

Camrelizumab Plus Carboplatin and Paclitaxel as First-Line Treatment for Advanced Squamous NSCLC (CameL-Sq): A Phase 3 Trial



Shengxiang Ren, MD,^a Jianhua Chen, MD,^b Xingxiang Xu, MD,^c Tao Jiang, PhD,^a Ying Cheng, MD,^d Gongyan Chen, MD,^e Yueyin Pan, MD,^f Yong Fang, MD,^g Qiming Wang, MD,^h Yunchao Huang, MD,ⁱ Wenxiu Yao, MD,^j Rui Wang, MD,^k Xingya Li, MD,^l Wei Zhang, MD,^m Yanjun Zhang, MD,ⁿ Sheng Hu, MD,^o Renhua Guo, MD,^p Jianhua Shi, MD,^q Zhiwu Wang, MD,^r Peiguo Cao, MD,^s Donglin Wang, MD,^t Jian Fang, MD,^u Hui Luo, MD,^v Yi Geng, MD,^w Chunyan Xing, MD,^x Dongqing Lv, MD,^y Yiping Zhang, MD,^z Junyan Yu, MD,^{aa} Shundong Cang, MD,^{bb} Zeyu Yang, PhD,^{cc} Wei Shi, MD,^{cc} Jianjun Zou, MD,^{cc} Caicun Zhou, MD,^{a,*} on behalf of the CameL-sq Study Group

^aDepartment of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, People's Republic of China

^bDepartment of Medical Oncology-Chest (1), Hunan Cancer Hospital, Changsha, People's Republic of China

^cRespiratory Department, Northern Jiangsu People's Hospital, Yangzhou, People's Republic of China

^dDepartment of Medical Oncology, Jilin Cancer Hospital, Changchun, People's Republic of China

^eFirst Ward of Respiratory Medicine, Harbin Medical University Cancer Hospital, Harbin, People's Republic of China

^fDepartment of Chemotherapy Oncology, Anhui Provincial Hospital, Hefei, People's Republic of China

^gDepartment of Medical Oncology, Sir Run Run Shaw Hospital Zhejiang University School of Medicine, Hangzhou, People's Republic of China

^hDepartment of Oncology, Henan Cancer Hospital, Zhengzhou, People's Republic of China

ⁱDepartment of Thoracic Surgery, Yunnan Cancer Hospital and the Third Affiliated Hospital of Kunming Medical University and Yunnan Cancer Centre, Kunming, People's Republic of China

^jDepartment of Thoracic Oncology, Sichuan Provincial Cancer Hospital, Chengdu, People's Republic of China

^kDepartment of Medical Oncology, Anhui Chest Hospital, Hefei, People's Republic of China

^lDepartment of Medical Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, People's Republic of China

^mDepartment of Respiratory Medicine, The First Affiliated Hospital of Nanchang University, Nanchang, People's Republic of China

ⁿThe 3rd department of Medical Oncology, Shaanxi Provincial Cancer Hospital, Xi'an, People's Republic of China

^oDepartment of Thoracic Oncology, Hubei Cancer Hospital, Wuhan, People's Republic of China

^pDepartment of Oncology, Jiangsu Province Hospital, Nanjing, People's Republic of China

^qInternal Medicine Ward 2, LinYi Cancer Hospital, Linyi, People's Republic of China

^rSecond Department of Radiotherapy and Chemotherapy, Tangshan People's Hospital, Tangshan, People's Republic of China

^sOncology Department, The Third Xiangya Hospital of Central South University, Changsha, People's Republic of China

^tDepartment of Medical Oncology, Chongqing University Cancer Hospital, Chongqing, People's Republic of China

^uThe Second Department of Thoracic Oncology, Beijing Cancer Hospital, Beijing, People's Republic of China

*Corresponding author.

Drs. Ren, Chen, and Xu contributed equally to this work.

Disclosure: Dr. Zhou reported receiving honoraria as a speaker from Roche, Lily People's Republic of China, Boehringer Ingelheim, Merck, Hengrui, Qilu, Sanofi, Merck Sharp & Dohme, Innovent Biologics, C-Stone, Luye Pharma, TopAlliance Biosciences, and Amoy Diagnostics; and advisory fees from Innovent Biologics, Hengrui, Qilu, and TopAlliance Biosciences. Dr. Ren reported receiving honoraria as a speaker from Boehringer Ingelheim, Lilly, Merck Sharp & Dohme, Roche, Hengrui, and Junshi; advisory fees from Roche, Merck Sharp & Dohme, and Boehringer Ingelheim; and research funding from Hengrui. Dr. Yang, Ms. Shi, and Ms. Zou were employees of Hengrui. The remaining authors declare no conflict of interest.

Part of the results was presented at the 2021 European Lung Cancer Virtual Congress, Online, March 25, 2021 (Virtual).

Address for correspondence: Prof. Caicun Zhou, Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, No. 507, Zhengmin Road, Shanghai 200433, People's Republic of China. E-mail: caicunzhou_dr@163.com

© 2021 International Association for the Study of Lung Cancer. Published by Elsevier Inc. All rights reserved.

ISSN: 1556-0864

<https://doi.org/10.1016/j.jtho.2021.11.018>

^yThe Second Department of Thoracic Oncology, Jiangxi Cancer Hospital, Nanchang, People's Republic of China

^wOncology Department, Baoji Central Hospital, Baoji, People's Republic of China

^xDepartment of Respiratory Medicine, Jinan Central Hospital, Jinan, People's Republic of China

^yDepartment of Breath Internal Medicine, Taizhou Hospital of Zhejiang Province, Taizhou, People's Republic of China

^zDepartment of Thoracic Oncology, Zhejiang Cancer Hospital, Hangzhou, People's Republic of China

^{aa}Department of Internal Medicine-Oncology, Heping Hospital Affiliated to Changzhi Medical College, Changzhi, People's Republic of China

^{bb}Department of Medical Oncology, Henan Provincial People's Hospital, Zhengzhou, People's Republic of China

^{cc}Department of Medicine, Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai, People's Republic of China

Received 9 October 2021; revised 14 November 2021; accepted 19 November 2021

Available online - 16 December 2021

ABSTRACT

Introduction: Camrelizumab, a humanized immunoglobulin G4- κ monoclonal antibody against programmed cell death protein 1, has exhibited antitumor activity and tolerability across various tumors, including lung cancers. We conducted this double-blind, randomized phase 3 trial to investigate the efficacy and safety of camrelizumab or placebo plus chemotherapy as first-line treatment for patients with advanced squamous NSCLC. The predictive value of circulating tumor DNA (ctDNA) dynamics was also analyzed.

Methods: Camel-sq, a double-blind, randomized phase 3 trial (NCT03668496), was conducted in 53 centers in the People's Republic of China. A total of 389 patients with stage IIIB-IV squamous NSCLC were randomized (1:1) to receive 4 to 6 cycles of carboplatin plus paclitaxel with camrelizumab or placebo (every 3 wk), followed by maintenance therapy with camrelizumab or placebo. Peripheral blood ctDNA samples were collected at baseline and the time after two cycles of treatment.

Results: Of 389 eligible patients, 193 patients allocated camrelizumab plus chemotherapy and 196 patients allocated placebo plus chemotherapy were included in the efficacy and safety analysis. The results revealed significantly prolonged progression-free survival (median, 8.5 vs. 4.9 mo; $p < 0.0001$) and overall survival (median, not reached vs. 14.5 mo; $p < 0.0001$) with camrelizumab-chemotherapy versus placebo-chemotherapy. No unexpected treatment immune-related adverse events were observed in both groups. Biomarker analysis revealed that ctDNA clearance after two cycles of treatment was independently associated with dramatically longer progression-free survival ($p < 0.0001$) and overall survival ($p < 0.0001$) in camrelizumab plus chemotherapy group.

Conclusions: Our findings support camrelizumab plus chemotherapy as a first-line treatment option in advanced squamous NSCLC. On-treatment ctDNA dynamics exhibited the potency to predict the efficacy of camrelizumab plus chemotherapy.

Keywords: Biomarker; Chemotherapy; Immunotherapy; Lung squamous cell carcinoma; PD-1

Introduction

Squamous NSCLC, which constitutes 25% to 30% of NSCLC, is a challenge to treat with its specific clinicopathologic characteristics and rare incidence of targetable mutations.^{1,2} For decades, the standard first-line treatment for advanced squamous NSCLC has been platinum-based doublet chemotherapy, providing a median overall survival (OS) of 8.1 to 10.3 months.³ There is a compelling need for novel and effective first-line treatment options.

The emergence of immune checkpoint inhibitors (ICIs) has drastically altered the landscape of cancer treatment. In advanced squamous NSCLC, pembrolizumab, atezolizumab, and more recently, cemiplimab as monotherapy have been established as a standard first-line treatment for patients with high programmed death-ligand 1 (PD-L1) expression.⁴⁻⁶ On the basis that cytotoxic agents may potentiate ICIs with immunologic effects,⁷ several studies have further evaluated the combination of an ICI and chemotherapy as first-line treatment for advanced squamous NSCLC and reported differential efficacy for the various ICIs.⁸⁻¹² The global KEYNOTE-407 and IMpower131 studies both reported substantial improved progression-free survival (PFS) with the addition of pembrolizumab or atezolizumab to platinum-based chemotherapy; however, only KEYNOTE-407 reported OS to benefit irrespective of PD-L1 status. In addition, RATIONALE 307 and ORIENT-12, two phase 3 studies evaluating the combination therapy (tislelizumab or sintilimab plus chemotherapy) in the Chinese patient population, both significantly prolonged the PFS.^{11,12}

Camrelizumab (SHR-1210), a humanized immunoglobulin G4- κ monoclonal antibody against programmed cell death protein 1 (PD-1), has exhibited antitumor activity and tolerability across multiple tumor types, including lung cancers.¹³⁻¹⁷ In a single-arm phase 2 trial in pretreated patients with advanced NSCLC,

camrelizumab monotherapy improved the objective response rate and survival outcomes compared with historical data of standard second-line chemotherapy.¹⁷ In our previous phase 3 CameL study, camrelizumab plus pemetrexed and platinum was compared with chemotherapy alone as first-line therapy for advanced nonsquamous NSCLC without sensitizing *EGFR* or *ALK* alterations. The addition of camrelizumab resulted in significant improvement in PFS and OS, leading to the approval of the combination regimen for this population in the People's Republic of China.¹⁸ Herein, we report the results from CameL-sq, a phase 3 trial assessing the efficacy and safety of camrelizumab in combination with chemotherapy as a first-line treatment for advanced squamous NSCLC.

In addition, previous studies have suggested that cell-free circulating tumor DNA (ctDNA), as a noninvasive tool, could be used to predict the efficacy of ICI monotherapy.^{19,20} Furthermore, a recent study found that integrating pretreatment and on-treatment ctDNA dynamics could identify patients who will achieve durable clinical benefit when receiving ICIs.²¹ However, the predictive and prognostic value of ctDNA dynamics for ICI plus chemotherapy remains unknown. Thus, the current study also performed the biomarker analysis from peripheral blood ctDNA samples collected at the beginning of initial treatment (C0) and after two cycles of treatment (C2).

Methods

Study Design and Patients

CameL-sq was a randomized, placebo-controlled, double-blind phase 3 trial conducted in 53 centers in the People's Republic of China. The study was done in compliance with the Good Clinical Practice guidelines, the provisions of the Declaration of Helsinki, and relevant local laws and regulations. The protocol and all amendments were reviewed and approved by the institutional review board or independent ethics committee of each site. All participants provided written informed consent before enrollment.

Eligible patients were aged 18 to 75 years, had pathologically confirmed stage IIIB-IV squamous NSCLC, had not previously received systemic therapy for metastatic disease, had at least one measurable lesion per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and had archival (within 12 mo from first study dose) or fresh tumor tissues available for biomarker testing. Key exclusion criteria included patients with active or symptomatic central nervous system metastases, use of immunosuppressants within 2 weeks before study treatment, known

sensitizing *EGFR* or *ALK* alterations (test not mandatory), and history or presence of autoimmune disease or interstitial pneumonia. The complete study protocol is provided in the Appendix.

Randomization and Masking

Patients were randomized in a one-to-one ratio to receive camrelizumab plus chemotherapy or placebo plus chemotherapy using a centralized, interactive web response system. Randomization was stratified according to smoking history (≥ 400 cigarette-y vs. < 400 cigarette-y vs. never), presence of liver or brain metastases (both sites vs. one site vs. none), and sex (men vs. women). Imaging of the brain and upper abdomen was mandated at screening. Investigator at each site registered patients through the web response system and assigned them on the basis of a randomization sequence generated by the sponsor's randomization specialist with Statistical Analysis System version 9.4 (SAS Institute, Cary, NC). The patients, investigators, evaluators, and the sponsor were blinded to treatment allocation. However, after progressive disease is confirmed by blinded independent central review (BICR), the patient of disease progression and attending investigator could be unblinded to allow in-study crossover.

Procedure

Patients received camrelizumab (200 mg) or matching placebo in combination with carboplatin (area under the curve 5 mg/mL per min) plus paclitaxel (175 mg/m²) for 4 to 6 cycles at the investigator's discretion, followed by maintenance therapy with camrelizumab or placebo until disease progression, intolerable toxicity, patient withdrawal, or investigator's decision. All treatments were administered intravenously on day 1 of each cycle in 3-week cycles. Continuation of camrelizumab monotherapy after disease progression was permitted if there was evidence of clinical benefit. Patients in the placebo plus chemotherapy group with BICR-assessed disease progression were permitted to cross over to receive camrelizumab monotherapy per investigator judgment. The maximum duration of camrelizumab exposure was 2 years. In case of adverse events, administration of camrelizumab could be interrupted for up to 12 weeks, but no dose adjustment was allowed. Doses of carboplatin and paclitaxel could be reduced or withheld as pre-specified in the protocol ([Supplementary Tables 1-11](#)).

End Points

The primary end point was BICR-assessed PFS, defined as the time from randomization to the first RECIST version 1.1-defined disease progression or death from any cause, whichever occurred first. Key secondary

end points included OS, investigator-assessed PFS, objective response rate, disease control rate, and duration of response, as assessed by BICR and the investigators. Tumor imaging with high-resolution computed tomography or contrast-enhanced magnetic resonance imaging was performed every 6 weeks for the first 48 weeks and every 9 weeks thereafter until radiographic disease progression. Complete or partial response or stable disease was required to be confirmed with a subsequent scan at least 4 weeks after the initial documentation. Survival was followed up every 3 months after treatment discontinuation. Exploratory end points included efficacy analysis by biomarker. PD-L1 tumor proportion score (TPS) was centrally assessed using a PD-L1 immunohistochemistry kit (clone, E1L3N, AmoyDx, Xiamen, People's Republic of China).

Safety was monitored with laboratory tests and adverse events and was assessed every 3 weeks during the treatment period and then every 3 months after the last dose of treatment. Adverse events were graded by the investigators according to the Common Terminology Criteria for Adverse Events version 4.03.

Biomarker Analysis

Fresh or formalin-fixed paraffin-embedded (FFPE) baseline samples were collected before any treatments. After sample collection, fresh biopsy tissues were snap-frozen in liquid nitrogen within 30 minutes. Peripheral blood samples (10 mL, ethylenediaminetetraacetic acid tubes) were collected at baseline and the time after two cycles of treatment. Peripheral blood cells and plasma were separated by centrifugation (at $1600 \times g$) for 10 minutes. Supernatant plasma was transferred to a 2-mL centrifuge tube and centrifuged (at $16,000 \times g$) for 10 minutes. Genomic DNA was extracted from FFPE tumor tissue samples using GeneRead DNA FFPE Kit (Qiagen 180134), and genomic DNA was extracted from peripheral blood lymphocyte with TGuide S32 Magnetic Blood Genomic DNA Kit (TIANGEN, People's Republic of China), following the manufacturer's protocols. Circulating cell-free DNA extraction was done using the MagMAX Cell-Free DNA Isolation kit (ThermoFisher Scientific, Waltham, MA). DNA concentration was measured by Qubit dsDNA HS (High Sensitivity) Assay Kit (Thermo Fisher Scientific), whereas the quality of DNA was assessed by Agilent 2100 BioAnalyzer (Agilent, Santa Clara, CA). The details of library preparation and sequencing and bioinformatic analysis are summarized in Supplemental Material.

Statistical Analyses

We calculated that 285 events of disease progression or death would be needed to provide a power of 90% at

a one-sided significance level of 0.025 to detect a hazard ratio (HR) of 0.68 with camrelizumab plus chemotherapy versus placebo plus chemotherapy, with the use of a log-rank test. Assuming a drop-out rate of 10%, a total number of 360 patients was planned.

All efficacy analyses were performed in the full analysis set, including all eligible patients who were randomized and received at least one dose of study treatment. Safety was assessed in all randomized patients who received at least one dose of study treatment. The Kaplan-Meier method was used to estimate the median survival time of PFS, duration of response, and OS, with the 95% confidence intervals (CI) estimated using the Brookmeyer and Crowley method. Between-group comparisons in PFS and OS were assessed using a stratified log-rank test. HR and corresponding 95% CIs were assessed using the stratified Cox proportional hazards model. Sensitivity analyses for PFS and OS were also performed with PD-L1 TPS added as a covariate for the Cox model. A further sensitivity analysis for OS was conducted using the rank preserving structural failure time (RPSFT) model, adjusting for the potential effect of crossover. Prespecified subgroup analyses for PFS and OS were conducted using an unstratified Cox model. Objective response rate and disease control rate were analyzed, and the corresponding 95% CIs were estimated using the Clopper-Pearson method; between-group comparisons were assessed using the stratified Cochran-Mantel-Haenszel method. Descriptive statistics were used to summarize safety data.

For biomarker analysis, Fisher's exact test was introduced to analyze the significant difference of mutations between-group ctDNA-cleared and group ctDNA-uncleared. R package ClusterProfiler (Bioconductor project, Yu et al.22) was used to analyze the enriched pathway of mutations in each subgroup. The Figure 4D showed the P-value calculated by Hypergeometric test, BgRatio and GeneRatioof enrichment results.

All statistical analyses were performed with Statistical Analysis System version 9.4. Two-side p less than 0.05 was considered statistically significant. The trial is registered with [ClinicalTrials.gov](https://www.clinicaltrials.gov/ct2/show/study/NCT03668496), NCT03668496.

Results

Patient Characteristics

Between November 26, 2018 and December 31, 2019, 606 patients were screened and 390 were enrolled and randomized. Of them, 193 patients allocated camrelizumab plus chemotherapy, and 196 of 197 patients (one did not receive any assigned treatment) allocated placebo plus chemotherapy was included in the efficacy and safety analysis (Supplementary Fig. 1). Baseline characteristics were well balanced between

Table 1. Baseline Characteristics

	Camrelizumab Plus Chemotherapy (n = 193)	Placebo Plus Chemotherapy (n = 196)
Age		
Median (range), y	64 (34-74)	62 (34-74)
≥65 y	84 (44%)	71 (36%)
<65 y	109 (56%)	125 (64%)
Sex		
Men	179 (93%)	180 (92%)
Women	14 (7%)	16 (8%)
Smoking history		
≥400 cigarette-y	162 (84%)	157 (80%)
<400 cigarette-y	9 (5%)	16 (8%)
Never	22 (11%)	23 (12%)
Eastern Cooperative Oncology Group performance status		
0	38 (20%)	43 (22%)
1	155 (80%)	153 (78%)
Disease stage		
IIIB/IIIC	54 (28%)	55 (28%)
IV	139 (72%)	141 (72%)
Liver or brain metastases at enrollment ^a	25 (13%)	22 (11%)
Liver metastases	21 (11%)	19 (10%)
Brain metastases	4 (2%)	3 (2%)
PD-L1 tumor proportion score		
<1%	91 (47%)	97 (49%)
≥1%	95 (49%)	93 (47%)
1-49%	58 (30%)	49 (25%)
≥50%	37 (19%)	44 (22%)
Not evaluable	7 (4%)	6 (3%)

Data are n (%) unless otherwise indicated.

^aNo patients with both liver and lung metastases were enrolled.

PD-L1, programmed death-ligand 1.

treatment groups (Table 1). Most patients were men (93% in the camrelizumab plus chemotherapy group and 92% in the placebo group), with a smoking history of at least 400 cigarette-years (84% and 80%), had an ECOG performance status of 1 (80% and 78%), and had stage IV disease (72% and 72%); 49% of patients in the camrelizumab plus chemotherapy group and 47% in the placebo group had a PD-L1 TPS of greater than or equal to 1%.

As of the data cutoff on November 6, 2020, the median follow-up was 13.5 months (range 1.1–23.6) in the camrelizumab plus chemotherapy group and 11.6 months (range 1.0–23.3) in the placebo group. A total of 67 (35%) patients in the camrelizumab plus chemotherapy group and 10 (5%) patients in the placebo group remained on the assigned treatment; the main reason for discontinuing study treatment was disease progression in both groups (77 [40%] and 161 [82%] patients, respectively) (Supplementary Fig. 1). In patients allocated to placebo plus chemotherapy, 103 (53%) received subsequent anti-PD-1/PD-L1 therapy, including 92 (47%) who crossed over to receive camrelizumab.

Efficacy

At data cutoff, 123 (64%) patients in the camrelizumab plus chemotherapy group and 167 (85%) patients in the placebo group had disease progression or died. Camrelizumab plus chemotherapy significantly improved the primary end point of PFS compared with placebo plus chemotherapy (HR, 0.37 [95% CI 0.29–0.47]; $p < 0.0001$) (Fig. 1A) on the basis of BICR assessment. The median PFS was 8.5 months (95% CI 6.9–10.4) in the camrelizumab plus chemotherapy group versus 4.9 months (95% CI 4.2–5.5) in the placebo plus chemotherapy group; the 12-month PFS rates were 37.9% (95% CI 30.7–45.0) versus 9.2% (95% CI 5.4–14.1), respectively. Prespecified sensitivity analyses including PD-L1 TPS as an additional covariate for the Cox model also supported the PFS benefit in patients treated with camrelizumab plus chemotherapy (Supplementary Table 1). Results of PFS analysis on the basis of investigator assessment were consistent with the primary analysis (HR, 0.30 [95% CI 0.23–0.40]; $p < 0.0001$) (Supplementary Table 2).

At the time of data cutoff, there were 65 (34%) deaths in the camrelizumab plus chemotherapy group

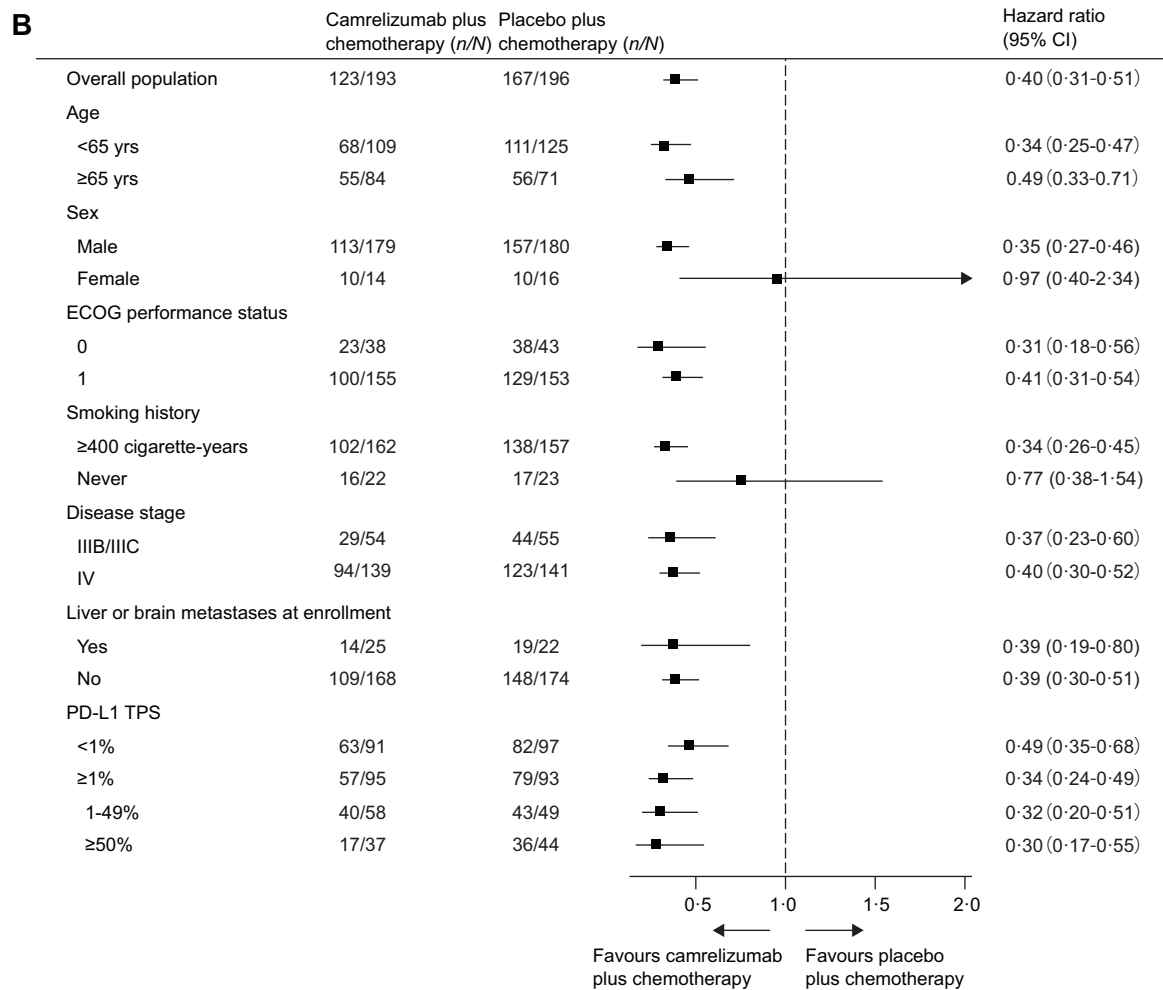
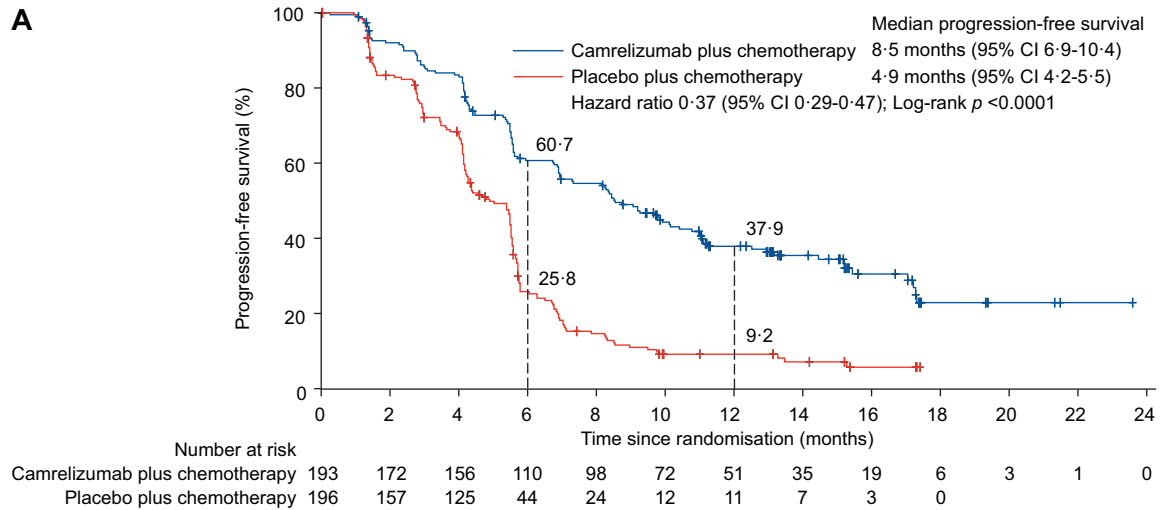


Figure 1. Progression-free survival per blinded independent central review. (A) Kaplan-Meier estimates of progression-free survival. (B) Subgroup analysis of progression-free survival according to baseline characteristics. For the stratified log-rank test, the stratification factors were smoking history (≥400 cigarette-y vs. <400 cigarette-y or never), presence of liver or brain metastases (yes vs. no), and sex (men vs. women). Subgroup stratum with a sample size of less than 5% of either treatment group was not displayed. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

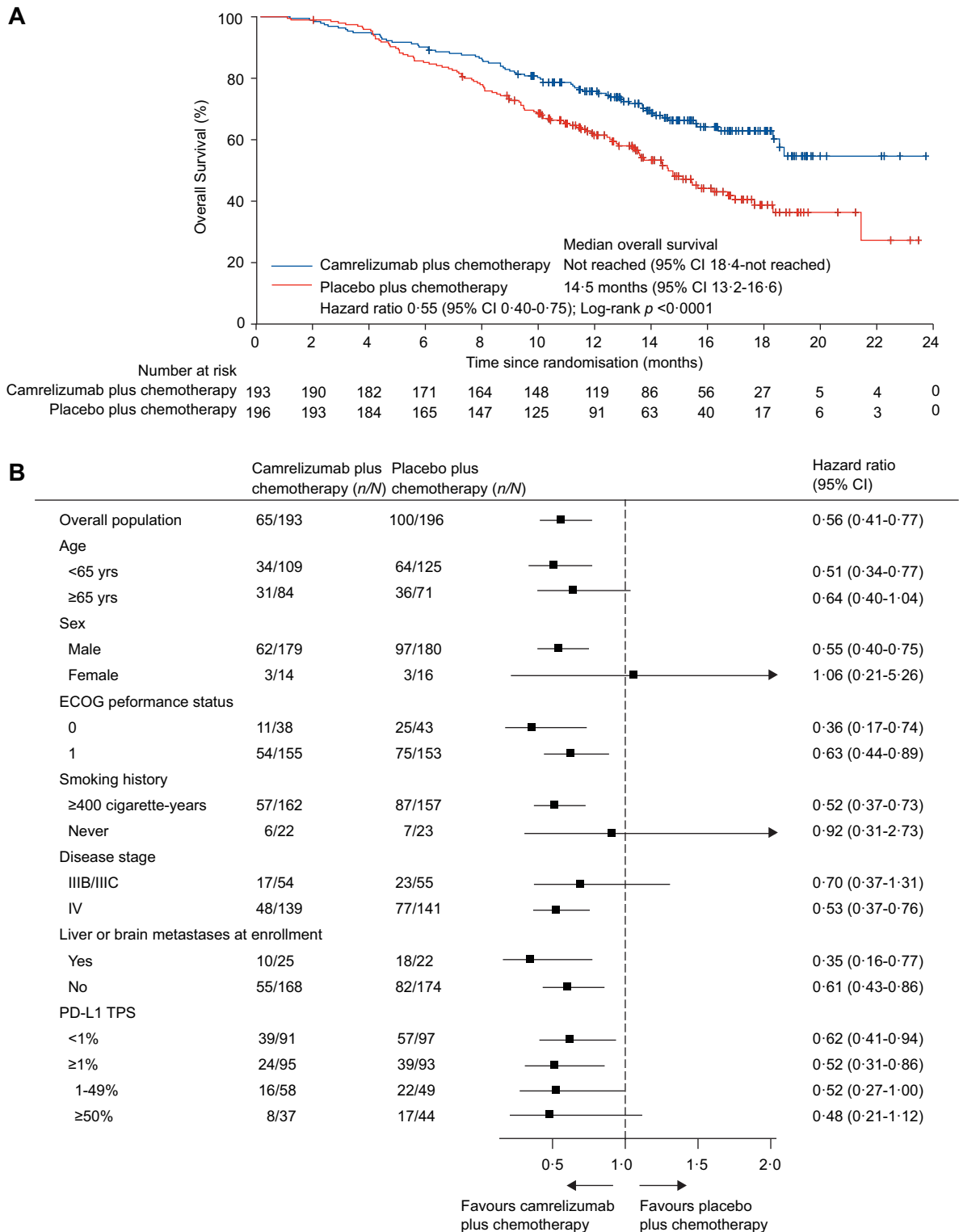


Figure 2. Overall survival. (A) Kaplan-Meier estimates of overall survival. (B) Subgroup analysis of overall survival according to baseline characteristics. For the stratified log-rank test, the stratification factors were smoking history (≥400 cigarette-years vs. <400 cigarette-years or never), presence of liver or brain metastases (yes vs. no), and sex (men vs. women). Subgroup stratum with a sample size of <5% of either treatment group was not displayed. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

and 100 (51%) in the placebo plus chemotherapy group. Camrelizumab plus chemotherapy improved OS compared with placebo plus chemotherapy (HR, 0.55 [95% CI 0.40–0.75]; $p < 0.0001$) (Fig. 2A). The median OS was not reached (95% CI 18.4 mo to not reached) versus 14.5 months (95% CI 13.2–16.6); the 12-month OS rates were 75.1% (95% CI 68.2–80.7) versus 61.5% (95% CI 54.1–68.0). When the effect of PD-L1 status was adjusted in the Cox model, the OS benefit with camrelizumab plus chemotherapy versus placebo plus chemotherapy remained similar (Supplementary Table 1). When the effect of crossover on OS was adjusted using the RPSFT model, the HR estimate was 0.50 (95% CI 0.35–0.72; $p < 0.0001$) (Supplementary Fig. 2) in favor of camrelizumab plus chemotherapy.

Prespecified subgroup analyses revealed generally consistent BICR-assessed PFS (Fig. 1B) and OS (Fig. 2B) with the overall population. In patients with PD-L1 TPS of less than 1%, the HRs for PFS and OS were 0.49 (95% CI 0.35–0.68) and 0.62 (95% CI 0.41–0.94), respectively, with camrelizumab plus chemotherapy versus placebo plus chemotherapy; in patients with PD-L1 TPS of greater than or equal to 1%, the HRs were 0.34 (95% CI 0.24–0.49) and 0.52 (95% CI 0.31–0.86), respectively.

The proportion of patients with BICR-assessed confirmed objective response was higher in the camrelizumab plus chemotherapy group (125 [64.8%] patients) than in the placebo group (72 [36.7%] patients), with a difference of 28.0% (95% CI 18.5–37.6, $p < 0.0001$) (Supplementary Table 3). A total of 15 (7.8%) patients treated with camrelizumab plus chemotherapy and three (1.5%) patients treated with placebo plus chemotherapy achieved a complete response. Among the responders, the median duration of response was 13.1 months (95% CI 9.3–15.7) in the camrelizumab group versus 4.4 months (95% CI 4.2–4.9) in the placebo group; the proportion of patients with an ongoing response at 12 months was 51.5% (95% CI 41.7–60.4) versus 18.2% (95% CI 9.5–29.1) (Supplementary Table 3 and Supplementary Fig. 3). Tumor response and duration of response on the basis of investigator assessment were consistent with BICR assessment (Supplementary Table 2).

Safety

The median number of treatment cycles was 12 (range 1–32) for camrelizumab in the camrelizumab plus chemotherapy group and 7^{1–25} for the placebo in the placebo plus chemotherapy group; the mean relative dose-intensity were 92% and 95%, respectively. The median number of chemotherapy cycles completed was 5 (range 1–6) for paclitaxel and 5 (range 1–6) for carboplatin in both groups. The mean relative dose

intensities were 88% versus 90% for paclitaxel and 89% versus 91% for carboplatin in the camrelizumab group compared with the placebo group (Supplementary Table 4).

Treatment-related adverse events were reported for 193 (100%) patients treated with camrelizumab plus chemotherapy and 195 (99%) patients treated with placebo plus chemotherapy. Grade 3 or more treatment-related adverse events occurred in 142 (74%) patients in the camrelizumab group and 141 (72%) patients in the placebo group, with the most common being decreased neutrophil count (107 [55%] patients in the camrelizumab group versus 116 [59%] patients in the placebo group), decreased white blood cell count (58 [30%] vs. 51 [26%]), and anemia (20 [10%] vs. 14 [7%]) (Table 2). Treatment-related adverse events leading to discontinuation of any treatment component were reported for 24 (12%) patients in the camrelizumab group and 8 (4%) in the placebo group. A total of 64 (33%) patients treated with camrelizumab plus chemotherapy and 41 (21%) treated with placebo plus chemotherapy had treatment-related serious adverse events (Supplementary Table 5). The incidences of treatment-related adverse events adjusted for exposure are provided in Supplementary Tables 6 and 7. Fatal adverse events of any cause occurred in 20 (10%) patients in the camrelizumab group and 27 (14%) in the placebo group. Of them, 6 (3%) cases in the camrelizumab group and 3 (2%) in the placebo group were considered possibly related to treatment (Supplementary Table 8).

Immune-related adverse events of any grade and grade 3 or worse were reported for 148 (77%) patients and 32 (17%) patients, respectively, in the camrelizumab plus chemotherapy group (Supplementary Table 9). The most common immune-related adverse event was reactive cutaneous capillary endothelial proliferation (RCCEP) (133 [69%] patients), followed by hypothyroidism, (22 [11%] patients) and rash (12 [6%]). RCCEP of grades 1, 2, and 3 were reported in 112 (58%), 17 (9%), and 4 (2%) patients, respectively. Reactive capillary endothelial proliferation occurring at sites other than the skin included eyelid ($n = 8$, 4%), oral mucosa ($n = 7$, 4%), and nasal mucosa ($n = 2$, 1%).

Biomarker Analysis

To investigate the predictive value of ctDNA quantification, the mean variant allele frequencies (VAF) of variants, and their on-treatment dynamics in patients treated with camrelizumab plus chemotherapy, peripheral blood plasma were prospectively collected at C0 and C2. There were 134 of 193 (69.4%) patients with high-quality ctDNA samples who were eligible in

Table 2. Treatment-Related Adverse Events

	Camrelizumab Plus Chemotherapy (n = 193)		Placebo Plus Chemotherapy ^a (n = 196)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Hematological toxicities				
White blood cell count decreased	153 (79%)	58 (30%)	153 (78%)	51 (26%)
Neutrophil count decreased	150 (78%)	107 (55%)	154 (79%)	116 (59%)
Anemia	121 (63%)	20 (10%)	124 (63%)	14 (7%)
Platelet count decreased	79 (41%)	13 (7%)	80 (41%)	7 (4%)
Lymphocyte count decreased	24 (12%)	8 (4%)	12 (6%)	2 (1%)
Nonhematological toxicities				
Alopecia	113 (59%)	1 (<1%)	116 (59%)	1 (<1%)
RCCEP	133 (69%)	4 (2%)	8 (4%)	0
Hypoaesthesia	57 (30%)	1 (<1%)	60 (31%)	2 (1%)
Asthenia	63 (33%)	3 (1.6%)	52 (27%)	3 (2%)
Decreased appetite	54 (28%)	1 (<1%)	50 (26%)	0
Nausea	46 (24%)	0	40 (20%)	1 (<1%)
Alanine aminotransferase increased	40 (21%)	3 (2%)	38 (19%)	0
Aspartate aminotransferase increased	39 (20%)	1 (<1%)	25 (13%)	0
Pain in extremity	31 (16%)	1 (<1%)	28 (14%)	0
Weight decreased	23 (12%)	0	28 (14%)	1 (<1%)
Arthralgia	21 (11%)	2 (<1%)	20 (10%)	0
Vomiting	16 (8%)	1 (<1%)	24 (12%)	2 (1%)
Gamma-glutamyltransferase increased	15 (8%)	1 (<1%)	23 (12%)	1 (<1%)
Pyrexia	22 (11%)	1 (<1%)	14 (7%)	0
Rash	25 (13%)	1 (<1%)	11 (6%)	0
Hypothyroidism	28 (15%)	0	8 (4%)	0
Diarrhea	18 (9%)	4 (2%)	14 (7%)	1 (<1%)
Pneumonia	14 (7%)	7 (4%)	16 (8%)	9 (5%)

Data are n (%). Adverse events of any grade occurring in at least 10% of patients or grade 3 or worse adverse events occurring in at least 2% of patients in either group are listed.

^aSafety data after crossover were not included.

RCCEP, reactive cutaneous capillary endothelial proliferation.

the camrelizumab plus chemotherapy group. The ctDNA concentration and mean VAF at C0 ranged from 0.00 to 356.67 ng/mL and 0.00% to 48.16%, respectively. The mean VAF at C2 discriminated patients with a partial response from those with stable disease or disease progression ($p = 0.0034$, $p = 0.0043$; respectively); no discrimination was obtained with ctDNA concentration or mean VAF at C0 or ctDNA concentration at C2 (Supplementary Fig. 4). Moreover, the mean VAF at C2 had a stronger association with RECIST response compared with ctDNA concentration or mean VAF at C0 or ctDNA concentration at C2 (Supplementary Fig. 5). We then asked whether early dynamic changes in ctDNA levels could predict the benefit of camrelizumab plus chemotherapy. The results revealed that patients with ctDNA cleared (defined by conversion from ctDNA positive at C0 to ctDNA negative at C2) and ctDNA negative (defined by patients without detectable ctDNA at both C0 and C2) had significantly longer PFS (12.9 vs. 11.0 vs. 5.3 mo; $p < 0.001$) (Fig. 3A) and OS (not reached vs. not reached vs. 12.4 mo; $p < 0.001$) (Fig. 3B) than those with

ctDNA uncleared (defined by patients with positive ctDNA at C2).

To characterize the distinct clinicopathological and genomic features between patients with ctDNA cleared and ctDNA uncleared, we performed whole-exome sequencing on tumor tissues at baseline. We first observed that patients in ctDNA cleared group had similar clinicopathologic features (e.g., age, sex, smoking history, and PD-L1 expression) and tumor mutational burden levels to those in the ctDNA uncleared group (Fig. 4A). As to the specific gene alterations, we found that tumors from the ctDNA uncleared group had a significantly higher proportion of *KMT2D* ($p = 0.0021$) (Fig. 4B) and *SMO* ($p = 0.0333$) (Fig. 4C) mutations than those from the ctDNA cleared group. Notably, tumors from the ctDNA uncleared group, compared with those from the ctDNA cleared group, were enriched in the MAPK pathway ($p = 0.0047$, $p = 0.1158$; respectively) (Fig. 4D).

Discussion

The phase 3 CameL-sq trial met its primary end point by exhibiting significantly improved PFS (HR, 0.37; 95%

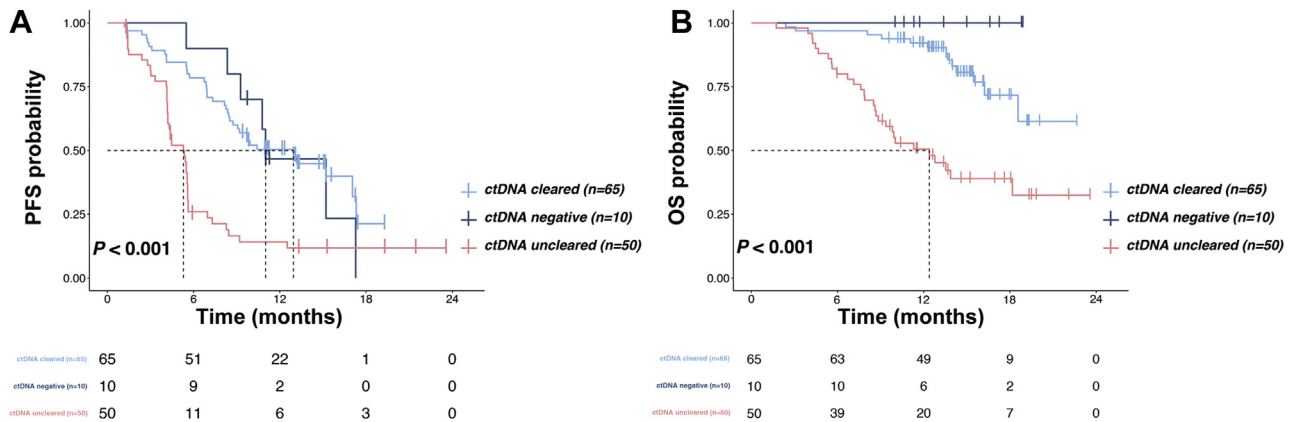


Figure 3. Biomarker analysis. (A) Kaplan-Meier estimates of progression-free survival in patients with ctDNA cleared (defined by conversion from ctDNA positive at C0 to ctDNA negative at C2) versus those with ctDNA negative (defined by patients without detected ctDNA at C0 and C2) versus those with ctDNA uncleared (defined by patients with detectable ctDNA at C0 and C2). (B) Kaplan-Meier estimates of overall survival in patients with ctDNA cleared versus those with ctDNA negative versus those with ctDNA uncleared. ctDNA, circulating tumor DNA; OS, overall survival; PFS, progression-free survival.

CI 0.29–0.47) with the addition of camrelizumab to standard chemotherapy in the treatment of advanced squamous NSCLC in the first-line setting. The PFS benefits for camrelizumab plus chemotherapy were driven by a high objective response rate (64.8%) and remarkable response durability (median, 13.1 mo). The enhanced antitumor activity with camrelizumab plus chemotherapy also translated into a reduction in risk of death by 45%. In addition, survival benefits observed with camrelizumab plus chemotherapy were generally consistent across predefined subgroups.

Previously, two global trials, KEYNOTE-407 and IMpower131, have assessed an ICI in combination with platinum-based chemotherapy in untreated patients with metastatic squamous NSCLC.^{8–10} Pembrolizumab or atezolizumab plus traditional doublet chemotherapy could significantly prolong PFS, whereas atezolizumab failed to prolong OS in the overall population. In addition, two other regional phase 3 trials, RATIONALE 307 and ORIENT-12, evaluated an ICI plus standard chemotherapy in Chinese patients with advanced squamous NSCLC (20%–30% with stage III disease unsuitable for curative treatment), with improved PFS reported for both trials (OS not mature or unreported) (Supplementary Table 10).^{11,12} In CameL-sq, patient baseline characteristics were similar to those in RATIONALE 307 and ORIENT-12, whereas the proportions of men (92% vs. 81%–82%) and with an ECOG performance status of 1 (79% vs. 67%–71%) in CameL-sq were higher compared with KEYNOTE-407 and IMpower131. The low proportion of women enrolled in CameL-sq, RATIONALE 307, and ORIENT-12 (all 8%) were attributed to the historically low prevalence of smoking among Chinese women.²³ The median PFS of 4.9 months observed in the control arm in CameL-sq was

comparable with the 4.9 to 5.6 months reported in previous studies of squamous NSCLC^{2,9–12}; however, the combination immunotherapy arm exhibited a robust prolonged survival with a PFS gain of 3.6 months (vs. 0.6–2.9 mo), a reduced risk of disease progression or death by 63% (vs. 29%–52%), and a clear improvement in OS (HR, 0.55 [95% CI 0.40–0.75]), despite the crossover of 47% patients from the placebo plus chemotherapy group after disease progression. This survival benefit was also confirmed with adjustment for the influence of crossover using the RPSFT model (HR, 0.50 [95% CI 0.35–0.72]).

In our study, 51% of patients had PD-L1 TPS of less than 1% compared with 34% to 40% reported in previous trials of advanced squamous NSCLC in the first-line setting.^{8,11,12} Notably, the benefits of camrelizumab plus chemotherapy were not limited to patients with positive PD-L1 (TPS ≥ 1%). Although we observed a trend toward greater efficacy with PD-L1 enrichment, which was consistent with results of KEYNOTE-407 and IMpower131,^{2,10} the benefits among patients with negative PD-L1 expression were also substantial with camrelizumab plus chemotherapy (HR, 0.49 [95% CI 0.35–0.68] for PFS and 0.62 [95% CI 0.41–0.94] for OS). Taken together with the similar finding from the CameL clinical trial,¹⁸ our data support camrelizumab plus chemotherapy as a first-line regimen for patients with advanced NSCLC without sensitizing *EGFR* or *ALK* alterations, regardless of histologic type or PD-L1 expression status.

The safety profile of camrelizumab plus carboplatin-based chemotherapy was generally consistent with the previous reports in nonsquamous NSCLC.¹⁸ The most common grade 3 or more treatment-related adverse events were hematologic toxicities, and there was no

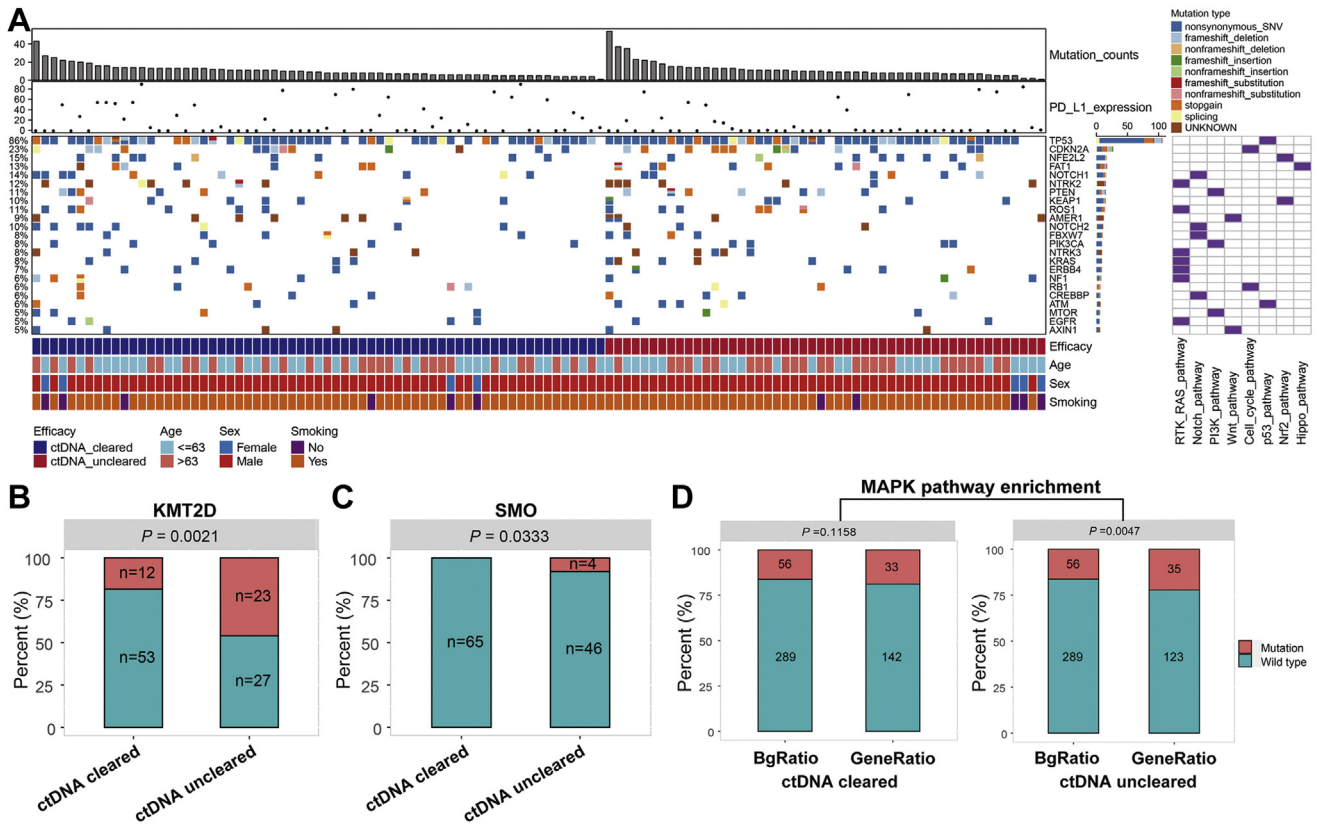


Figure 4. Genomic analysis. (A) Mutational landscape of the included patients with high-quality ctDNA samples in camrelizumab plus chemotherapy group. Left upper panel: mutation counts and PD-L1 expression level. Left middle panel: The matrix of mutations in a selection of frequently mutated genes ($\geq 5\%$) and their frequency; columns represent samples. Left bottom panel: ctDNA clearance information and clinical features (age, sex, smoking history). Right upper panel: color annotation of mutation type. Right lower panel: detected frequently mutated genes in the related pathway. (B) Comparison of the total number of KMT2D mutations between ctDNA cleared and uncleared group; orange color represents the number of patients with KMT2D mutations; cyan color represents the number of patients without KMT2D mutations; p value was calculated by Fisher's exact test. (C) Comparison of the total number of SMO mutations between ctDNA cleared and uncleared group; orange color represents the number of patients with SMO mutations; cyan color represents the number of patients without SMO mutations; p value was calculated by Fisher's exact test. (D) Comparison of MAPK pathway enrichment between ctDNA cleared and uncleared group; p value was calculated by hypergeometric test, BgRatio, and GeneRatio of enrichment results. BgRatio, orange color represents the number of annotated genes involved in the MAPK pathway from the sequencing panel; cyan color represents the number of annotated genes involved in all pathways from the sequencing panel. GeneRatio, orange color represents the number of detected gene mutations involved in MAPK pathway from this group; cyan color represents the number of all annotated genes from this group. ctDNA, circulating tumor DNA; PD-L1, programmed death-ligand 1.

evident increase in adverse events associated with chemotherapy with the addition of camrelizumab. The incidences of immune-related endocrinopathies, pneumonitis, liver function impairment, diarrhea and colitis were generally comparable with those reported for other PD-1/PD-L1 inhibitors plus chemotherapy in squamous NSCLC.^{2,10,11} RCCEP is the most frequent adverse event reported for camrelizumab monotherapy, which occurs in 76.7% to 97.3% of patients across various tumor types.^{15,16,24-26} RCCEP are mostly mild (grade 1-2 severity), self-limiting, and rarely cause treatment discontinuation.²⁷ In the present study, the incidence of RCCEP was 69% in patients treated with camrelizumab

plus carboplatin and paclitaxel. The impact of chemotherapy on the incidence of RCCEP differs by chemotherapy regimen when used in combination with camrelizumab.^{15,28} In addition, the incidence of RCCEP would decrease to 21.9% when combined with apatinib,²⁹ a VEGFR-TKI in advanced NSCLC, suggesting that RCCEP may be attributed to immune stress responses of the cutaneous capillary endothelial cells and could be reversed by antiangiogenesis therapy.²⁷

As a noninvasive tool, ctDNA is an attractive material to assess and dynamically monitor immunotherapy response. Several retrospective proof-of-principle studies have indicated the predictive or prognostic

significance of ctDNA quantification and dynamics for ICI monotherapy in various solid tumors.^{19–21,30} In this phase 3 study, we firstly explore the predictive value of ctDNA dynamics for advanced squamous NSCLC treated with immunotherapy plus chemotherapy and found that patients with ctDNA negative at baseline or cleared after two cycles of treatment had significantly better survival benefit than those with ctDNA uncleared, suggesting that on-treatment ctDNA dynamics are a potent predictive biomarker for the treatment of camrelizumab plus chemotherapy. Similar results were also observed in a prospective clinical trial of ICI monotherapy across tumor types.³¹ More importantly, a recent study found that integration of noninvasive testing including pre-treatment and on-treatment ctDNA and circulating immune cell profiling could accurately predict durable clinical benefit from ICI-based treatment in advanced NSCLC,³² suggesting the noninvasive detection might be a potent strategy to guide personalized ICI plus chemotherapy in patients with advanced NSCLC in the future.

There are several potential limitations. First, PD-L1 expression status was not included as a randomization stratification factor. However, the effect on treatment outcomes should be minimal as PD-L1 expression status was well balanced across study groups. Second, only Chinese patients were enrolled. Therefore, the efficacy and safety observed here for camrelizumab combination therapy may not be extrapolated to the White population. Third, OS is still immature in the current analysis. Longer follow-up is needed to fully assess the survival benefits of the combination therapy. Finally, we observed distinct genomic features (e.g., *KMT2D* mutations, *SMO* mutations, and MAPK pathway) between tumors from ctDNA cleared and uncleared group, but the underlying mechanism warrant further investigation.

In summary, this phase 3 trial of advanced squamous NSCLC revealed that the addition of camrelizumab to carboplatin and paclitaxel as first-line treatment was associated with significant and clinically meaningful improvement in PFS with a manageable safety profile. Patients with ctDNA clearance after two cycles of treatment had significantly better PFS and OS than those with ctDNA positive in camrelizumab plus chemotherapy group. These findings support the application of camrelizumab plus carboplatin and paclitaxel as an additional standard first-line treatment option for patients with advanced squamous NSCLC.

CRedit Authorship Contribution Statement

Shengxiang Ren: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation;

Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing.

Jianhua Chen: Data curation; Investigation; Project administration; Resources.

Xingxiang Xu: Data curation; Investigation; Project administration; Resources.

Tao Jiang: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Software; Visualization; Writing - original draft.

Ying Cheng: Data curation; Investigation; Project administration; Resources.

Gongyan Chen: Data curation; Investigation; Project administration; Resources.

Yueyin Pan: Data curation; Investigation; Project administration; Resources.

Yong Fang: Data curation; Investigation; Project administration; Resources.

Qiming Wang: Data curation; Investigation; Project administration; Resources.

Yunchao Huang: Data curation; Investigation; Project administration; Resources.

Wenxiu Yao: Data curation; Investigation; Project administration; Resources.

Rui Wang: Data curation; Investigation; Project administration; Resources.

Xingya Li: Data curation; Investigation; Project administration; Resources.

Wei Zhang: Data curation; Investigation; Project administration; Resources.

Yanjun Zhang: Data curation; Investigation; Project administration; Resources.

Sheng Hu: Data curation; Investigation; Project administration; Resources.

Renhua Guo: Data curation; Investigation; Project administration; Resources.

Jianhua Shi: Data curation; Investigation; Project administration; Resources.

Zhiwu Wang: Data curation; Investigation; Project administration; Resources.

Peiguo Cao: Data curation; Investigation; Project administration; Resources.

Donglin Wang: Data curation; Investigation; Project administration; Resources.

Jian Fang: Data curation; Investigation; Project administration; Resources.

Hui Luo: Data curation; Investigation; Project administration; Resources.

Yi Geng: Data curation; Investigation; Project administration; Resources.

Chunyan Xing: Data curation; Investigation; Project administration; Resources.

Dongqing Lv: Data curation; Investigation; Project administration; Resources.

Yiping Zhang: Data curation; Investigation; Project administration; Resources

Junyan Yu: Data curation; Investigation; Project administration; Resources.

Shundong Cang: Data curation; Investigation; Project administration; Resources.

Zeyu Yang: Resources; Software; Supervision; Validation; Visualization.

Wei Shi: Project administration; Resources; Software; Supervision; Validation.

Jianjun Zou: Project administration; Resources; Software; Supervision; Validation.

Caicun Zhou: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Project administration; Resources; Supervision; Validation; Writing - review & editing.

Acknowledgments

This study was funded by Jiangsu Hengrui Pharmaceuticals, which participated in study design, data collection, data analysis, and data interpretation. All authors had full access to all the data in the study, and the corresponding authors had final responsibility for the decision to submit for publication. This study was also supported, in part, by grants from the National Natural Science Foundation of People's Republic of China (No. 81871865, 81874036, and 81972167), the Backbone Program of Shanghai Pulmonary Hospital (No. FKGG1802), Shanghai Pujiang Talent Plan (No. 2019PJD048), Shanghai Science and Technology Committee Foundation (NO. 19411950300), Program of Shanghai Academic Research Leader (NO. 21XD1423200), and Shanghai Key disciplines of Respiratory (No. 2017ZZ02012). The authors thank all patients and their families and all the staff at the study centers. The authors also thank Dr. Xiuzhi Wu for providing medical writing support. Thanks for the help of Yaxi Zhang and Jiao Zhang for the bioinformatics analysis in this study.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the Journal of Thoracic Oncology at www.jto.org and at <https://doi.org/10.1016/j.jtho.2021.11.018>.

References

- Duma N, Santana-Davila R, Molina JR. Non-small cell lung cancer: epidemiology, screening, diagnosis, and treatment. *Mayo Clin Proc.* 2019;94:1623-1640.
- Socinski MA, Obasaju C, Gandara D, et al. Current and emergent therapy options for advanced squamous cell lung cancer. *J Thorac Oncol.* 2018;13:165-183.
- National Health Commission of the People's Republic of China. Chinese Guidelines for Diagnosis and Treatment of Primary Lung cancer 2018 (English Version). *Chin J Cancer Res.* 2019;31:1-28.
- Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-small-cell lung Cancer. *N Engl J Med.* 2016;375:1823-1833.
- Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. *N Engl J Med.* 2020;383:1328-1339.
- Sezer A, Kilickap S, Gümüş M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. *Lancet.* 2021;397:592-604.
- Bracci L, Schiavoni G, Sistigu A, Belardelli F. Immune-based mechanisms of cytotoxic chemotherapy: implications for the design of novel and rationale-based combined treatments against cancer. *Cell Death Differ.* 2014;21:15-25.
- Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med.* 2018;379:2040-2051.
- Paz-Ares L, Vicente D, Tafreshi A, et al. A randomized, placebo-controlled trial of pembrolizumab plus chemotherapy in patients with metastatic squamous NSCLC: protocol-specified final analysis of KEYNOTE-407. *J Thorac Oncol.* 2020;15:1657-1669.
- Jotte R, Cappuzzo F, Vynnychenko I, et al. Atezolizumab in combination with carboplatin and nab-paclitaxel in advanced squamous NSCLC (IMpower131): results from a randomized Phase III trial. *J Thorac Oncol.* 2020;15:1351-1360.
- Wang J, Lu S, Yu X, et al. Tislelizumab plus chemotherapy vs. chemotherapy alone as first-line treatment for advanced squamous Non-small-cell lung cancer: A Phase 3 randomized clinical trial. *JAMA Oncol.* 2021;7(5):709-717.
- Zhou C, Wu L, Fan Y, et al. Sintilimab plus platinum and gemcitabine as first-line treatment for advanced or metastatic squamous NSCLC: results from a randomized, double-blind, Phase 3 trial (ORIENT-12). *J Thorac Oncol.* 2021;16(9):1501-1511.
- Huang J, Xu J, Chen Y, et al. Camrelizumab versus investigator's choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (Escort): a multicentre, randomised, open-label, phase 3 study. *Lancet Oncol.* 2020;21:832-842.
- Qin S, Ren Z, Meng Z, et al. Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomised, phase 2 trial. *Lancet Oncol.* 2020;21:571-580.
- Fang W, Yang Y, Ma Y, et al. Camrelizumab (SHR-1210) alone or in combination with gemcitabine plus cisplatin for nasopharyngeal carcinoma: results from two single-arm, phase 1 trials. *Lancet Oncol.* 2018;19:1338-1350.
- Song Y, Wu J, Chen X, et al. A single-arm, multicenter, Phase II study of camrelizumab in relapsed or refractory classical Hodgkin lymphoma. *Clin Cancer Res.* 2019;25:7363-7369.

17. Wu Y, Huang C, Fan Y, et al. JCSE01.09 A Phase II umbrella study of camrelizumab in different PD-L1 expression cohorts in pre-treated advanced/metastatic non-small cell lung cancer. *J Thorac Oncol*. 2019;14:5128.
18. Zhou C, Chen G, Huang Y, et al. Camrelizumab plus carboplatin and pemetrexed versus chemotherapy alone in chemotherapy-naïve patients with advanced non-squamous non-small-cell lung cancer (Camel): a randomised, open-label, multicentre, phase 3 trial. *Lancet Respir Med*. 2021;9:305-314.
19. Goldberg SB, Narayan A, Kole AJ, et al. Early assessment of lung cancer immunotherapy response via circulating tumor DNA. *Clin Cancer Res*. 2018;24:1872-1880.
20. Lee JH, Long GV, Boyd S, et al. Circulating tumour DNA predicts response to anti-PD1 antibodies in metastatic melanoma. *Ann Oncol*. 2017;28:1130-1136.
21. Zhang Q, Luo J, Wu S, et al. Prognostic and predictive impact of circulating tumor DNA in patients with advanced cancers treated with immune checkpoint blockade. *Cancer Discov*. 2020;10:1842-1853.
22. Yu G, Wang LG, Han Y, He QY. clusterProfiler: an R package for comparing biological themes among gene clusters. *OmicS*. 2012;16:284-287.
23. Cheng TY, Cramb SM, Baade PD, Youlden DR, Nwogu C, Reid ME. The international epidemiology of lung cancer: latest trends, disparities, and tumor characteristics. *J Thorac Oncol*. 2016;11:1653-1671.
24. Mo H, Huang J, Xu J, et al. Safety, anti-tumour activity, and pharmacokinetics of fixed-dose SHR-1210, an anti-PD-1 antibody in advanced solid tumours: a dose-escalation, phase 1 study. *Br J Cancer*. 2018;119:538-545.
25. Huang J, Xu B, Mo H, et al. Safety, activity, and biomarkers of SHR-1210, an anti-PD-1 antibody, for patients with advanced esophageal carcinoma. *Clin Cancer Res*. 2018;24:1296-1304.
26. Huang J, Mo H, Zhang W, et al. Promising efficacy of SHR-1210, a novel anti-programmed cell death 1 antibody, in patients with advanced gastric and gastroesophageal junction cancer in China. *Cancer*. 2019;125:742-749.
27. Wang F, Qin S, Sun X, et al. Reactive cutaneous capillary endothelial proliferation in advanced hepatocellular carcinoma patients treated with camrelizumab: data derived from a multicenter phase 2 trial. *J Hematol Oncol*. 2020;13:47.
28. Mei Q, Zhang W-Y, Liu Y, et al. Camrelizumab plus gemcitabine, vinorelbine and pegylated liposomal doxorubicin in relapsed/refractory primary mediastinal B-cell lymphoma: a single-arm, open-label, phase 2 trial. *Clin Cancer Res*. 2020;26(17):4521-4530.
29. 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;27:1296-1304.
30. Raja R, Kuziora M, Brohawn PZ, et al. Early reduction in ctDNA predicts survival in patients with lung and bladder cancer treated with durvalumab. *Clin Cancer Res*. 2018;24:6212-6222.
31. Bratman SV, Yang SYC, Iafolla MAJ, et al. Personalized circulating tumor DNA analysis as a predictive biomarker in solid tumor patients treated with pembrolizumab. *Nat Cancer*. 2020;1:873-881.
32. Nabet BY, Esfahani MS, Moding EJ, et al. Noninvasive early identification of therapeutic benefit from immune checkpoint inhibition. *Cell*. 2020;183(2):363-376.e13.