Original Article

Efficacy and safety of camrelizumab plus apatinib in previously treated patients with advanced non-small cell lung cancer harboring *EGFR* or *ALK* genetic aberration

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Background: Camrelizumab plus apatinib shows encouraging antitumor activity and acceptable toxicity in chemotherapy-pretreated patients with advanced non-small cell lung cancer (NSCLC); however, clinical benefits from this combination regimen in NSCLC patients with EGFR mutations or ALK rearrangements (EGFR+/ALK+) have not been reported. We assessed the efficacy and safety of this combined regimen in pretreated patients with advanced NSCLC and defined EGFR/ALK status (EGFR+/ALK+) in a phase 1b/2 trial.

Methods: Previously treated patients with advanced EGFR+/ALK+ NSCLC were enrolled and given camrelizumab 200 mg intravenously every 2 weeks plus apatinib at the recommended dose of 250 mg orally once daily. Patients harboring sensitive EGFR mutations or ALK fusion genes had received at least one EGFR/ALK TKI and a platinum-based chemotherapy regimen before the enrollment. The primary endpoint was objective response rate (ORR).

Results: All 43 enrolled patients comprised the efficacy and safety analysis population. The confirmed ORR was 18.6% (95% CI: 8.4–33.4%) and the clinical benefit response rate was 27.9% (95% CI: 15.3–43.7%). Median progression-free survival (PFS) was 2.8 months (95% CI: 1.9–5.5 months) and median overall survival was not reached (95% CI: 7.3 months–not reached), with a median follow-up period of 15.7 months (range, 0.5–24.4 months). The most common grade ≥3 treatment-related adverse events (TRAEs) were hypertension (16.3%), proteinuria (11.6%) and palmar-plantar erythrodysaesthesia syndrome (9.3%). No unexpected

adverse events were recorded.

Conclusions: Camrelizumab plus apatinib showed moderate antitumor activity and acceptable safety profile in previously treated patients with advanced NSCLC and EGFR or ALK genetic aberrations, which warranted further validation.

Trial Registration: ClinicalTrials.gov identifier: NCT03083041. Registered March 17, 2017.

Keywords: Camrelizumab; Apatinib; PD-L1 expression; immunotherapy

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Introduction

Targeted therapies and immunotherapy have expanded therapeutic options in patients with advanced non-small cell lung cancer (NSCLC) over the past decade (1). The therapy landscape for NSCLC patients with epidermal growth factor receptor (*EGFR*) tyrosine kinase mutations and anaplastic lymphoma kinase (ALK) rearrangements (*EGFR+/ALK+*) have been radically revolutionized based on genetic alteration in actionable oncogene drivers (2). Despite the prominent activity of tyrosine kinase inhibitors (TKIs) in these patients (3), acquired resistance almost inevitably develops (4,5), and there are no standard options after *EGFR/ALK* TKIs and platinum-based chemotherapy.

In recent years, immune checkpoint inhibitors (ICIs) have become additional important treatment options for advanced NSCLC (6-8). However, a previous retrospective study indicated that NSCLC harboring *EGFR* mutations or *ALK* rearrangements are associated with low objective response rates (ORRs) to programmed death 1 (PD-1)/PD ligand 1 (PD-L1) inhibitors (9). In addition, the only evidence available to date in regard of PD-1 axis blockade (durvalumab monotherapy) as the third- or later-line treatment in patients with *EGFR+/ALK+* NSCLC comes from the ATLANTIC phase 2 study (10). So far, the definite clinical benefits of anti-PD-1/PD-L1 monotherapy or combination regimen in pretreated patients with *EGFR+/ALK+* NSCLC who have progressed after prior TKI and/or chemotherapy are still unclear.

Camrelizumab (SHR-1210) is a humanized anti-PD-1 IgG4 monoclonal antibody. The combination of camrelizumab and chemotherapy (carboplatin and pemetrexed) has been approved for the treatment of patients with chemotherapy-naive, advanced non-squamous NSCLC without *EGFR* and *ALK* alterations in China in June 2020 (11). Apatinib, a vascular endothelial growth factor receptor 2 (VEGFR2) TKI, has been approved as a third- or subsequent line treatment for advanced gastric cancer in China (12). Recently, combining anti-PD-1 antibodies with anti-angiogenic agents has been attracting great interest. Preliminary preclinical study has revealed that apatinib alleviates hypoxia through modulating tumor immune microenvironment, enhances tumoral infiltration of $CD8^+$ T cells, and limits immunosuppressive activity of tumor-associated macrophages (13). Additionally, encouraging results from the phase 1b/2 trials also indicated that camrelizumab plus apatinib, administrated at the recommended phase II dose (RP2D; apatinib 250 mg), showed promising antitumor activities and manageable safety profile in patients with advance hepatocellular carcinoma, gastric cancer or non-squamous NSCLC (14,15). Nevertheless, no relevant clinical evidence is available for the antitumor activity of the combination therapy of anti-PD-1 inhibitor plus angiogenesis inhibitors in patients with advanced *EGFR+/ALK+* NSCLC. There is an unmet clinical need for more effective subsequent treatment options in this patient population. Therefore, we conducted a phase 1b/2 trial to explore the efficacy and safety of camrelizumab plus apatinib in pretreated patients with advanced *EGFR+/ALK+* NSCLC and present the results in accordance with the TREND reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-22/rc).

Methods

Study design

This phase 1b/2, open-label, multicenter, multicohort study enrolled patients with advanced NSCLC at 16 medical centers in China. It was registered at Clinical Trials.gov with the identifier NCT03083041. This trial consisted of 2 parts:

a phase 1b dose-escalation part and a phase 2 dose-expansion part. Part 1 was designed to evaluate the tolerability, safety, pharmacokinetics, and pharmacodynamics of camrelizumab in combination with apatinib and to determine the RP2D of apatinib. Part 2 was designed to further assess the efficacy and safety of camrelizumab plus apatinib at RP2D (15). Here, we only reported the preliminary efficacy and safety of camrelizumab plus apatinib in previously treated patients with *EGFR+/ALK+* NSCLC.

Patients

Eligible patients were aged 18–70 years old, who had a histologically or cytologically confirmed advanced NSCLC (stage IIIB or IV) harboring *EGFR* mutations within exons 18–21 or *ALK* fusion gene rearrangements. Patients had disease progression or recurrence occurred after at least one platinum-based doublet chemotherapy and patients harboring sensitive *EGFR* mutations or *ALK* fusion genes should also have received at least one TKI(s) targeting *EGFR* or *ALK*. Other key eligibility criteria included at least 1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; a life expectancy of ≥12 weeks; and adequate organ functions. Patients were excluded if they had any of the following: active or history of autoimmune disease; use of immunosuppressive agents within 2 weeks before study entry; previous treatment with anti-PD-1/PD-L1 monoclonal antibody or apatinib; untreated central nervous system metastases; evidence of major blood vessel invasion; and intratumor cavitation or necrosis. All patients were required to provide a fresh or archival tissue sample for exploratory analyses. The study protocol and amendments were reviewed and approved by the Ethics Committees of each study site (Table S1). The study was conducted in compliance with the Good Clinical Practice Guidelines, the Declaration of Helsinki and its amendments. All patients provided written informed consent before enrollment.

Procedures

Patients enrolled were administered a fixed dose of camrelizumab (200 mg intravenously once every 2 weeks) plus the RP2D of apatinib (250 mg orally once daily established by the phase 1b study) every 4-week cycle until disease progression, intolerable toxicity, patient withdrawal, investigator withdrawal, or camrelizumab treatment for up to 2 years, whichever occurred first (16). Dose modification of camrelizumab was not allowed and dose interruptions of camrelizumab were permitted for up to 12 weeks. Dose interruption, dose reduction, administration schedule modifications (initial modification: 5 days on, 2 days off; subsequent modification: 1 day on, 1 day off) were allowed. Investigator-assessed tumor response were performed every 2 cycles during the first 6 months, and every 3 cycles thereafter according to the RECIST version 1.1. Initial complete response (CR) or partial response (PR) was required to be confirmed at least 4 weeks later. Patients who had radiologically progressive disease (PD) could continue study treatment at the investigator's discretion. Patients who discontinued study treatment for reasons other than radiographic disease progression continued tumor assessment every 3 months until documented disease progression, start of a new anticancer therapy, or death. After treatment discontinuation, patients were followed every 2 months to collect survival.

Adverse events (AEs) were collected and coded according to the Medical Dictionary for Regulatory Activities Version 23.1, and graded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, and the causality to study drugs was recorded. AEs and serious AEs were monitored until 90 days after the last dose of camrelizumab or 30 days after the last dose of apatinib, whichever occurred later.

Detection of PD-L1 expression

PD-L1 expression was centrally assessed using immunohistochemistry (IHC) method with 22C3 pharmDx kit (Agilent Technologies, Santa Clara, CA, USA). PD-L1 positivity was defined as the tumor proportion score (TPS) ≥1%, which was estimated as percentage of viable tumor cells (TCs) showing partial or complete membrane staining (17).

Endpoints and assessments

The primary endpoint was ORR per RECIST version 1.1, defined as the proportion of patients achieving a confirmed CR or PR based on investigators' assessment. The secondary endpoints included clinical benefit rate [CBR; defined as the proportion of patients with CR or PR, or stable disease (SD) lasting ≥24 weeks], duration of response (DoR; defined as time from first evidence of CR or PR to

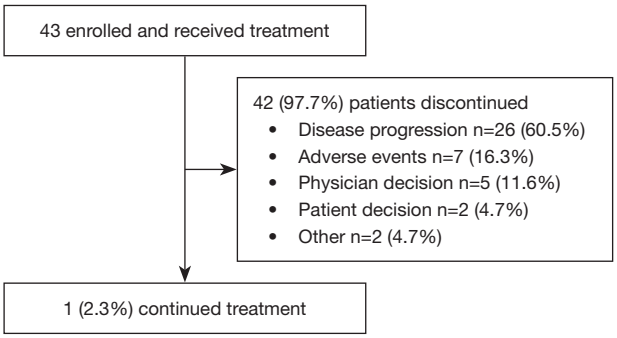

Figure 1 Flow chart of patients with advanced *EGFR+/ALK+* non-small cell lung cancer (n=43). *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase.

disease progression or death, whichever occurred first), progression-free survival (PFS; defined as time from first dose of study treatment to disease progression per RECIST version 1.1 or death, whichever occurred first), OS (defined as time from first dose of study treatment to death due to any cause), 12-month OS rate, and safety. Exploratory analysis on ORR, and survival data by PD-L1 TPS or *EGFR* subtypes were also performed.

Statistical analysis

Assuming an ORR of 30% and a dropout rate of 20%, a sample size of 38 patients was able to ensure the width of 90% confidence interval (CI) for ORR would be 0.30.

The full analysis set included all patients who received at least one dose of study treatment, and all patients who received at least one dose of study treatment and had safety assessment after treatment initiation were included in the safety analysis set. The ORR and CBR and the corresponding 95% CIs were calculated using the Clopper-Pearson method. Median and range of time to response (TTR) were calculated. Kaplan-Meier method was used to estimate the DoR, PFS and OS, and the corresponding 95% CIs were calculated with the Brookmeyer and Crowley method. The 95% CIs of 12-month OS rate were calculated using the log-log transformation according to the normal approximation with back transformation to CIs on the untransformed scale. Exploratory analyses of response and survival in correlation to tumor PD-L1 expression or *EGFR* mutation subtypes were also performed. All statistical analyses were conducted with the SAS software version 9.4 (SAS Institute Inc. Cary, NC, USA).

Results

Patient characteristics and disposition

Between November 13, 2017 and January 16, 2019, a total of 43 previously treated patients with advanced *EGFR+/ALK+* NSCLC received the combination regimen of intravenous camrelizumab 200 mg every 2 weeks plus oral apatinib 250 mg once daily (*Figure 1*). Due to the similarity in gene mutation and treatment settings in the 3 patients from the phase 1b study and 40 patients from Cohort 2 of the dose-expansion phase 2 study, their data were combined for analysis.

All enrolled patients were previously treated, and majority of patients harboring sensitive *EGFR* mutations or *ALK* fusion genes (n=40; 93.0%) had received at least one *EGFR/ALK* TKI and a platinum-based doublet chemotherapy regimen. Of them, 40 (93.0%) patients had received first- or second-generation EGFR TKIs (first-generation, n=39; second-generation, n=1) and the remaining 3 (7.0%) patients carrying *EGFR 20ins* mutation did not receive targeted therapy due to drug-resistant mutation. A total of 10 (23.3%) patients had received third-generation EGFR TKIs (osimertinib, n=9; avitinib, n=1). Furthermore, 9 (20.9%) patients had developed *EGFR T790M* resistance mutations after the treatment of first- or second-generation TKI, among whom 4 had received osimertinib treatment. The median age of enrolled patients was 55 years (range, 33–69 years). Thirty-nine (90.7%) patients had an ECOG performance status of 1, 19 (44.2%) patients were current or former smokers, and 12 (27.9%) patients had metastases in more than two organs. In addition, 22 (51.2%) patients had PD-L1 TPS ≥1% and 13 (30.2%) patients had PD-L1 TPS <1% tumors. Demographics and baseline characteristics of patients are shown in *Table 1*.

As of data cutoff (June 12, 2020), the median follow-up duration was 15.7 months (range, 0.5–24.4 months). Among all 43 patients, 1 (2.3%) patient was still receiving study treatment. The reasons for study treatment discontinuation were disease progression (n=26, 60.5%), AEs (n=7, 16.3%), physician decision (n=5, 11.6%), patient decision (n=2, 4.7%) and others (n=2, 4.7%).

Efficacy

At data cutoff, 43 patients were included in the full analysis set. Best change in sum of diameters of target lesion from baseline is presented in *Figure 2A*, 20 (46.5%) patients showed decreased total tumor burden. As shown in *Table 2*,

Table 1 Baseline characteristics

Characteristics	All patients (n=43)
Age, years, median [range]	55 [33–69]
Male, n (%)	25 (58.1)
ECOG performance status, n (%)	
0	4 (9.3)
1	39 (90.7)
Disease stage, n (%)	
IV	43 (100.0)
Tumor histology, n (%)	
Adenocarcinoma	41 (95.3)
Squamous	2 (4.7)
Smoking status, n (%)	
Never smoked	24 (55.8)
Current or former smoker	19 (44.2)
No. of organs with metastasis, n (%)	
≤2	31 (72.1)
>2	12 (27.9)
PD-L1 TPS, n (%)	
<1%	13 (30.2)
≥1%	22 (51.2)
Unknown	8 (18.6)
EGFR mutation*, n (%)	
Positive	40 (93.0)
Negative	1 (2.3)
Unknown	2 (4.7)
ALK rearrangement*, n (%)	
Positive	4 (9.3)
Negative	28 (65.1)
Unknown	11 (25.6)
Previous therapy, n (%)	
Surgery	11 (25.6)
Chemotherapy	43 (100.0)
Targeted therapy*,†	40 (93.0)
EGFR TKI	37 (86.0)
ALK TKI	5 (11.6)
Radiotherapy	11 (25.6)
Others	3 (7.0)
Median duration from diagnosis (range), years	2.0 (0.4–7.4)

*, one patient had a concomitant EGFR and ALK mutation and had previously received both EGFR-TKI and ALK-TKI; †, there were three patients carrying EGFR 20ins mutation, which were drug-resistant mutation, therefore, no targeted therapy was available. ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1; TPS, tumor proportion score; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor.

no patient achieved CR, 8 (18.6%) patients achieved PR as their best response, 17 (39.5%) patients had SD, 12 (27.9%) patients had PD, and the overall responses of 6 (14.0%) patients were not evaluable. The confirmed ORR assessed by investigators per RECIST version 1.1 was 18.6% (95% CI: 8.4–33.4%). The CBR with this combination regimen was 27.9% (95% CI: 15.3–43.7%). Proportions of patients who achieved an objective response across all subgroups by baseline characteristics are shown in Table S2. None of the 4 patients with *ALK* fusion genes had an objective response (Table S3). Treatment duration and tumor response in 8 responders are shown in *Figure 2B*, and the decreased tumor burden sustained over several assessments. Response occurred at a median of 1.8 months (range, 1.8–2.0 months), and the median DoR was 6.5 months (95% CI: 3.5–18.2 months).

A total of 37 (86.0%) patients had PFS events (documented progressive disease or death), and the median PFS was 2.8 months (95% CI: 1.9–5.5 months; *Figure 3A*). As of data cutoff, 20 (46.5%) patients had died. The median OS was not reached (NR) (95% CI: 7.3 months–NR months; *Figure 3B*), and the estimated 6-, 9- and 12-month OS rate with this combination regimen was 73.9% (95% CI: 57.8–84.6%), 62.0% (95% CI: 45.6–74.7%) and 57.2% (95% CI: 41.0–70.5%), respectively. After the end of the study treatment, 32 (74.4%) patients received at least one subsequent antitumor therapy, and the results are presented in Table S4.

Efficacy by EGFR mutation and PD-L1 expression

Among all 40 patients with *EGFR* mutation, 22 (55.0%)

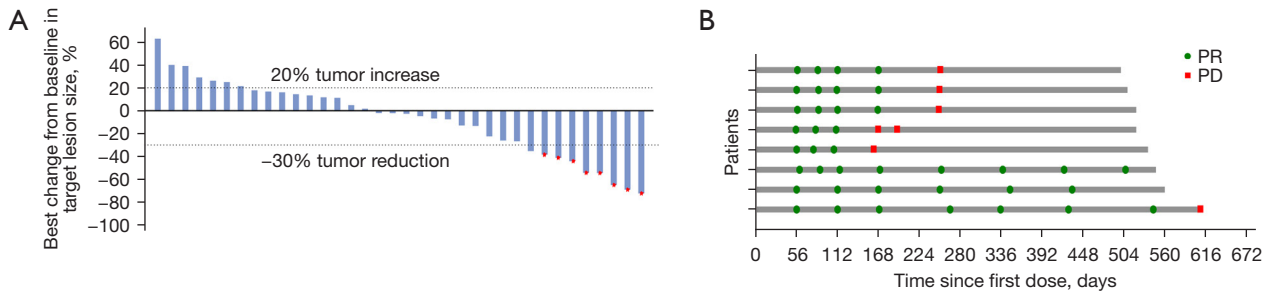

Figure 2 Clinical activity of camrelizumab plus apatinib in advanced non-small cell lung cancer patients harboring *EGFR* or *ALK* genetic aberrations. (A) Best percentage changes in sum of the diameters of target lesion from baseline. (B) Treatment duration and tumor response in 8 responders (0 CR and 8 PR). *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; CR, complete response; PR, partial response; PD, progressive disease. Red asterisks indicated confirmed responses.

Table 2 Investigator-assessed best overall tumor response and survival data

Variables	All patients (n=43)
Median follow-up (range), months	15.7 (0.5–24.4)
Best overall response, n (%)	
CR (confirmed)	0
PR (confirmed)	8 (18.6)
SD	17 (39.5)
PD	12 (27.9)
NE*	6 (14.0)
Confirmed ORR, n (%; 95% CI)	8 (18.6; 8.4–33.4)
CBR (CR/PR/SD ≥24 weeks), n (%) [95% CI]	12 (27.9) [15.3–43.7]
PFS, months, median (95% CI)	2.8 (1.9–5.5)
OS, months, median (95% CI)	NR (7.3–NR)
12-month OS rate, % (95% CI)	57.2 (41.0–70.5)
TTR, months, median (range)	1.8 (1.8–2.0)
DoR, months, median (95% CI)	6.5 (3.5–18.2)

*, 6 patients were not evaluable due to study discontinuation (adverse events, n=3; withdrawal of consent, n=1; death, n=1; investigator decision, n=1). CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, objective response rate; CBR, clinical benefit rate; PFS, progression-free survival; OS, overall survival; TTR, time to response; DoR, duration of response; CI, confidence interval; NR, not reached.

patients had *EGFR 19del*, 14 (35.0%) patients had *EGFR L858R*, and 3 (7.5%) patients had *EGFR 20ins*. The ORR in patients with *EGFR L858R* was numerically higher than those with *EGFR 19del* (21.4% *vs.* 13.6%) in this phase 1b/2 trial. Similarly, longer median PFS was observed in patients with *EGFR L858R* than in those with *EGFR 19del* (5.3 *vs.* 2.8 months; Table S5).

In exploratory analysis, tumor PD-L1 expression were available in 35 (81.4%) of the 43 enrolled patients, including 22 PD-L1 TPS ≥1% and 13 TPS <1%. The ORR was 27.3% in patients with PD-L1 TPS ≥1% and 7.7% in those with TPS <1%. The median PFS was 2.0 and 5.1 months in patients with PD-L1 TPS ≥1% and TPS <1%, respectively (Figure S1A). The median OS was 8.9 months in patients with tumor PD-L1 TPS ≥1% and NR in those with TPS <1% (Figure S1B). The distribution of *EGFR* mutation (*L858R*, *19del* or *20ins*) in patients with tumor PD-L1 TPS ≥1% and those with tumor PD-L1 TPS <1% is presented in Table S6.

Safety

All 43 patients were evaluable for safety analysis. The median duration of camrelizumab exposure was 3.2 months (range, 0.5–18.3 months), and the median duration of apatinib exposure was 3.3 months (range, 0.4–17.9 months). Among the 43 patients, 10 (23.3%) patients discontinued any study treatment due to treatment-related adverse events (TRAEs), of which 7 (16.3%) discontinued both agents, 32 (74.4%) had dose interruption because of TRAEs, and 8 (18.6%) had apatinib dose reduction caused by TRAEs (Table S7). As illustrated in *Table 3*, all patients had at least 1 TRAE, and the most commonly reported TRAEs of any grade were hypertension (67.4%), proteinuria (65.1%), and increased aspartate aminotransferase (37.2%). The most common grade ≥3 TRAEs were hypertension (16.3%),

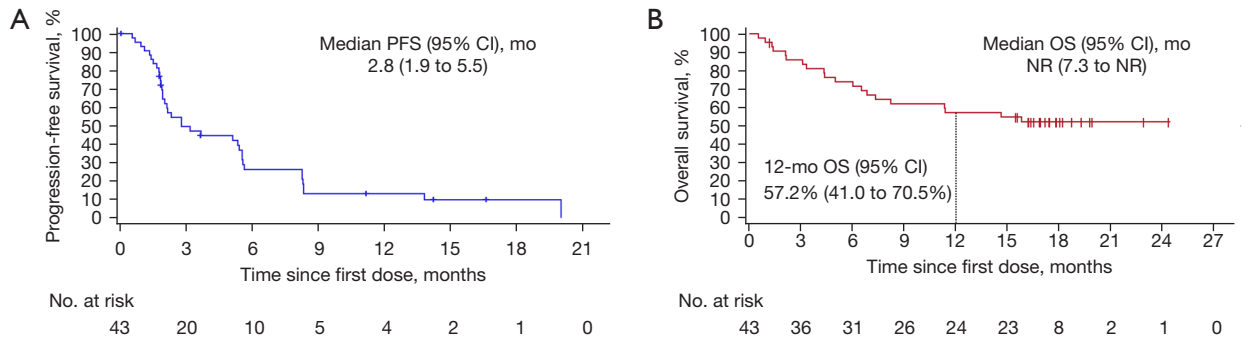

Figure 3 PFS and OS in advanced non-small cell lung cancer patients harboring *EGFR* or *ALK* genetic aberrations (n=43). (A) Kaplan-Meier curves for PFS; (B) Kaplan-Meier curves for OS. EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; PFS, progression-free survival; OS, overall survival; CI, confidence interval; NR, not reached.

proteinuria (11.6%), and palmar-plantar erythrodysesthesia (9.3%). Reactive cutaneous capillary endothelial proliferation (RCCEP), a common and self-resolving side effect associated with camrelizumab, occurred in 20.9% of patients, and all were grade 1 or 2. Treatment-related serious adverse events (SAEs) were reported in 12 (27.9%) patients, with hemoptysis [n=2 (4.7%)], immune-mediated pneumonitis [n=2 (4.7%)] and immune-mediated hepatitis [n=2 (4.7%)] as the most common events (Table S8).

As reported by the investigators, 3 (7.0%) patients died due to TRAEs (pneumonia, n=1; immune-mediate pneumonitis, n=1; hemoptysis, n=1). Other than RCCEP, the most frequently reported AEs of special interest were grade ≥3 immune-mediated hepatitis (4.7%) and grade ≥3 rash (4.7%) (Table S9).

Grade ≥3 immune-related AEs (irAEs) occurred in 10 (23.3%) patients, with rash [n=2 (4.7%)] and immune-mediated hepatitis [n=2 (4.7%)] as the most common events (Table S10). No unexpected AEs were observed.

Discussion

To the best of our knowledge, this was the first reported phase 1b/2 trial investigating the combination strategy of an ICI (camrelizumab) plus a VEGF-TKI (apatinib) in pretreated patients with advanced *EGFR+/ALK+* NSCLC. A prior meta-analysis involving Keynote 010, CheckMate 057, OAK and POPLAR trials demonstrated that the application of anti-PD-(L)1 monotherapy, including nivolumab, pembrolizumab, or atezolizumab, did not show more benefits in previously treated *EGFR*-mutant NSCLC patients than in the wild-type population (18-23). In the phase 2 ATLANTIC trial (10), NSCLC patients with both *EGFR/ALK*-alterations and high PD-L1 expression (defined as ≥25% of TCs) were administered durvalumab as third- or later-line therapy, despite that NSCLC patients with *EGFR/ALK* alterations who had PD-L1 expression ≥25% showed a relatively high response rate, the overall response obtained was still lower than that in the wild-type population and could not translated into improved survival outcomes.

With respect to combination regimen, the IMpower150 trial indicated that the addition of bevacizumab to atezolizumab and chemotherapy as first-line therapy confers the clinical efficacy observed in the subgroup of patients with sensitive *EGFR* mutations (24). Notably, in the IMpower 150 trial, the better outcomes described in the atezolizumab + bevacizumab + carboplatin + paclitaxel group for *EGFR+/ALK+* patients were not found in those who received atezolizumab plus chemotherapy without bevacizumab, emphasizing the crucial role of VEGF inhibition and angiogenesis in the process of EGFR/ALK cancer immunity.

The enrollment of an independent patient cohort defined by advanced *EGFR+/ALK+* NSCLC in our trial permitted prospective evaluation of the combination regimen with camrelizumab and apatinib in a patient population with the different clinical treatment outcome compared to those with *EGFR-/ALK-* NSCLC. Our study provided a crucial contribution to the evidence on the efficacy and safety of this combination regimen in previously treated patients with advanced *EGFR+/ALK+* NSCLC. The ORR and CBR of pretreated patients with advanced *EGFR+/ALK+* NSCLC who received this combination regimen were 18.6% and 27.9%, the median PFS was 2.8 months and the median OS had not been reached at the time of data cutoff with a median follow-up period of 15.7 months, suggesting that the

Table 3 Treatment-related adverse events that occurred in ≥10% of patients

Adverse events	All patients, n (%)	
	Any grade	≥Grade 3
Any TRAE	43 (100.0)	28 (65.1)
Hypertension	29 (67.4)	7 (16.3)
Proteinuria	28 (65.1)	5 (11.6)
Aspartate aminotransferase increased	16 (37.2)	1 (2.3)
Palmar-plantar erythrodysaesthesia syndrome	15 (34.9)	4 (9.3)
Alanine aminotransferase increased	15 (34.9)	0
Asthenia	13 (30.2)	0
Rash	11 (25.6)	2 (4.7)
White blood cell count decreased	10 (23.3)	1 (2.3)
Neutrophil count decreased	9 (20.9)	0
RCCEP	9 (20.9)	0
Blood bilirubin increased	8 (18.6)	1 (2.3)
Platelet count decreased	8 (18.6)	1 (2.3)
Decreased appetite	8 (18.6)	0
Gamma-glutamyltransferase increased	7 (16.3)	2 (4.7)
Hemoptysis	6 (14.0)	1 (2.3)
Headache	6 (14.0)	1 (2.3)
Blood creatinine increased	6 (14.0)	0
Vomiting	6 (14.0)	0
Dysphonia	6 (14.0)	0
Hypertriglyceridemia	5 (11.6)	2 (4.7)
Hypokalemia	5 (11.6)	1 (2.3)
Occult blood positive	5 (11.6)	0
Hypocalcemia	5 (11.6)	0
Pyrexia	5 (11.6)	0
Anemia	5 (11.6)	0

TRAE, treatment-related adverse event; RCCEP, reactive cutaneous capillary endothelial proliferation.

improved ORR, durable DoR and PFS with camrelizumab plus apatinib might be translated into prominent OS benefit in previously treated patients with advanced *EGFR+/ALK+* NSCLC. In recent years, the ATLANTIC phase 2 trial provided the largest prospective cohort with anti-PD-1/PD-L1 monotherapy in advanced *EGFR+/ALK+* NSCLC patients, the median OS in Cohort 1 (pretreated patients with advanced *EGFR+/ALK+* NSCLC) was 13.3 months (95% CI: 6.3–24.5 months) in patients with increased PD-L1 expression (defined as ≥25% of TCs) and 9.9 months (95% CI: 4.2–13.3 months) in those with TCs <25% (25). Although cross-trial comparisons can be challenging, in our phase 1b/2 trial, the OS was comparable and competitive to that observed in the similar patient population from ATLANTIC phase 2 trial (10). Our results also supported the point of view that combination of anti-PD-1/PD-L1 agent and low-dose antiangiogenic inhibitor could elicit T cell activation, improve tumor immune microenvironment and drive the responses of TCs to immune checkpoint blockade, which brings about more sufficient anti-tumor immunity than anti-PD-1 monotherapy (26).

Not all *EGFR* mutations are identical, which could partly interpret the reason some *EGFR* mutation subtypes respond variously to ICIs. A retrospective study involving multicenters in U.S. revealed that among 171 patients with *EGFR* mutation who received ICI treatment, patients with *EGFR exon 19del* tumors showed lower tumor mutation burden (TMB) than those with *EGFR L858R*. Furthermore, NSCLC patients with *EGFR exon 19del* tumors showed worse treatment response or prognosis compared to those with *EGFR L858R*. However, *EGFR T790M* status or PD-L1 expression was not found to influence responses or survival outcomes (27). The results from the IMMUNOTARGET registry indicated that 125 NSCLC patients with *EGFR* mutations receiving ICIs achieved an ORR of 12.2%, with the median PFS of 2.1 months. Among them, patients with *exon 21 EGFR* mutations indicated prolonged PFS than those with *exon 19* deletions or *T790M* mutations (28). In our study, improved ORR and prolonged PFS and OS were also observed in patients with *EGFR L858R* compared with those with *EGFR 19del*, highlighting that robust genetic background might exert important influence on the antitumor activity of this combination regimen in advanced *EGFR+/ALK+* NSCLC. In addition, a recent study discovered that *L858R*-mutant tumors were infiltrated with more T cells marked with $CD8^+$ $PD\text{-}1^+$ compared with *19del*-mutant tumors, which implied that tumor immune microenvironment (TIME) might be different among *EGFR* mutation subtypes (29). This might partly explain the better clinical benefits in patients with *EGFR L858R* subgroup than those with *EGFR 19del* in our trial. However, these findings warranted further

validation and confirmation in the further trials with larger sample size.

PD-L1 expression has been widely applied as a biomarker for prediction of response to immunotherapy in NSCLC patients. Nevertheless, PD-L1 expression in tumors harboring actionable driver mutations might not be necessarily associated with clinical responses to ICIs. In our phase 1b/2 trial, the proportion of patients achieving a response was higher in patients with PD-L1 TPS ≥1% than in those with PD-L1 TPS <1%; however, the survival benefit from this combination regimen did not indicate the trend in favor of patients with PD-L1 TPS ≥1%. This discordance between ORR and survival benefits observed in our study might be partially attributed to the multiple confounding factors, such as the relatively small sample size in each PD-L1 TPS category, influences of subsequent anti-tumor therapies and so on, which requires further investigation.

The incidence and severity of TRAEs with camrelizumab plus apatinib were consistent with previously reported toxic effects for camrelizumab or apatinib (11,30). The most common grade 3 or higher TRAEs were hypertension (16.3%), proteinuria (11.6%) and palmar-plantar erythrodysaesthesia (9.3%), which were slightly higher than the incidences reported for apatinib monotherapy (30). No new safety signals were identified. Remarkably, RCCEP, a clinically controllable and self-limiting TRAE induced by camrelizumab, only occurred in 9 (20.9%) patients receiving this combination regimen, with no grade 3 or higher events reported; the incidence was similar to that observed with the identical combination regimen for pretreated advanced non-squamous NSCLC without driver mutations (21.9%) and obviously decreased compared with that reported for camrelizumab monotherapy (74.0%) (31) or camrelizumab plus chemotherapy (77.6%) (32) in advanced NSCLC. Our results verified that addition of apatinib to camrelizumab could reduce the incidence of RCCEP, further suggesting that the mechanism of RCCEP may be correlated with the VEGFA/VEGFR-2 signaling pathway (14,15). Overall, TRAEs that occurred with this combination regimen were unsurprising and well-tolerated. Increased aspartate aminotransferase and alanine aminotransferase might be associated with camrelizumab (11), while the occurrence of hypertension, proteinuria and palmar-plantar erythrodysaesthesia might be related with apatinib (30). This combination regimen also resulted in slightly increased occurrences of asthenia and common hematological toxicity, including decreased white blood cell count, decreased neutrophil count, and decreased platelet count, which might be attributed to the overlapping AE profiles of camrelizumab plus apatinib.

The current study had several limitations. First, the trial was a single-arm phase 1b/2 study design, with no standard-of-care or PD-1/PD-L1 monotherapy arm as a control. Second, due to the small sample size, the proportion of patients with PD-L1 TPS ≥1% was relatively low, nevertheless, improved ORR and prolonged survival data had been derived regardless of PD-L1 expression. Third, the goal of an ORR of 30% was not reached, partially due to the relatively high proportion of patients who discontinued treatment due to TRAE (16.3%) and those who were not evaluable for tumor response (7.0% for reasons other than TRAEs); on the other hand, despite the modest ORR, OS was remarkable with a 12-month rate of 57.2%, suggesting potential benefits beyond initial treatment period. Fourth, the upper age limit for the present study was set at 70 years based on the compliance and tolerance of Chinese patients. Considering the generally lower treatment tolerance in patients with more advanced age, the findings of this study may not extrapolate to patients over 70 years and further research in this population is needed. Moreover, the median OS was still not reached, and long-term follow-up survival data are required to be reported in near future.

In conclusion, our phase 1b/2 trial demonstrated that camrelizumab plus apatinib showed moderate antitumor activity and acceptable safety profile in previously treated patients with advanced NSCLC harboring *EGFR* or *ALK* genetic aberrations, which warranted further validation.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol and amendments were reviewed and approved by the Ethics Committees of each study site. The study was conducted in compliance with the Good Clinical Practice Guidelines, the Declaration of Helsinki and its amendments. All patients provided written informed consent before enrollment.

References

1. Yuan M, Huang LL, Chen JH, et al. The emerging treatment landscape of targeted therapy in non-small-cell lung cancer. Signal Transduct Target Ther 2019;4:61.
2. Shukla NA, Yan MN, Hanna N. The Story of Angiogenesis Inhibitors in Non-small-cell Lung Cancer: The Past, Present, and Future. Clin Lung Cancer 2020;21:308-13.
3. Recondo G, Facchinetti F, Olaussen KA, et al. Making the first move in EGFR-driven or ALK-driven NSCLC: first-generation or next-generation TKI? Nat Rev Clin Oncol 2018;15:694-708.
4. Lin JJ, Shaw AT. Resisting Resistance: Targeted Therapies in Lung Cancer. Trends Cancer 2016;2:350-64.
5. Wu SG, Shih JY. Management of acquired resistance to EGFR TKI-targeted therapy in advanced non-small cell lung cancer. Mol Cancer 2018;17:38.
6. Lim SM, Hong MH, Kim HR. Immunotherapy for Non-small Cell Lung Cancer: Current Landscape and Future Perspectives. Immune Netw 2020;20:e10.
7. Califano R, Kerr K, Morgan RD, et al. Immune Checkpoint Blockade: A New Era for Non-Small Cell Lung Cancer. Curr Oncol Rep 2016;18:59.
8. Marrone KA, Brahmer JR. Immune Checkpoint Therapy in Non-Small Cell Lung Cancer. Cancer J 2016;22:81-91.
9. Gainor JF, Shaw AT, Sequist LV, et al. EGFR Mutations and ALK Rearrangements Are Associated with Low Response Rates to PD-1 Pathway Blockade in Non-Small Cell Lung Cancer: A Retrospective Analysis. Clin Cancer Res 2016;22:4585-93.
10. Garassino MC, Cho BC, Kim JH, et al. Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study. Lancet Oncol 2018;19:521-36.
11. Wu F, Gao G, Zhou C, et al. A phase III, randomized, open-label, multicenter study of SHR-1210 (anti-PD-1 antibody) in combination with pemetrexed and carboplatin as first line therapy in subjects with advanced/metastatic non-squamous non-small cell lung cancer. Ann Oncol 2018;29:viii545.
12. Li J, Qin S, Xu J, et al. Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Apatinib in Patients With Chemotherapy-Refractory Advanced or Metastatic Adenocarcinoma of the Stomach or Gastroesophageal Junction. J Clin Oncol 2016;34:1448-54.
13. Zhao S, Ren S, Jiang T, et al. Low-Dose Apatinib Optimizes Tumor Microenvironment and Potentiates Antitumor Effect of PD-1/PD-L1 Blockade in Lung Cancer. Cancer Immunol Res 2019;7:630-43.
14. Xu J, Zhang Y, Jia R, et al. Anti-PD-1 Antibody SHR-1210 Combined with Apatinib for Advanced Hepatocellular Carcinoma, Gastric, or Esophagogastric Junction Cancer: An Open-label, Dose Escalation and Expansion Study. Clin Cancer Res 2019;25:515-23.
15. 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;27:1296-304.
16. Zhou C, Gao G, Wu F, et al. A phase Ib study of SHR-1210 plus apatinib for heavily previously treated advanced non-squamous non-small cell lung cancer (NSCLC) patients. J Clin Oncol 2018;36:e21017.

17. Büttner R, Gosney JR, Skov BG, et al. Programmed Death-Ligand 1 Immunohistochemistry Testing: A Review of Analytical Assays and Clinical Implementation in Non-Small-Cell Lung Cancer. J Clin Oncol 2017;35:3867-76.
18. Lee CK, Man J, Lord S, et al. Clinical and Molecular Characteristics Associated With Survival Among Patients Treated With Checkpoint Inhibitors for Advanced Non-Small Cell Lung Carcinoma: A Systematic Review and Meta-analysis. JAMA Oncol 2018;4:210-6.
19. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:1627-39.
20. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123-35.
21. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387:1540-50.
22. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255-65.
23. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837-46.
24. Reck M, Mok TSK, Nishio M, et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. Lancet Respir Med 2019;7:387-401.
25. Garassino MC, Cho BC, Kim JH, et al. Final overall survival and safety update for durvalumab in third- or later-line advanced NSCLC: The phase II ATLANTIC study. Lung Cancer 2020;147:137-42.
26. Allen E, Jabouille A, Rivera LB, et al. Combined antiangiogenic and anti-PD-L1 therapy stimulates tumor immunity through HEV formation. Sci Transl Med 2017;9:eaak9679.
27. Hastings K, Yu HA, Wei W, et al. EGFR mutation subtypes and response to immune checkpoint blockade treatment in non-small-cell lung cancer. Ann Oncol 2019;30:1311-20.
28. Mazieres J, Drilon A, Lusque A, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. Ann Oncol 2019;30:1321-8.
29. Zhou J, Yu X, Hou L, et al. Epidermal growth factor receptor tyrosine kinase inhibitor remodels tumor microenvironment by upregulating LAG-3 in advanced non-small-cell lung cancer. Lung Cancer 2021;153:143-9.
30. Wu F, Zhang S, Xiong A, et al. A Phase II Clinical Trial of Apatinib in Pretreated Advanced Non-squamous Non-small-cell Lung Cancer. Clin Lung Cancer 2018;19:e831-42.
31. Wu Y, Huang C, Fan Y, et al. P1.01-61 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:S382-3.
32. Zhou C, Chen G, Huang Y, et al. OA04.03 A Randomized Phase 3 Study of Camrelizumab plus Chemotherapy as 1st Line Therapy for Advanced/Metastatic Non-Squamous Non-Small Cell Lung Cancer. J Thorac Oncol 2019;14:S215-6.

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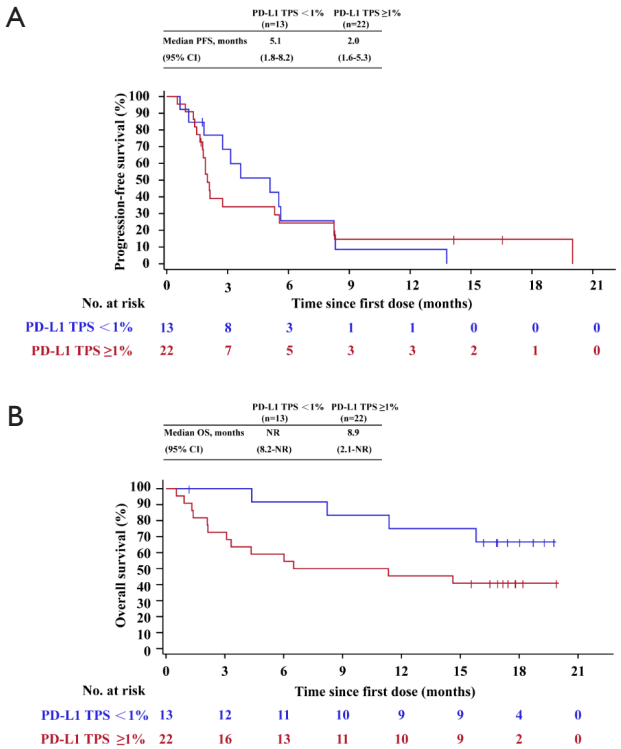

Figure S1 Kaplan-Meier curves for PFS and OS. (A) PFS in patients with tumor PD-L1 TPS ≥1% and those with tumor PD-L1 TPS <1%. (B) OS in patients with tumor PD-L1 TPS ≥1% and those with tumor PD-L1 TPS <1%. PFS, progression-free survival; OS, overall survival; CI, confidence interval; NR, not reached; PD-L1, programmed death-ligand 1, TPS, tumor proportion score.

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Table S1 Participating institutions

Participating institutions	Investigators	Approval Number
Shanghai Pulmonary Hospital, Tongji University	Guanghui Gao/Jian Ni/Shengxiang Ren/ Caicun Zhou	16162ZL-7
The First Affiliated Hospital of Zhejiang University	Yina Wang	2019-(35)
Fudan University Shanghai Cancer Center	Min Fan	1805184-7-1902B
Jiangsu Province Hospital	Renhua Guo	2018-MD-058.A2
The First Affiliated Hospital of Anhui Medical University	Kangsheng Gu	PJ2018-04-07(5)
The First Affiliated Hospital of USTC, Anhui Provincial Hospital	Yueyin Pan	2019-(32)
Beijing Cancer Hospital	Jun Zhao	2018YW07-ZY03
Harbin Medical University Cancer Hospital	Gongyan Chen	2018-52
The First Hospital of China Medical University	Yunpeng Liu	2018YL020-1
Shandong Cancer Hospital	Zhehai Wang	SDZLEC-2018-012-05
The First Affiliated Hospital of Guangzhou Medical University	Jianxing He	EC-2018-006(YW)-04
Fujian Medical University Union Hospital	Xiaoyan Lin	2018YW009-06
Henan Cancer Hospital	Zhiyong Ma	2018028
Henan Provincial People's Hospital	Shundong Cang	2018-018-05
Affiliated Hospital of Hebei University	Aimin Zang	HDFY-LL-2019-037
Jiangxi Cancer Hospital	Zhihua Liu	2018008-YW007

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Table S2 Objective response rates by subgroups

Variables	Subgroups	Number of responders	ORR, % (95% CI)
Sex	Male (n=25)	4	16.0 (4.5, 36.1)
	Female (n=18)	4	22.2 (6.4, 47.6)
Age	<65 years (n=38)	7	18.4 (7.7, 34.3)
	≥65 years (n=5)	1	20.0 (0.5, 71.6)
ECOG performance status	1 (n=39)	7	17.9 (7.5, 33.5)
	0 (n=4)	1	25.0 (0.6, 80.6)
Smoking status	Current or former smoked (n=19)	4	21.1 (6.1, 45.6)
	Never smoked (n=24)	4	16.7 (4.7, 37.4)
No. of organs with metastasis	≤2 (n=31)	7	22.6 (9.6, 41.1)
	>2 (n=12)	1	8.3 (0.2, 38.5)
PD-L1 TPS	≥1% (n=22)	6	27.3 (10.7, 50.2)
	<1% (n=13)	1	7.7 (0.2, 36.0)
	Unknown (n=8)	1	12.5 (0.3, 52.7)
EGFR L858R	Yes (n=14)	3	21.4 (4.7, 50.8)
	No (n=29)	5	17.2 (5.8, 35.8)
EGFR 19del	Yes (n=22)	3	13.6 (2.9, 34.9)
	No (n=21)	5	23.8 (8.2, 47.2)
EGFR 20ins	Yes (n=3)	1	33.3 (0.8, 90.6)
	No (n=40)	7	17.5 (7.3, 32.8)

ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1; TPS, tumor proportion score; EGFR, epidermal growth factor receptor; ORR, objective response rate; CI, confidence interval.

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Table S3 Efficacy outcomes in patients with ALK-rearranged NSCLC

Patient ID	Age	Gender	BoR	PFS (mo)	OS (mo)
1	33	Male	SD	5.6	11.4
2	52	Female	PD	1.8	6.5
3	47	Female	PD	2.0	3.1
4	60	Female	SD	1.8+	15.7+

BoR, best overall response; OS, overall survival; PD, progressive disease; PFS, progression-free survival; SD, stable disease.

Table S4 Subsequent anti-tumor therapies that were initiated after the last dose of the study treatment

Variables	All patients n=43
Any subsequent therapy*	32 (74.4)
Targeted therapy	24 (55.8)
EGFR-TKI	10 (27.9)
ALK-TKI	3 (7.0)
Anti-angiogenic drugs	22 (51.2)
Systemic chemotherapy	23 (53.5)
Immunotherapy	3 (7.0)
Radiotherapy[#]	6 (14.0)
Antineoplastic Chinese traditional medicines	4 (9.3)

* 11 patients did not receive any subsequent anti-tumor therapies. [#] Radiotherapy included brain radiation (4 patients), bone radiation (2 patients) and lung radiation (2 patients). Percentages were calculated with the number of patients in the full analysis set as denominator. Data are n (%). EGFR, epidermal growth factor receptor; TKI, *tyrosine kinase inhibitor*; ALK, anaplastic lymphoma kinase.

Table S5 Antitumor activity of camrelizumab plus apatinib in advance NSCLC patients with EGFR mutation

	Number of patients	ORR, % (95% CI)	Median PFS (months)	Median OS (months)
All patients with EGFR mutation*	40	20.0 (9.1-35.6)	3.2 (1.9-5.5)	NR (7.3-NR)
EGFR 19del[#]	22	13.6 (2.9-34.9)	2.8 (1.8-5.5)	NR (4.4-NR)
EGFR L858R[#]	14	21.4 (4.7-50.8)	5.3 (1.6-8.2)	NR (4.3-NR)
EGFR 20ins	3	33.3 (0.8-90.6)	8.3 (1.9-8.3)	NR (6.0-NR)

* Two patients, who harbored *EGFR S768I*/*G719X*/*T790M*+ and *T790M*+ respectively, were not included into the three subgroups analysis. [#] One patient harbored both *EGFR 19del* and *EGFR L858R*. ORR, objective response rate; EGFR, epidermal growth factor receptor; PFS, progression-free survival; OS, overall survival; NR, not reached.

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Table S6 The distribution of EGFR mutation (L858R, 19del or 20ins) in patients with tumor PD-L1 TPS ≥1% or those with tumor PD-L1 TPS <1%

EGFR subtypes	PD-L1 TPS ≥1% (n=22)	PD-L1 TPS <1% (n=13)	PD-L1 TPS not available (n=8)
L858R (N=14)*	8 (36.4)	4 (30.8)	2 (25.0)
19del (N=22)*	10 (45.5)	9 (69.2)	3 (37.5)
20ins (N=3)	2 (9.1)	1 (7.7)	0

* One patient harbored both *EGFR 19del* and *EGFR L858R*. Data are n (%). EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1, TPS, tumor proportion score.

Table S7 Summary of treatment-related adverse events

	All patients (n=43)
Any TRAE	43 (100.0)
≥Grade 3 TRAE	28 (65.1)
Treatment-related SAEs	12 (27.9)
TRAEs leading to any treatment discontinuation	10 (23.3)
Camrelizumab discontinuation	7 (16.3)
Apatinib discontinuation	10 (23.3)
TRAEs leading to discontinuation of all study treatment	7 (16.3)
TRAEs leading to any treatment interruption	32 (74.4)
Camrelizumab interruption	16 (37.2)
Apatinib interruption	30 (69.8)
TRAEs leading to apatinib dose reduction	8 (18.6)
TRAEs leading to death	3 (7.0)

Data are n (%). TRAE, treatment-related adverse event.

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Table S8 Summary of treatment-related serious adverse events

Treatment-related SAEs	All patients N=43	
	Any Grade	Grade ≥3
Any	12 (27.9)	7 (16.3)
Immune-mediated hepatitis	2 (4.7)	2 (4.7)
Hemoptysis	2 (4.7)	1 (2.3)
Immune-mediated pneumonitis	2 (4.7)	1 (2.3)
Interstitial lung disease	1 (2.3)	1 (2.3)
Diabetes mellitus	1 (2.3)	1 (2.3)
Hepatic function abnormal	1 (2.3)	1 (2.3)
Pancreatitis acute	1 (2.3)	1 (2.3)
Pneumonia	1 (2.3)	1 (2.3)
Decreased appetite	1 (2.3)	0
Vomiting	1 (2.3)	0
RCCEP	1 (2.3)	0

Data are n (%). SAE, serious adverse event; RCCEP, reactive cutaneous capillary endothelial proliferation.

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Table S9 Adverse events of special interest regardless of study treatment

AESI	All patients, n=43
Any	17 (39.5)
Grade ≥2 interstitial pneumonia	1 (2.3)
Interstitial lung disease	1 (2.3)
Grade ≥2 diarrhea/colitis	0
Diarrhea	0
Other Grade ≥3 immune-mediated AEs	9 (20.9)
RCCEP	9 (20.9)
Immune-mediated hepatitis	2 (4.7)
Rash	2 (4.7)
Lymphocyte count decreased	1 (2.3)
White blood cell count decreased	1 (2.3)
Immune-mediated pneumonitis	1 (2.3)
Hyponatremia	1 (2.3)
Platelet count decreased	1 (2.3)
Palmar-plantar erythrodysaesthesia syndrome	1 (2.3)
Pneumonia	1 (2.3)
Diabetes mellitus	1 (2.3)
Acute pancreatitis	1 (2.3)
Hypochloremia	1 (2.3)
Blood bilirubin increased	0
Alanine aminotransferase increased	0
Type 2 diabetes mellitus	0
Blood alkaline phosphatase increased	0
Hepatic function abnormal	0
Gamma-glutamyltransferase increased	0
Aspartate aminotransferase increased	0
Proteinuria	0

Data are n (%). AESI, adverse events of special interest; RCCEP, reactive cutaneous capillary endothelial proliferation.

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Table S10 Immune-mediated AEs regardless of attribution to study treatment

Immune-mediated AEs	All patients, N=43	
	Any Grade	Grade ≥3
Any	26 (60.5)	10 (23.3)
Rash	8 (18.6)	2 (4.7)
Aspartate aminotransferase increased	8 (18.6)	0
RCCEP	7 (16.3)	0
Alanine aminotransferase increased	6 (14.0)	0
Asthenia	6 (14.0)	0
Pyrexia	4 (9.3)	0
White blood cell count decreased	3 (7.0)	1 (2.3)
Blood thyroid stimulating hormone increased	3 (7.0)	0
Blood bilirubin increased	3 (7.0)	0
Diarrhea	3 (7.0)	0
Immune-mediated hepatitis	2 (4.7)	2 (4.7)
Lymphocyte count decreased	2 (4.7)	1 (2.3)
Palmar-plantar erythrodysaesthesia syndrome	2 (4.7)	1 (2.3)
Immune-mediated pneumonitis	2 (4.7)	1 (2.3)
Hypochloremia	2 (4.7)	1 (2.3)
Hyponatremia	2 (4.7)	1 (2.3)
Bilirubin conjugated increased	2 (4.7)	0
Cough	2 (4.7)	0
Autoimmune hypothyroidism	2 (4.7)	0
Hypokalemia	2 (4.7)	0
Anemia	2 (4.7)	0
Platelet count decreased	1 (2.3)	1 (2.3)
Pancreatitis acute	1 (2.3)	1 (2.3)
Interstitial lung disease	1 (2.3)	1 (2.3)
Diabetes mellitus	1 (2.3)	1 (2.3)
Pneumonia	1 (2.3)	1 (2.3)
C-reactive protein increased	1 (2.3)	0
Thyroglobulin decreased	1 (2.3)	0
Urine bilirubin increased	1 (2.3)	0
Tri-iodothyronine decreased	1 (2.3)	0
Blood cholesterol increased	1 (2.3)	0
Blood creatine phosphokinase increased	1 (2.3)	0
Blood parathyroid hormone increased	1 (2.3)	0
Blood alkaline phosphatase increased	1 (2.3)	0
Blood glucose increased	1 (2.3)	0
Tri-iodothyronine free decreased	1 (2.3)	0
Tri-iodothyronine free increased	1 (2.3)	0
Neutrophil count decreased	1 (2.3)	0
Skin erosion	1 (2.3)	0
Pruritus	1 (2.3)	0
Peripheral swelling	1 (2.3)	0
Mouth ulceration	1 (2.3)	0
Vomiting	1 (2.3)	0
Dyspnoea	1 (2.3)	0
Hypoxia	1 (2.3)	0
Hypophysitis	1 (2.3)	0
Immune-mediated thyroiditis	1 (2.3)	0
Autoimmune thyroiditis	1 (2.3)	0
Gastroenteritis	1 (2.3)	0
Headache	1 (2.3)	0
Arthralgia	1 (2.3)	0
Urinary incontinence	1 (2.3)	0
Vulvar erosion	1 (2.3)	0
Hypertension	1 (2.3)	0
Eye pain	1 (2.3)	0

Data are n (%). AEs, adverse events; RCCEP, reactive cutaneous capillary endothelial proliferation.

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