paclitaxel as first-line treatment for advanced squamous NSCLC (CameL-Sq): a phase 3 trial. *J Thorac Oncol*. 2022;17(4):544–557. https://doi.org/10.1016/j.jtho.2021.11.018.
19 Zhou C, Chen G, Huang 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*. 2021;9(3):305–314. https://doi.org/10.1016/S2213-2600(20)30365-9.
20 Zhao S, Ren S, Jiang T, et al. Low-dose apatinib optimizes tumor microenvironment and potentiates antitumor effect of PD-1/PD-L1 blockade in lung cancer. *Cancer Immunol Res*. 2019;7(4):630–643. https://doi.org/10.1158/2326-6066.Cir-17-0640.
21 Ren S, He J, Fang Y, et al. Camrelizumab plus apatinib in treatment-naive patients with advanced nonsquamous NSCLC: a multicenter, open-label, single-arm, phase 2 trial. *JTO Clin Res Rep*. 2022;3(5):100312. https://doi.org/10.1016/j.jtocrr.2022.100312.
22 Zhou C, Wang Y, Zhao J, et al. Efficacy and biomarker analysis of camrelizumab in combination with apatinib in patients with advanced nonsquamous NSCLC previously treated with chemotherapy. *Clin Cancer Res*. 2021;27(5):1296–1304. https://doi.org/10.1158/1078-0432.CCR-20-3136.
23 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–247. https://doi.org/10.1016/j.ejca.2008.10.026.
24 US Department of Health and Human Services. *Common Terminology criteria for adverse events (CTCAE) v4. 03*. Washington, DC: US Department of Health and Human Services; 2010.
25 Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365–376. https://doi.org/10.1093/jnci/85.5.365.
26 Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC study Group on quality of life. *Eur J Cancer*. 1994;30A(5):635–642. https://doi.org/10.1016/0959-8049(94)90535-5.
27 Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol*. 1998;16(1):139–144. https://doi.org/10.1200/JCO.1998.16.1.139.
28 West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20(7):924–937. https://doi.org/10.1016/s1470-2045(19)30167-6.
29 Green MR, Manikhas GM, Orlov S, et al. Abraxane, a novel Cremophor-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. *Ann Oncol*. 2006;17(8):1263–1268. https://doi.org/10.1093/annonc/mdl104.
30 Rizvi NA, Riely GJ, Azzoli CG, et al. Phase I/II trial of weekly intravenous 130-nm albumin-bound paclitaxel as initial chemotherapy in patients with stage IV non-small-cell lung cancer. *J Clin Oncol*. 2008;26(4):639–643. https://doi.org/10.1200/jco.2007.10.8605.
31 Xu J, Zhang Y, Jia R, et al. Anti-PD-1 antibody SHR-1210 combined with apatinib for advanced hepatocellular carcinoma, gastric, or esophagogastric junction cancer: an open-label, dose escalation and expansion study. *Clin Cancer Res*. 2019;25(2):515–523. https://doi.org/10.1158/1078-0432.Ccr-18-2484.

32 Song G, Zhang FF, Cheng HD. Thalidomide for prevention of camrelizumab-induced reactive cutaneous capillary endothelial proliferation. *Australas J Dermatol*. 2022;63(2):217–221. https://doi.org/10.1111/ajd.13812.

33 Li W, Wei Z, Yang X, et al. Salvage therapy of reactive capillary hemangiomas: apatinib alleviates the unique adverse events induced by camrelizumab in non-small cell lung cancer. *J Cancer Res Ther*. 2019;15(7):1624–1628. https://doi.org/10.4103/jcrt.JCRT_997_19.

34 Tang X, Qi C, Zhou H, Liu Y. A novel metabolic-immune related signature predicts prognosis and immunotherapy response in lung adenocarcinoma. *Heliyon*. 2022;8(8):e10164. https://doi.org/10.1016/j.heliyon.2022.e10164.

35 Wang Y, Chen H, Zhang T, et al. Plasma cytokines interleukin-18 and C-X-C motif chemokine ligand 10 are indicative of the anti-programmed cell death protein-1 treatment response in lung cancer patients. *Ann Transl Med*. 2021;9(1):33. https://doi.org/10.21037/atm-20-1513.

36 Kang DH, Park CK, Chung C, et al. Baseline serum interleukin-6 levels predict the response of patients with advanced non-small cell lung cancer to PD-1/PD-L1 inhibitors. *Immune Netw*. 2020;20(3):e27. https://doi.org/10.4110/in.2020.20.e27.

37 Yuen KC, Liu LF, Gupta V, et al. High systemic and tumor-associated IL-8 correlates with reduced clinical benefit of PD-L1 blockade. *Nat Med*. 2020;26(5):693–698. https://doi.org/10.1038/s41591-020-0860-1.