Study protocol: A single-arm, multicenter, phase II trial of camrelizumab plus apatinib for advanced nonsquamous NSCLC previously treated with first-line immunotherapy

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Abstract
Background: For advanced nonsquamous non-small cell lung cancer (NSCLC), the mechanisms of resistance to first-line immunotherapy are not clear. Immune checkpoint inhibitors (ICIs) in combination with agents targeting other pathways may serve as second-line therapy options. Apatinib (a vascular endothelial growth factor receptor 2 tyrosine kinase inhibitor) could increase the efficacy of camrelizumab (an ICI agent). The efficacy and safety of this combination regimen as a second-line therapy for NSCLC patients after failure on first-line immunotherapy has not previously been evaluated.

Methods: In this single-arm, multicenter, phase II trial, metastatic nonsquamous NSCLC patients previously treated with single-agent ICI or ICI plus chemotherapy will be enrolled. Participants will receive intravenous camrelizumab 200 mg D1 and oral apatinib 250 mg D1-21 for a 21-day cycle. The study treatment will continue until disease progression, unacceptable toxicity, or withdrawal of consent. The primary endpoint is progression-free survival by investigator. Secondary endpoints are overall survival, objective response rate, disease control rate, duration of response by investigator, quality of life, safety, and toxicity.

Conclusions: This trial will provide evidence of the benefit of treatment with camrelizumab combined with apatinib in advanced nonsquamous NSCLC patients who were previously treated with first-line immunotherapy.

Keywords
apatinib, camrelizumab, immune checkpoint inhibitors, non-small cell lung cancer, second-line treatment

INTRODUCTION
Lung cancer is considered the most common cause of cancer death.1 Non-small cell lung cancer (NSCLC) accounts for nearly 85% of lung cancer cases.2 About 70% of patients with NSCLC are diagnosed at an advanced stage.3 For advanced or metastatic disease with negative driver gene and programmed death-ligand 1 (PD-L1) expression ≥1%, the standard first-line treatment is immune checkpoint inhibitors (ICIs), with or without chemotherapy,4 and second-line therapy is chemotherapy.

For advanced NSCLC, although the mechanisms of resistance to first-line immunotherapy are not clear, studies have shown the efficacy of ICI rechallenge on patients with progression during first-line ICIs. A retrospective analysis of the phase III OAK study indicated that patients who received atezolizumab treatment beyond progression (TBP) had a numerically longer median overall survival (OS).5 The OS in the atezolizumab TBP arm (n = 168; 19.6% had received second-line therapy), other anticancer treatment arm (n = 94), and no anticancer treatment arm (n = 70) were 12.7 months...
Longed survival in lung cancer mouse models. Promisingly inhibited tumor growth and metastases, and pro-
receptor 2 (VEGFR2) TKI, combined with an ICI significa-
low-dose apatinib, a vascular endothelial growth factor
vs. chemotherapy 

phase II trial was designed to assess the efficacy and safety
patients after failure on first-line immunotherapy. This
can bring benefit to advanced nonsquamous NSCLC
Therefore, we hypothesized that camrelizumab plus apatinib
ously treated with immunotherapy has not been explored.

second-line therapy for NSCLC patients who were previ-

interval [CI]: 0.23–0.69). In the KEYNOTE-146/study
111, 21 patients were enrolled in the NSCLC cohort, in which
11 (52.4%) had received prior ICIs and 11 (52.4%) had received
≥2 prior lines of therapy. All participants received pembrol-
lizumab plus lenvatinib (a multitargeted tyrosine kinase inhibi-
tor [TKI]). As a result, seven (33.3%) achieved objective
response and the median PFS was 5.9 months. Each anti-
programmed death 1 (PD-1)/PD-L1 antibody targeted different
sites of PD-1/PD-L1. Thus, patients who previously treated
with immunotherapy may benefit from the same or different
kind of ICIs with or without antiangiogenic agents.

Camrelizumab (SHR-1210) is an anti-PD-1 antibody,
whose binding sites (CC’ and FG loop of PD-1) is distinct
from pembrolizumab (C’D loop) and nivolumab (BC loop). CameL, a phase III trial, has confirmed the efficacy of
camrelizumab plus chemotherapy as first-line treatment for
advanced or metastatic nonsquamous NSCLC. The hazard
ratio for PFS (camrelizumab plus chemotherapy [n = 205]
vs. chemotherapy [n = 207]) was 0.60 (95% CI: 0.45–0.79).

Furthermore, an in vivo and clinical study suggested
low-dose apatinib, a vascular endothelial growth factor
receptor 2 (VEGFR2) TKI, combined with an ICI significa-

tively inhibited tumor growth and metastases, and pro-
longed survival in lung cancer mouse models. Promising
anticancer activity has also been observed in pretreated
advanced NSCLC patients. Another phase II trial has also
shown the efficacy of camrelizumab in combination with
apatinib on NSCLC after failure of first-line chemotherapy,
with an objective response rate (ORR) of 30.9%, median PFS
of 5.7 months, and median OS of 15.5 months.12

However, the efficacy of camrelizumab plus apatinib as
a second-line therapy for NSCLC patients who were previ-
ously treated with immunotherapy has not been explored.
Therefore, we hypothesized that camrelizumab plus apatinib
can bring benefit to advanced nonsquamous NSCLC
patients after failure on first-line immunotherapy. This
phase II trial was designed to assess the efficacy and safety
of the combination regimen.

The protocol was approved by the ethics committees of all
participating centers, and the trial will be conducted in
compliance with the Good Clinical Practice principles and
the Declaration of Helsinki. All patients will provide written
informed consent before participation.

Eligibility criteria

Patients aged 18–75 years, with stage IIB/IV nonsquamous
NSCLC, previously treated with single-agent ICI (including
camrelizumab) or ICIs in combination with chemotherapy
as first-line treatment, whose best objective response was
stable disease or better, and PFS was longer than 3 months
with an Eastern Cooperative Oncology Group (ECOG) per-
formance status of 0 or 1, life expectancy ≥12 weeks, mea-
surable disease according to the Response Evaluation
Criteria in Solid Tumors (RECIST), version 1.1, and ade-
quate organ function are eligible for inclusion in the study.
Key exclusion criteria are previous treatment with anticancer
virus therapy, T cell costimulation therapy (e.g., cytotoxic
T lymphocyte-associated protein 4 [CTLA-4] inhibitors), or
antiangiogenic drugs, intolerance to the ICI during first-line
treatment, autoimmune disease, pulmonary tuberculosis,
active brain metastasis or pneumonitis, radiotherapy within
4 weeks, antiplatelet or anticoagulation treatment within
10 days after study treatment initiation, and the presence of
tumor invasion of local major blood vessels.

Treatment

Participants will receive intravenous camrelizumab 200 mg D1
and oral apatinib 250 mg D1–D21 for a 21-day cycle. Combin-
tation therapy will continue until disease progression, unaccept-
able toxicity, or withdrawal of consent. After progression, study
treatment can continue at the discretion of the investigators.

When adverse events (AEs) prespecified according to
the protocol occur, camrelizumab will be suspended until
AEs revert to grade 1 or less, or be discontinued. Dose
reduction of camrelizumab is not permitted. Additionally, if
camrelizumab suspension lasts for more than 9 weeks,
camrelizumab will also be discontinued.

When AEs caused by apatinib occur, treatment will be
suspended or administered every other day until AEs revert
to grade 1 or less, or discontinued according to the protocol.

Study assessment and endpoints

Tumors will be assessed using CT or MRI per RECIST ver-
sion 1.1 within 28 days before treatment initiation and then
every 6 weeks after the start of the study until disease pro-
gression or study treatment discontinuation. Quality of life
(QoL) will be determined by the European Organization for
the Research and Treatment of Cancer Quality of Life Ques-
tionnaire Core 30 (EORTC QLQ-C30; version 3, Chinese

METHODS

Study design

This nonrandomized, open-label, single-arm, multicenter,
phase II trial (NCT04670913) aimed to evaluate the efficacy
and safety of camrelizumab combined with apatinib in patients
with metastatic nonsquamous NSCLC previously treated with
first-line immunotherapy. Table 1 is the SPIRIT flow diagram.
Interventions:
Camrelizumab 200 mg D1
Apatinib 250 mg D1-21

Assessments:
Tumor X X (every 6 weeks)
Quality of life X X X X X
Survival X X X X X
Adverse events X X X X X
Serum and plasma samples e X X

†One cycle is 21 days.
‡Last assessment of quality of life is at 30 days after the end of treatment.
§Survival was assessed every 3 months.
¶Last assessment of adverse events is at 90 days after the end of camrelizumab treatment or 30 days after the end of apatinib treatment (whichever is later).

Clinical and laboratory follow-up at all visits except for the visit at 30 days after discontinuing treatment, if applicable.

Statistical considerations
The median PFS has previously been reported to be 2.8 months for docetaxel. The expected median PFS is 5.1 months for the study treatment. Assuming an enrolment period of 12 months and a follow-up period of 6 months, 24 patients were calculated with a power of 80% and a one-sided \( \alpha \) of 5%. Considering the 20% dropout rate, 30 patients are required for the study.

All patients, who have received at least one dose of study, will be considered in the efficacy analysis. Safety will be assessed in all patients who received at least one dose of the treatment and safety evaluation.

The curves of PFS, OS and DoR will be plotted using Kaplan–Meier method, and the median and 95% CIs of these endpoints will be estimated by log–log method.

For ORR and DCR, the rates and corresponding 95% CIs will be calculated using the Clopper-Pearson method.

Descriptive statistics will be applied for EORTC QLQ-C30/LC13 of each timepoint and the changes from baseline, and safety analysis.

DISCUSSION
ICIs are the standard first-line treatment for advanced or metastatic NSCLC patients with negative driver gene and PD-L1 expression level ≥1%. A previous study has indicated the efficacy of atezolizumab TBP. ICI rechallenge after first-line immunotherapy failure has also demonstrated potential benefit.

A phase III trial has shown that camrelizumab plus chemotherapy as first-line treatment can bring benefit to advanced or metastatic nonsquamous NSCLC. Pilot studies have demonstrated that the combination treatment enhanced...
the anticancer capability as higher-line therapy in advanced NSCLC patients previously treated with chemotherapy.\textsuperscript{11,12}

Additionally, for advanced hepatocellular carcinoma and cervical cancer, camrelizumab plus apatinib is also a potential option. Thus, the regimen has promising anticancer activity in solid tumors and is worthy of further investigation.

However, there is a lack of assessment of combined treatment for NSCLC patients previously treated with immunotherapy. The present single-arm, multicenter, phase II trial aims to evaluate the efficacy and safety of camrelizumab combined with apatinib.

In addition, as an antiangiogenic agent, apatinib could also inhibit reactive cutaneous capillary endothelial proliferation (an immune-related adverse event arising from camrelizumab), which is an immune response of skin capillary endothelial cells. Thus, for camrelizumab, we postulate that additional apatinib could increase efficacy and reduce the certain toxicity on advanced nonsquamous NSCLC patients previously treated with first-line immunotherapy.

The present study has several limitations. First, because the present trial is an exploratory study, the sample size has not been calculated and is set at 30. Second, it is a single-arm, phase II trial, and if the regimen demonstrates potent anticancer activity, the efficacy should be confirmed in a randomized, controlled phase III study.

There are three similar trials. All of them are still ongoing, and no results have so far been revealed. A single-arm, phase II trial (NCT03689855) was designed to assess atezolizumab in combination with ramucirumab (an anti-VEGFR2 antibody). In the other two randomized, controlled phase III trials, the efficacy and safety of atezolizumab plus cabozantinib (a multitargeted TKI) versus docetaxel (NCT04471428), and pembrolizumab plus lenvatinib versus docetaxel plus lenvatinib (NCT03976375) will be compared. The present trial and these three studies will provide evidence of the benefit of ICIs combined with antiangiogenic agents/multitargeted TKI for advanced nonsquamous NSCLC patients previously treated with first-line immunotherapy.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
2. Chen Z, Fillmore CM, Hamme rman PS, Kim CF, Wong K-K. Non-small-cell lung cancers: a heterogeneous set of diseases. Nat Rev Cancer. 2014;14:535–46.
3. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc. 2008;83:584–94.
4. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines\textsuperscript{6}) Non-Small Cell Lung Cancer Version 1.2021. \text{https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf}. Accessed 25 Nov 2020.
5. Gandara DR, von Pawel J, Mazieres J, Sullivan R, Helland Å, Han J-Y, et al. Atezolizumab treatment beyond progression in advanced NSCLC: results from the randomized, phase III OAK study. J Thorac Oncol. 2018;13:1906–18.
6. Fujita K, Uchida N, Kanai O, Okamura M, Nakatani K, Mio T. Retreatment with pembrolizumab in advanced non-small cell lung cancer patients previously treated with nivolumab: emerging reports of 12 cases. Cancer Chemother Pharmacol. 2018;81:1105–9.
7. Ge X, Zhang Z, Zhang S, Yuan F, Zhang F, Yan X, et al. Immunotherapy beyond progression in patients with advanced non-small cell lung cancer. Transl Lung Cancer Res. 2020;9:2391–400.
8. Taylor MH, Lee C-H, Makker V, Raso D, Dutuc CE, Wu J, et al. Phase IB/II trial of lenvatinib plus pembrolizumab in patients with advanced renal cell carcinoma, endometrial cancer, and other selected advanced solid tumors. J Clin Oncol. 2020;38:1154–63.
9. Lee HT, Lee SH, Heo Y-S. Molecular interactions of antibody drugs targeting PD-1, PD-L1, and CTLA-4 in immu-no-oncology. Molecules. 2019;24:1190.
10. Zhou C, Chen G, Huang Y, Zhou J, Lin L, Feng J, et al. Camrelizumab plus carboplatin and pemetrexed versus chemotherapy alone in chemotherapy-naive patients with advanced non-squamous non-small-cell lung cancer (Camel): a randomised, open-label, multicentre, phase 3 trial. Lancet Respir Med. 2021;9:305–14.
11. Zhao S, Ren S, Jiang T, Zhu B, Li X, Zhao C, et al. Low-dose apatinib optimizes tumor microenvironment and potentiates antitumor effect of PD-1/PD-L1 blockade in lung cancer. Cancer Immunol Res. 2019;7:630–43.
12. Zhou C, Wang Y, Zhao J, Chen G, Liu Z, Gu K, et al. Efficacy and biomarker analysis of camrelizumab in combination with apatinib in patients with advanced non-squamous NSCLC previously treated with chemotherapy. Clin Cancer Res. 2021;27:1296–304.
13. Wu Y-L, Lu S, Cheng Y, Zhou C, Wang J, Mok T, et al. Nivolumab versus docetaxel in a predominantly Chinese patient population with previously treated advanced NSCLC: CheckMate 078 randomized phase III clinical trial. J Thorac Oncol. 2019;14:867–75.

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