First-line treatment with camrelizumab plus famitinib in advanced or metastatic NSCLC patients with PD-L1 TPS ≥1%: results from a multicenter, open-label, phase 2 trial

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ABSTRACT
Background The combination of immune-checkpoint inhibitors and antiangiogenic agents can synergistically modulate the tumor microenvironment and represents a promising treatment option. Here, we evaluated the efficacy and safety of camrelizumab plus famitinib (a receptor tyrosine kinase inhibitor) as a first-line treatment for advanced or metastatic NSCLC patients with a programmed death ligand-1 (PD-L1) tumor proportion score (TPS) of ≥1%, in an open-label, multicenter, phase 2 basket trial.

Methods Eligible patients received camrelizumab (200 mg once every 3 weeks via intravenous infusion) plus oral famitinib at an initial dose of 200 mg once daily. The primary endpoint was the objective response rate (ORR), as assessed by the investigator per Response Evaluation Criteria in Solid Tumors V.1.1. Key secondary endpoints included disease control rate (DCR), duration of response, progression-free survival (PFS), overall survival (OS), 12-month OS rate, and safety profile.

Results Of the enrolled 41 patients, 21 (51.2%) had a PD-L1 TPS of 1–49%. As of the cut-off date on June 22, 2022, the combination regimen of camrelizumab and famitinib achieved an ORR of 53.7% (95% CI 37.4% to 69.3%) and a DCR of 92.7% (95% CI 80.1% to 98.5%). The median PFS was 16.6 months (95% CI 8.3 to not reached), and OS data were not yet mature, with an estimated 12-month OS rate of 76.8% (95% CI 60.0% to 87.3%). The most common treatment-related adverse events of grade 3 or higher included hypertension (22.0%), increased alanine aminotransferase (12.2%), decreased neutrophil count (9.8%), proteinuria (7.3%), decreased platelet count (7.3%), and hypokalemia (7.3%). One (2.4%) patient died from grade 5 hemoptysis, which was considered possibly related to the study treatment by the investigator.

Conclusion Camrelizumab plus famitinib demonstrated promising antitumor activity in advanced or metastatic NSCLC patients and had an acceptable safety profile.

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Blocking vascular endothelial growth factor pathways can ameliorate hypoxia by modulating the tumor microenvironment, increasing tumorous CD8+ T cell infiltration, and reducing macrophage recruitment. Adding antiangiogenic agents to immune checkpoint inhibitors could enhance therapeutic responses. In advanced NSCLC, combinations such as sintilimab plus anlotinib in first-line treatment, or pembrolizumab plus ramucirumab or lenvatinib in later lines, have shown encouraging clinical benefits.

WHAT THIS STUDY ADDS
⇒ Cohort 2 of this phase 2 trial demonstrated that camrelizumab in combination with famitinib had promising antitumor activity with an objective response rate of 53.7% and a median progression-free survival of 16.6 months in advanced or metastatic NSCLC patients with a programmed death ligand-1 (PD-L1) tumor proportion score (TPS) of ≥1%, and the safety profile was both tolerable and manageable.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ This combination therapy has the potential to serve as an effective chemotherapy-free treatment alternative for advanced or metastatic NSCLC patients exhibiting a PD-L1 TPS of ≥1%. An ongoing multicenter, randomized phase 3 clinical trial (NCT05042375) is expected to validate these findings and possibly extend the insights gained from this study.

These findings suggest that this combination regimen could be an alternative therapeutic option and warrant further investigation.

Trial registration number NCT04346381.
BACKGROUND
The introduction of programmed death-l (PD-1) and PD ligand-l (PD-L1) blockage has revolutionized the first-line treatment landscape for patients with advanced NSCLC who have EGFR/ALK wild-type tumors. Currently, the US Food and Drug Administration (FDA) has approved pembrolizumab as a first-line monotherapy for advanced NSCLC with a PD-L1 Tumor Proportion Score (TPS) of ≥1%. Furthermore, pembrolizumab, avelumab, and cemiplimab have been successively approved by the FDA and the European Medicines Agency as first-line monotherapies for advanced NSCLC patients with a PD-L1 expression TPS of ≥50%. Likewise, the addition of pembrolizumab, avelozilumab, or nivolumab plus ipilimumab to platinum-based chemotherapy has also been approved for the first-line treatment of metastatic NSCLC, regardless of PD-L1 expression. However, it is important to note that although the addition of immune checkpoint inhibitors (ICIs) to front-line chemotherapy has improved response rates and expanded the target patient population, it has also led to an increased incidence of treatment-related adverse events (TRAEs) that may negatively impact treatment tolerability and quality of life.

Blockade of vascular endothelial growth factor (VEGF) signaling pathways has been shown to ameliorate hypoxia by modulating the tumor microenvironment, increasing the infiltration of CD8+T cells into tumors, and reducing the recruitment of tumor-associated macrophages. Therefore, combining antiangiogenic agents with ICIs may amplify therapeutic efficacy. As of now, the US FDA has approved several such combinations for the treatment of advanced solid cancers. These approved combinations include atezolizumab plus bevacizumab for hepatocellular carcinoma, avelumab plus axitinib or pembrolizumab plus axitinib for renal cell carcinoma, and pembrolizumab plus lenvatinib for endometrial carcinoma. In patients with advanced NSCLC, several such combinations have demonstrated promising clinical benefits: for instance, sintilimab in combination with anlotinib in the first-line setting, and pembrolizumab plus ramucirumab or lenvatinib in the later-line settings.

Camrelizumab is a high-affinity, humanized IgG4-κ monoclonal antibody targeting PD-1, and it has demonstrated promising antitumor activity across a range of advanced solid tumors. In China, camrelizumab in combination with chemotherapy has recently been approved as a first-line treatment option for patients with squamous NSCLC or non-squamous NSCLC without EGFR and ALK alterations. Famitinib, a structural analog of sunitinib, is a novel and promising multitarget receptor tyrosine kinase inhibitor (TKI) against VEGF receptor 2/3, stem-cell factor receptor, platelet-derived growth factor receptor β, proto-oncogene tyrosine-protein kinase receptor and FMS-like tyrosine kinase-1/3 receptor. Since these targets are involved in processes such as tumor angiogenesis, proliferation, and immune suppression, famitinib holds potential to enhance the antitumor responses mediated by camrelizumab. The combination of camrelizumab (200mg every 3 weeks) and famitinib (20mg once daily) has demonstrated both antitumor activity and tolerability in patients with advanced genitourinary or gynecologic carcinomas. In view of these promising results, we launched a phase 2 basket trial to assess the efficacy and safety of camrelizumab in combination with famitinib in patients with various advanced solid tumors. This report presents the results of this combination therapy in treatment-naïve advanced or metastatic NSCLC patients who have a PD-L1 TPS of ≥1%.

METHODS
Study design and patients
This study is an open-label, multicenter, phase 2 basket trial (ClinicalTrials.gov registration: NCT04346381) evaluating the efficacy and safety of camrelizumab plus famitinib for the treatment of advanced solid tumors (online supplemental table S1). The study design is presented in online supplemental table S2, and the data presented here are from cohort 2, which included treatment-naïve NSCLC patients with a PD-L1 TPS≥1%. In brief, eligible patients were between 18 and 75 years old, had advanced or metastatic NSCLC with wild-type EGFR and ALK (tested per local standards), had PD-L1 TPS≥1%, and had not previously received systemic therapy for advanced or metastatic disease. Patients were also allowed to be enrolled if they had received neoadjuvant or adjuvant chemotherapy/radiotherapy and had a recurrence-free interval (defined as the time from the completion of therapy to the first recurrence or metastasis) of longer than 6 months. To assess PD-L1 expression, all patients were required to provide a tumor sample (fresh or archival). Other key eligibility criteria included at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1, a life expectancy of at least 12 weeks, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate organ function. Key exclusion criteria were listed in online supplemental table S3.

Procedures
All enrolled patients received camrelizumab 200mg intravenously on day 1 of each 21-day cycle once every 3 weeks and an initial dose of oral famitinib 20mg once daily. Treatment continued until confirmed progression of the disease based on RECIST V.1.1, intolerable toxicity, withdrawal by the investigator, patient decision or withdrawal of consent, poor compliance, or loss to follow-up, whichever came first. If a patient met the criteria for disease progression for the first time, treatment could still proceed if the investigator determined that the patient was tolerating the regimen well and deriving clinical benefit. In such cases, treatment would continue until further confirmation of disease progression, obtained at least 4 weeks or later. Camrelizumab dose modification
or dose interruptions of camrelizumab for more than 12 weeks were not allowed, and the cumulative exposure to camrelizumab should not exceed 2 years (up to 35 doses). Dose interruption, dose reduction (to 15 mg once daily), and modifications in famitinib dosing frequency (15 mg for 14 days on, 7 days off) were permitted; however, dose increases were not allowed. Online supplemental table S4 provides detailed guidelines for adjusting the doses of camrelizumab and famitinib due to treatment-related toxicity.

Endpoints
The primary endpoint of this study was the confirmed objective response rate (ORR), as per RECIST V.1.1, which was defined as the percentage of patients whose best overall responses were confirmed complete response (CR) or partial response (PR), as determined by the investigator. The secondary endpoints included: disease control rate (DCR, defined as the proportion of patients with a CR, PR or durable stable disease (SD) as their best overall response); duration of response (DoR, defined as the time interval between the first documented evidence of CR or PR and the progression of disease or death, whichever came first); time to response (TTR, defined as the time from the initiation of study treatment to the first documented CR or PR according to RECIST V.1.1); progression-free survival (PFS) (defined as the time between the start of treatment and the first documented progression of disease per RECIST V.1.1 or death from any cause, whichever came first); overall survival (OS) (defined as the time from the start of study treatment to death due to any cause); OS rates at 6, 9, and 12 months, as well as the safety profile. The associations between the efficacy of this combination regimen and PD-L1 TPS or other biomarkers were analyzed as exploratory endpoints.

Assessments
Tumor response was assessed by the investigator at baseline and every three cycles after the initiation of study treatment using CT or MRI, in accordance with RECIST V.1.1. A CR or PR had to be confirmed at least 4 weeks after the initial documented response. The first documented progression of disease progression was necessary to be confirmed at 4–6 weeks beyond progression, except in cases of rapid radiological progression (defined as a ≥50% increase in the sum of the diameters of target lesions compared with baseline) and/or clinical progression (characterized by significant changes in clinical symptoms or laboratory markers, deterioration in performance status, or rapid tumor progression or tumor involving vital organ or sites such as spinal cord compression). Tumor response assessments were performed every 3 months for those who discontinued treatment in the absence of radiological disease progression until documented progression of disease, start of first subsequent anticancer therapy, loss of follow-up, death, or study completion, whichever came first. The survival status of patients was monitored every 2 months until death.

Vital signs, 12-lead ECGs, laboratory tests, and adverse event (AE) reports were monitored for safety. AEs were monitored for 50 days after the last dose of study treatment (both serious AEs and immune-mediated AEs were collected up to 90 days after the final dose of camrelizumab), and all AEs were graded based on the NCI Common Terminology Criteria for Adverse Events, V.5.0.

In the central laboratory, PD-L1 expression was quantified using the TPS method with the IHC 22C3 pharmDx kit (Agilent Technologies, Santa Clara, California, USA), and the results were categorized into either TPS 1%–49% and TPS≥50%, or TPS 1%–20% and TPS≥20%. Tumor mutational burden (TMB) was measured in pretreatment tumor biopsies or archival tissues using a pancancer panel from BGI (Shenzhen, China), implemented on the MGISEQ-2000 platform (MGI Tech, Shenzhen, China), which covers 636 genes across 1.95 Mb. TMB was calculated based on the number of somatic mutations, including base substitution and indels, per megabase and was categorized as either high or low using a cut-off level of 10 mutations per megabase (muts/Mb).

Statistical analyses
To minimize the sample size if the study treatment was deemed ineffective for a specific tumor type, Simon’s two-stage minimax design was applied. In the cohort 2, the desirable target ORR was set at 45%, while the uninteresting level of ORR under the null hypothesis was set at 25%. This was based on historical data from the KEYNOTE-042 study, in which the ORR for first-line treatment with pembrolizumab monotherapy in 637 NSCLC patients with PD-L1 TPS ≥1% was 27.3%. Based on these assumptions, with a one-sided α-error of 2.5% and a power of 80%, the study required 21 evaluable patients to be treated during stage 1, and stage 2 would proceed if at least 6 responders were observed during stage 1, involving the treatment of the additional 22 evaluable patients. Overall, the combination regimen would be considered active if 17 or more responders were observed among the 43 patients.

However, by the time the 41st patient was enrolled in the cohort 2, 15 patients had already achieved objective responses, and tumor response assessments had yet to be conducted in 12 additional patients. Given these circumstances, there was a high probability of observing at least 17 objective responses in total. Cohort 2 was terminated after enrolling 41 patients, as the conclusion would not be affected even if two more patients were added, provided that a total of 17 or more responders were observed. In total, 22 of the 41 patients enrolled in cohort 2 achieved objective responses, indicating that the combination regimen was indeed considered active.

The full-analysis set (FAS) and safety analysis included all patients who received at least one dose of study treatment. The ORR and DCR were calculated using the Clopper-Pearson exact method, based on binomial distribution, with 95% CIs. For time-to-event endpoints,
medians were estimated using the Kaplan-Meier method, and their corresponding 95% CIs were calculated using the Brookmeyer-Crowley method. The Kaplan-Meier method was also employed to estimate the probabilities of OS at 6, 9, and 12 months, and their corresponding 95% CIs were calculated using the log-log transformation (based on normal approximation method) with back transformation to a CI on the untransformed scale. TTR was summarized using median, minimum, and maximum values. All statistical analyses were done by using SAS (V.9.4).

RESULTS
Demographics and baseline characteristics
This study enrolled 41 treatment-naïve patients with advanced or metastatic NSCLC, whose tumors expressed PD-L1 with a TPS of ≥1%, between June 17, 2020 and August 26, 2021, from 16 sites in China. All patients received a combination of camrelizumab plus famitinib. Table 1 presents the demographics and baseline characteristics of the patients. The median age was 64 years old (range 53–74), and 85.4% of the patients were male. The majority of patients had an ECOG PS of 1 (35/41; 85.4%) and were either current or former smokers (28/41; 68.3%). A total of 11 (26.8%) patients had squamous carcinomas, and 30 (73.2%) had non-squamous carcinomas. Thirty-nine (95.1%) patients presented with metastases, irrespective of the organs involved; one (2.4%) patient had brain metastasis, and three (7.3%) patients had liver metastases. In cohort 2, which comprised 41 patients, 21 (51.2%) had a PD-L1 TPS ranging from 1% to 49%, while 20 (48.8%) had a TPS of ≥50%. Notably, 7 patients (17.1%) had a TPS of exactly 1%. The lower tertile for PD-L1 expression was set at TPS 20% (PD-L1 TPS>20%, n=26).

As of the last follow-up date on June 22, 2022, 19 (46.3%) patients remained on the study treatment, with a median duration of follow-up being 12.5 months (range 1.0–24.2). Treatment discontinuation was most commonly attributed to radiographic disease progression (camrelizumab discontinuation: n=11, 26.8%; famitinib discontinuation: n=9, 22.0%), followed by withdrawal by the patient (camrelizumab discontinuation: n=5, 12.2%; famitinib discontinuation: n=4, 9.8%) and AEs (camrelizumab discontinuation: n=1, 2.4%; famitinib discontinuation: n=7, 17.1%), as shown in figure 1. Eleven (26.8%) patients received at least one subsequent antitumor therapy after the end of the study treatment (online supplemental table S5).

Antitumor activity in all patients
The FAS included 41 patients: 22 (53.7%) achieved a PR, and 16 (39.0%) had SD. The confirmed ORR was 53.7% (95% CI 37.4% to 69.3%), and the DCR was 92.7% (95% CI 80.1% to 98.5%) (table 2). In total, 33 (80.5%) patients experienced a reduction in their target lesions from baseline (figure 2A). Sustained decreases in tumor

<table>
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<th>Table 1</th>
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<td>Characteristics</td>
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<tr>
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<tr>
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<td>20 (48.8)</td>
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Data are n (%) unless otherwise indicated.
*Data missing for remaining patients.
†One patient, who had previously experienced brain metastases and undergone whole-brain radiotherapy, demonstrated radiographic evidence of stable disease for at least 1 month and exhibited no accompanying clinical symptoms. This patient met the eligibility criteria for enrolment.
‡Among the patients, one underwent curative lung cancer surgery followed by postoperative mediastinal radiotherapy and adjuvant therapy, achieving a recurrence-free interval of over 6 months post-therapy. Another patient had brain metastases and received whole-brain radiotherapy treatment.
§PD-L1 TPS was assessed per central laboratory testing. However, one patient was un evaluable due to the sample issues, and this patient had PD-L1 TPS of 80% per local assessment.
¶Mandatory fresh biopsy or archival tissue for tTMB was not requested at enrolment.
burdens were observed over multiple assessments for these patients (figure 2B). Figure 2C indicates that the median DoR was not reached (NR, 95% CI 9.1 to NR), with a median TTR of 2.1 months (range 1.4–8.3). A DoR rate of 87.5% (95% CI 58.6% to 96.7%) was observed at 9 months and 77.8% (95% CI 44.2% to 92.6%) at 12 months. ORRs were consistent across all subgroups (eg, sex, age, smoking status, ECOG PS, histological type, presence of liver or brain metastases, PD-L1 TPS, and tissue tumor mutational burden, tTMB; online supplemental table S6).

By the time of the data cut-off, 16 (39.0%) patients had either experienced disease progression or died. According to Kaplan-Meier estimates, the median PFS was 16.6 months (95% CI 8.3 to NR; figure 3A). PFS rates at 6, 9, and 12 months were 76.7% (95% CI 60.0% to 87.2%), 63.8% (95% CI 45.5% to 77.3%), and 58.9% (95% CI 39.6% to 73.9%), respectively. In total, 11 (26.8%) patients died. The median OS with this combination regimen was not yet mature. The estimated 6-month, 9-month, and 12-month OS rates were 90.2% (95% CI 76.1% to 96.2%), 85.4% (95% CI 70.3% to 93.1%), and 76.8% (95% CI 60.0% to 87.3%), respectively (figure 3B).

Antitumor activity in subgroup by smoking status
Tumor responses and survival data in subgroups by smoking status are summarized in online supplemental table S7. The ORR was 60.7% (95% CI 40.6% to 78.5%) in 28 current or former smokers, and 33.3% (95% CI 9.9% to 65.1%) in 12 never smokers.

Antitumor activity in subgroup by PD-L1 TPS and tTMB status
Antitumor activity outcomes based on PD-L1 TPS are summarized in online supplemental table S8. The ORR was 47.6% (95% CI 25.7% to 70.2%) in the 21 patients with PD-L1 TPS 1%–49%, compared with 60.0% (95% CI 36.1% to 80.9%) in the 20 patients with PD-L1 TPS≥50%. On the other hand, 15 patients with PD-L1 TPS levels between 1% and 20% exhibited an ORR of 40.0% (95% CI 16.3% to 67.7%); the ORR for the 26 patients with PD-L1 TPS levels above 20% was 61.5% (95% CI 40.6% to 79.8%). The median PFS was 13.2 months (95% CI 6.2 to NR) in patients with PD-L1 TPS 1%–49%, and not reached (95% CI 4.8 to NR) in those with PD-L1 TPS≥50%, respectively (online supplemental figure S1A). The median PFS was 13.2 months (95% CI 6.2 to NR) in patients with PD-L1 TPS between 1% and 20%, and 16.6 months (95% CI 8.4 to NR) in those with PD-L1 TPS greater than 20%, respectively (online supplemental figure S1B).

Additionally, tTMB data were available for 27 (65.9%) patients, comprising 15 with low tTMB and 12 with high tTMB. The ORR was 46.7% (95% CI 21.3% to 73.4%) in the low tTMB group and 58.3% (95% CI 27.7% to 84.8%) in the high tTMB group. The median PFS was 13.2 months (95% CI 4.1 to NR) for patients with low tTMB and 16.6 months (95% CI 4.1 to NR) for those with high tTMB.

Safety
The median duration for camrelizumab exposure was 10.3 months (range 0.7–24.8), and the relative dose intensity (RDI, defined as the ratio of the delivered dose intensity to the standard dose intensity) was 98.4% (range 72.0–101.0). The median exposure of famitinib was 10.3 months (range 0.5–24.2), with a relative dose intensity of 81.5% (range 47.6–100.0). The relationship between
RDI and treatment outcomes is detailed in online supplemental table S9. In patients on camrelizumab plus famitinib, an RDI below 80% for either drug correlated with longer drug exposure compared with those with an RDI of 80% or higher for both drugs. Importantly, a reduced RDI did not appear to negatively impact treatment outcomes.

As shown in Table 3, 40 (97.6%) patients experienced at least one TRAE. The most common TRAEs of any grade were decreased neutrophil count (n=25, 61.0%), anemia (n=25, 61.0%), proteinuria (n=21, 51.2%), and increased alanine aminotransferase (ALT, n=19, 46.3%). Twenty-seven (65.9%) patients experienced TRAEs of grade 3 or higher; the most common, occurring in more than 5% of patients, were hypertension (n=9, 22.0%), increased ALT (n=5, 12.2%), decreased neutrophil count (n=4, 9.8%), proteinuria (n=3, 7.3%), decreased platelet count (n=3, 7.3%), and hypokalemia (n=3, 7.3%).

Reactive cutaneous capillary endothelial proliferation (RCCEP), a common and self-limiting TRAE caused by camrelizumab monotherapy, was observed in 19.5% of patients (n=8) receiving the combination of camrelizumab and famitinib. No RCCEP events of grade 3 or higher were reported; the events were categorized as grade 1 in 17.1% of patients (n=7) and as grade 2 in 2.4% (n=1).

Treatment-related SAEs of grade 3 or higher occurred in 11 (26.8%) patients, as detailed in online supplemental table S10. These included increased ALT (n=3, 7.3%), vomiting (n=2, 4.9%), increased aspartate aminotransferase (AST), decreased platelet count, ECG ST segment elevation, diarrhea, ileus paralytic, hemoptysis, fever, diabetes mellitus, immune-mediated hepatitis, and cerebral infarction (n=1 for each; 2.4%). One patient (2.4%), diagnosed with adenocarcinoma and with no history of hypertension, died from grade 5 hemoptysis. This fatal event occurred within a month after treatment initiation. Baseline radiographic assessments revealed that the patient had central-type lung cancer, characterized by a large 85 mm mass in the left hilum. This mass displayed cavitation and enveloped the left hilar vessels, likely contributing to the hemoptysis. According to the investigator’s assessment, the primary cause of death was attributed to tumor progression, and this AE was considered possibly related to the study treatment.

Figure 2  Antitumor activity of camrelizumab plus famitinib in all patients. (A) Best change from baseline in target lesions. (B) Treatment response and duration. (C) Percentage change from baseline in target lesion tumor burden over time. NE, not evaluable; PD, progressive disease; PD-L1, programmed death ligand-1; PR, partial response; SD, stable disease; TPS, tumor proportion score.
Only one (2.4%) patient discontinued camrelizumab because of grade 2 increased blood creatinine. Seven (17.1%) patients discontinued famitinib due to TRAEs that were cerebral infarction (4.9%, n=2, grade 2 and grade 3), and grade 2 increased blood creatinine, grade 2 atrial fibrillation, grade 3 increased ALT, grade 3 increased AST, grade 3 decreased platelet count, and grade 3 palmar-plantar erythrodysaesthesia syndrome (n=1 for each, 2.4%).

TRAEs leading to dose modification are listed in online supplemental table S11. TRAEs led to dose interruption of camrelizumab in 9 (22.0%) patients, with increased ALT (n=4, 9.8%), increased AST (n=3, 7.3%), and immune-mediated lung disease (n=2, 4.9%) occurring in more than one patient. Twenty-six (63.4%) patients experienced at least one TRAE leading to famitinib interruption, primarily including hypertension (n=10, 24.4%), increased ALT (n=6, 14.6%), increased AST (n=5, 12.2%), proteinuria (n=5, 12.2%), and decreased neutrophil count (n=4, 9.8%). TRAEs led to dose reduction of famitinib in 22 (53.7%) patients, with increased ALT, increased AST and hypertension (n=6 for each, 14.6%) occurring in more than four patients. TRAEs leading to the reduction in dosage frequency of famitinib occurred in 12 (29.3%) patients, with vomiting and decreased neutrophil count (n=2 for each, 4.9%) occurring in more than one patient. In regard to symptoms
arising from TRAEs, all subsequent AEs following dose reductions or interruptions were meticulously documented. To enhance analytical clarity, temporally contiguous AEs falling under the same preferred term were aggregated into single records, resulting in a total of 117 documented AEs. Following the initial dose modification, these AEs were categorized based on their resolution status: 14 AEs were classified as not recovered, 42 as recovering, and 61 as recovered.

Regardless of attribution, immune-mediated AEs of any grade occurred in 9 (22.0%) patients, with the most common being hypothyroidism, increased blood creatinine, and immune-mediated lung disease (n=2 for each; 4.9%; online supplemental table S12).

**DISCUSSION**

In this multicenter phase 2 trial, camrelizumab in combination with famitinib showed promising efficacy with an ORR of 53.7% and a median PFS of 16.6 months, providing a durable clinical benefit and an acceptable toxicity profile as a first-line setting in advanced or metastatic NSCLC patients with PD-L1 expression TPS ≥1% and EGFR and ALK wide-type. These results suggest that the combination of camrelizumab and famitinib might be a potent novel frontline regimen and warrant further validation in this patient population.

Patients treated with this combination regimen derived an ORR of 53.7%. Despite differences in study...
designs and population enrichment across trials, this rate was comparable with the rates achieved with camrelizumab-based chemotherapy (60.5%) in the phase 3 CameL trial,19 and with sintilimab plus anlotinib (69.2%) in a phase 1b study31; it was also slightly superior to that following pembrolizumab monotherapy (51.3%) in the phase 3 Keynote-042 China study,29 pembrolizumab plus ramucirumab (42.3%) in the phase I JVDF trial,30 or pembrolizumab plus lenvatinib (40.5%) in the phase 3 LEAP-007 trial,31 for the treatment of advanced or metastatic NSCLC patients without EGFR/ALK alterations whose tumor expressed PD-L1 TPS≥1%. Consistent ORRs were observed across all subgroups, including those with poor prognostic factors, suggesting that a wide range of patients could benefit from this combination regimen.

Despite the challenge of cross-trial comparisons, the median PFS with this combination regimen achieved the longest absolute value (16.6 months), when compared with that of camrelizumab plus chemotherapy (15.4 months),19 that of pembrolizumab plus ramucirumab (9.3 months)30 or pembrolizumab with lenvatinib (6.6 months),31 in the PD-L1-positive patient population. Remarkably, after a median follow-up of 12.5 months, the median OS with camrelizumab plus famitinib was still not mature, with a 12-month OS rate of 76.8%. This rate was comparable to the 68.8% observed in patients with a PD-L1 TPS of ≥1% who were treated with pembrolizumab monotherapy, as reported in the phase 3 Keynote-042 China study.39 However, the phase 3 LEAP-007 trial revealed that pembrolizumab (200mg every 3 weeks) plus lenvatinib (20mg once daily) did not extend OS compared with pembrolizumab monotherapy (14.1 months vs 16.4 months) in the treatment of patients with NSCLC, although this combination regimen resulted in an improved ORR (40.5% vs 27.7%) and prolonged PFS (6.6 months vs 4.2 months).30 The undesirable outcomes may be attributed to TRAE that led to the discontinuation of lenvatinib in 27.5% of patients on pembrolizumab plus lenvatinib, suggesting that a full dose of lenvatinib could compromise long-term OS benefit. Furthermore, the final OS analysis of the CONTACT-01 phase 3 trial reported similar results for atezolizumab plus cabozantinib (10.7 months) compared with docetaxel (10.5 months) in patients with metastatic NSCLC who progressed on anti-PD-L1 inhibitors and chemotherapy.32 On the other hand, camrelizumab plus famitinib not only produced a respectable ORR, durable DoR and PFS, but also demonstrated a notable benefits in OS, warranting further validation.

Our results aligned with existing literature, suggesting that NSCLC patients who are current or former smokers often experience favorable treatment outcomes. A plausible explanation for this differential response might be that smokers generally exhibit higher PD-L1 TPS scores, stronger immunogenicity, and more activated immune microenvironments,33-35 PD-L1 expression and TMB have established biomarkers for the efficacy of ICI monotherapy.2 14 19 26 36 In this cohort, compared with patients with lower PD-L1 expression, those with higher PD-L1 expression showed a higher ORR (60.0% for TPS≥50% vs 47.6% for TPS 1%–49%; 61.5% for TPS>20% vs 40.0% for TPS 1%–20%) and longer median PFS (NR for TPS≥50% vs 13.2 months for TPS 1%–49%; 16.6 months for TPS>20% v 13.2 months for TPS 1%–20%) when treated with camrelizumab plus famitinib. This trend was consistent with previously reported trial involving camrelizumab monotherapy in various PD-L1 expression cohorts of pretreated advanced/metastatic NSCLC.35

Meanwhile, we also observed a trend of improved ORR (58.3% vs 46.7%) and prolonged PFS (16.6 months vs 13.2 months) in patients with high tTMB compared with those with low tTMB. Although our study was not designed to detect a significant association between PD-L1 TPS or tTMB and clinical benefit with this chemotherapy-free combination regimen, our findings suggested that adding antiangiogenic TKIs to anti-PD-1 immunotherapy may benefit advanced or metastatic non-small cell lung cancer (NSCLC) patients, irrespective of PD-L1 expression or TMB status. Therefore, a more comprehensive analysis of biomarkers in advanced or metastatic NSCLC receiving this combination regimen is warranted.

In this cohort, the most common TRAEs were decreased neutrophil count and anemia, each observed in 61.0% of patients. This safety profile is consistent with previous findings in patients treated with the same regimen for advanced or metastatic renal cell carcinoma, urothelial carcinoma, and ovarian cancer,25-29 with no new safety signals identified. However, this differs from the TRAE spectrum reported in the LEAP-007 phase 3 trial,31 where the most common TRAEs for lenvatinib plus pembrolizumab were hypertension and hypothyroidism (36.2% each), and rates of decreased neutrophil count and anemia were below 10%. In a previous phase 2 trial, camrelizumab monotherapy, used as second-line treatment in previously treated advanced/metastatic NSCLC, resulted in TRAEs with anemia occurring in 6.8% of patients and decreased neutrophil count in≤5% of patients.37 Additionally, the CameL and CameL-Sq phase 3 trials showed that adding camrelizumab to chemotherapy did not obviously increase hematological toxicities compared with chemotherapy alone in NSCLC patients.39 40 Therefore, the hematological toxicities in our cohort are likely primarily due to famitinib. The majority of decreased neutrophil count and anemia cases were grade 1 or 2 and were effectively managed with dose interruption and/or reduction, along with standard supportive care. Hypertension, proteinuria, and PPE syndrome may also be attributable to famitinib, reflecting its antiangiogenic properties.21 38 39 In contrast to the 67%-97% incidence of RCCEP observed with camrelizumab monotherapy,40 its occurrence was considerably lower in this cohort (8/41; 19.5%); with no grade 3 or higher events reported. Consistent with earlier studies, a reduced incidence of RCCEP was observed in


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patients receiving combined camrelizumab plus VEGFR TKI therapy, suggesting a role for the VEGFA/VEGFR2 pathway in the pathogenesis of RCEP. This combination regimen led to a slight increase in the occurrences of TRAEs that resulted in famitinib dose reduction (15 mg once daily, 53.7%) and modifications in famitinib dosing frequency (29.3%). In cohort 2, the majority of patients who experienced a dose reduction or interruption showed improvement or recovery from TRAEs. Interestingly, a reduced RDI did not appear to negatively impact treatment outcomes. This phenomenon may be partly explained by a potential correlation between lower RDI and longer duration of drug exposure. The observed low rates of treatment discontinuation due to TRAEs in this cohort, 2.4% for camrelizumab and 17.1% for famitinib, indicated that the combination regimen was well tolerated. This observation was particularly noteworthy in comparison to the LEAP 007 clinical trial, where TRAEs resulted in discontinuation rates of 27.5% for lenvatinib and 14.6% for pembrolizumab in the lenvatinib plus pembrolizumab arm. The incidence rates of cerebral infarction have been reported as rare in previous clinical trials, both for camrelizumab monotherapy and for the combination treatment of camrelizumab and famitinib. One patient (2.4%) with adenocarcinoma and no history of hypertension experienced grade 5 hemoptysis and died within a month of starting treatment. Baseline scans revealed a large 85-mm mass in the left hilum, which may have contributed to the hemoptysis. The death was primarily attributed to tumor progression by the investigator, and its relation to the study treatment was deemed possible.

This study possessed several limitations that warrant discussion. First, due to its single-arm, exploratory design, a standard-of-care control arm featuring camrelizumab monotherapy was not available. Consequently, the study was not equipped to definitively assess whether the benefits of adding famitinib outweighed its associated toxicities, or to pinpoint specific patient subgroups that might have benefited the most from this combination regimen. To tackle these critical questions, an ongoing phase 3 trial (NCT05042375) is being conducted. This trial offered a more robust design, featuring three chemotherapy-free treatment arms: camrelizumab plus famitinib, pembrolizumab monotherapy, and camrelizumab monotherapy, all as first-line treatments for advanced NSCLC patients with a PD-L1 TPS of ≥1%. This configuration enabled a nuanced assessment of the risks and benefits by directly comparing camrelizumab monotherapy to the combination regimen of camrelizumab and famitinib. Second, aside from PD-L1 expression, some patients did not have sufficient samples for tTMB or other biomarker analysis. This underscores the need for further investigation to identify relevant biomarkers for this combination in similar patient populations.

In conclusion, camrelizumab plus famitinib, when used as a first-line treatment, showed encouraging and durable clinical activity with a tolerable toxicity profile in advanced or metastatic NSCLC patients with PD-L1 TPS≥1%. This combination might provide an attractive chemotherapy-free regimen option and should be further validated in an ongoing multicenter, randomized phase 3 clinical trial (NCT05042375).

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