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ORIGINAL ARTICLE

Anlotinib in combination with docetaxel for advanced nonsmall cell lung cancer after failure of platinum-based treatment: A phase 1/2 trial

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Abstract

Background: The combination of anlotinib with chemotherapy has demonstrated encouraging efficacy in the treatment of nonsmall cell lung cancer (NSCLC). The objective of this phase 1/2 trial was to establish the maximum tolerated dose of anlotinib in combination with docetaxel and to assess the efficacy and safety of this regimen in patients with advanced NSCLC who had progressed after platinum-based chemotherapy.

Methods: In the phase 1 trial, eight patients were enrolled to determine the maximum tolerated dose, which was identified as 10 mg for anlotinib in combination with docetaxel. In the phase 2 trial, in total, 88 patients were randomized, with 57 receiving anlotinib at the established maximum tolerated dose alongside docetaxel and 31 receiving docetaxel monotherapy. Tumor response was evaluated in 88 patients.

Results: In the phase 2 study, the combination of anlotinib and docetaxel demonstrated a significant improvement in progression-free survival compared with docetaxel monotherapy (median, 5.39 vs. 2.56 months; hazard ratio, 0.36; 95% confidence interval, 0.21–0.63; $p = .0002$). The objective response rate was also superior in the

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combination group (26.32% vs. 6.45%). The median overall survival was 16.82 months for the combination group versus 9.86 months for the monotherapy group (hazard ratio, 0.89; 95% confidence interval, 0.47–1.66; $p = .7114$). Safety analysis included 96 patients, and the most frequent treatment-emergent adverse events were decreased neutrophil count and decreased white blood cell count.

Conclusions: The addition of anlotinib to docetaxel was characterized by a manageable safety profile and also resulted in a significant improvement in progression-free survival among patients with advanced NSCLC who had previously failed platinum-based chemotherapy (ClinicalTrials.gov identifier NCT03726736).

KEYWORDS
advanced cancer, anlotinib, docetaxel, nonsmall cell lung cancer, phase 1/2

INTRODUCTION

Chemotherapy, immune checkpoint inhibitor (ICI) monotherapy, and their combinations are the current standard of care for patients with advanced or metastatic nonsmall cell lung cancer (NSCLC) who lack actionable mutations.[1,2] Despite these treatments, the prognosis remains poor after failure on first-line platinum-based chemotherapy, with median overall survival (OS) for second-line docetaxel therapy ranging from 5.0 to 11.9 months.[3–5] Although ICIs have shown superior median OS outcomes of 11.8–17.2 months,[4–7] their efficacy is notably diminished in patients with low or negative PD-L1 expression, which underscores the need for alternative therapeutic options.[5–7] The combination of anti-angiogenic agents with chemotherapy has demonstrated potential to enhance the efficacy of second-line treatment in advanced NSCLC.[8] Anti-angiogenic agents are believed to normalize tumor vasculature, thereby improving drug delivery and enhancing intratumoral concentrations of chemotherapeutic agents.[9,10] The combination of chemotherapy with anti-angiogenic agents has demonstrated benefits in NSCLC, as demonstrated in the REVEL trial (ClinicalTrials.gov identifier NCT01168973), in which the addition of ramucirumab to docetaxel improved both OS and progression-free survival (PFS) in patients with advanced NSCLC after platinum-based treatment failure.[11] Although ramucirumab is effective, its high cost limits accessibility, particularly in regions like China, highlighting the need for more cost-effective treatment options.

Anlotinib, a novel small-molecule tyrosine kinase inhibitor, targets a broad spectrum of receptors, including VEGFR1–VEGFR4, PDGFRα/PDGFRβ, FGFR1–FGFR4, and c-kit.[12] The ALTER 0303 trial (ClinicalTrials.gov identifier NCT02388919) demonstrated significant benefits of anlotinib in improving both PFS and OS as a third-line treatment in advanced NSCLC.[13] Furthermore, studies have highlighted the promising efficacy and safety of anlotinib in combination with chemotherapy as a first-line or third-line treatment option for NSCLC.[14–16] Given these findings, the potential of anlotinib combined with chemotherapy in the second-line setting warrants further investigation.

This phase 1/2 clinical trial was designed to determine the maximum tolerated dose (MTD) of anlotinib in combination with docetaxel and to evaluate the efficacy and safety of this regimen versus docetaxel monotherapy in patients with advanced NSCLC who progressed after platinum-based therapy.

MATERIALS AND METHODS

Patients

Patients with advanced NSCLC who lacked actionable driver mutations and experienced progression after first-line platinum-based chemotherapy were enrolled between December 2018 and January 2022. The key inclusion criteria were as follows: (1) age range, 18–75 years; (2) an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; (3) a life expectancy of at least 3 months; (4) histologically or cytologically confirmed stage IIIB, IIIC, or IV NSCLC; (5) the presence of at least one measurable target lesion, as defined by the Response Evaluation Criteria in Solid Tumors, version 1.1, with no local treatment within the past 3 months; (6) documented progression after first-line platinum-based chemotherapy; and (7) the absence of *EGFR*, *ALK*, or *ROS1* sensitizing mutations in patients with nonsquamous NSCLC. Key exclusion criteria included prior exposure to anlotinib, docetaxel, or other small-molecule VEGFR inhibitors as well as the presence of active and symptomatic brain metastases.

Study design

The phase 1 study used a single-center, 3 + 3, dose de-escalation design. Based on dosing recommendations from prior trials,[13,17] the initial dose of anlotinib was set at 12 mg daily administered from day 1 to day 14 of a 21-day cycle (once every 3 weeks). Dose adjustments to 10 mg daily and subsequently 8 mg daily were made in response to dose-limiting toxicities (DLTs) observed during the first cycle. In the absence of DLTs, anlotinib was continued at 12 mg daily in combination with docetaxel. If DLTs occurred in two or more out of three patients, the starting dose was reduced to 10 mg daily. If only one DLT was observed in three patients, the dose level was maintained,

and three additional patients were enrolled. If a DLT occurred in this subsequent cohort, the dose was reduced to 10 mg daily. Docetaxel was administered intravenously at a dose of 60 mg/m^2 on day 1 of each cycle (once every 3 weeks). Anlotinib, predominantly metabolized by CYP1A2 and CYP3A4/5, did not require dose adjustments when co-administered with docetaxel.[18]

The phase 2 trial was designed as a multicenter, randomized, controlled superiority study. Participants were randomized at a 2:1 ratio to receive either anlotinib in combination with docetaxel or docetaxel monotherapy. Stratified block randomization was applied based on histologic subtype (squamous vs. nonsquamous), with a block size of six. The dosing regimen for anlotinib and docetaxel in the phase 2 study was consistent with the dosing established in the phase 1 study. Because anlotinib is an approved and recommended third-line therapy for advanced NSCLC,[19] patients assigned to the docetaxel monotherapy arm were permitted to receive anlotinib as a subsequent line of therapy if their disease progressed.

Initially, the trial was designed to enroll patients who had failed first-line platinum-based chemotherapy. At the time of study initiation, ICIs were newly introduced in China and were not yet covered by health insurance. Because of the high cost and limited accessibility of ICIs, few patients opted for immunotherapy. As ICIs became more widely available and were covered by insurance in certain regions, some patients received immunotherapy. Therefore, the study cohort also included patients who had previously been treated with ICIs.

This clinical trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol received ethical approval from the Sir Run Run Shaw Hospital Ethics Committee (approval no. 20180821-14) and was registered on ClinicalTrials.gov (identifier NCT03726736). All participants provided written informed consent before enrollment.

Outcomes and assessment

The primary end point of the phase 1 trial was to establish the MTD of anlotinib in combination with docetaxel, defined as the dose at which fewer than 33% of patients experienced a DLT during the first treatment cycle. DLTs were characterized by drug-related grade 4 hematologic toxicity, febrile neutropenia (absolute neutrophil count <1000/μL with a body temperature ≥38.5°C), or grade ≥3 nonhematologic toxicity (excluding alopecia) in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

In the phase 2 trial, the primary end point was PFS, which was assessed by investigators according to Response Evaluation Criteria in Solid Tumors, version 1.1. Secondary end points included OS, the objective response rate (ORR), the disease control rate, duration of response, and safety. Separate analyses of tumor response, PFS, and OS were conducted for patients with squamous cell carcinoma (SCC), large cell carcinoma (LCC), adenocarcinoma (ADC), and those who previously failed immunotherapy. Tumor response was evaluated 21 days after the initial dose and subsequently at 6-week intervals.

Adverse events (AEs) were documented and graded in accordance with Common Terminology Criteria for Adverse Events, version 4.0. In addition, treatment-emergent AEs (TEAEs), serious AEs (SAEs), and treatment-related AEs (TRAEs) were recorded. Further details regarding the methodology are provided in the supplementary materials.

Statistical analysis

The expected median PFS for the anlotinib plus docetaxel combination was projected to be 6.0 months, compared with 3.0 months for docetaxel monotherapy, based on previous clinical data.[11,13,20,21] To achieve 80% power with a two-sided alpha of .05, it was estimated that, in total, 63 PFS events (40 in the combination group and 23 in the control group) would be required. NCSS&PASS 11.0 software (NCSS LLC) was used to calculate sample size, estimating that 59 individuals in the anlotinib plus docetaxel group and 29 in the docetaxel monotherapy group would be necessary, accounting for a 20% dropout rate.

The *full analysis set* included all patients in phase 2 who received at least one dose of the study drug and had at least one efficacy assessment, whereas the *safety set* comprised all patients who received at least one dose of the study drug and had safety data available after treatment. Data from the MTD cohort in phase 1 and 2 cohorts were also pooled for efficacy analysis.

The Kaplan–Meier method was used to estimate median survival times along with 95% confidence intervals (CIs). Hazard ratios (HRs) and their 95% CIs were calculated to compare treatment effects. Safety data were analyzed using descriptive statistics. Statistical significance was set at a two-sided p value < .05. All data analyses were performed using SAS software, version 9.1.3 (SAS Institute Inc.).

RESULTS

Demographic characteristics

The first patient was enrolled in the phase 1 trial in December 2018. The phase 2 trial began enrollment in June 2019, and informed consent dates matched the enrollment dates. In total, eight participants were enrolled in the phase 1 trial (Figure 1A). In the phase 2 study, 88 participants were randomized, with 57 receiving anlotinib in combination with docetaxel and 31 receiving docetaxel monotherapy (Figure 1B). By the cutoff date of February 28, 2023, 62 patients in the anlotinib plus docetaxel group and 31 patients in the docetaxel monotherapy group had discontinued study treatment (Figure 1B). Efficacy was evaluated in 88 patients (anlotinib plus docetaxel, n = 57; docetaxel monotherapy, n = 31), whereas safety was assessed in 96 patients (anlotinib plus docetaxel, n = 65; docetaxel monotherapy, n = 31). Baseline characteristics between the two treatment groups were generally well balanced (Table 1). Baseline patient characteristics in the phase 1 (MTD cohort) and 2 studies are provided in Table S1.

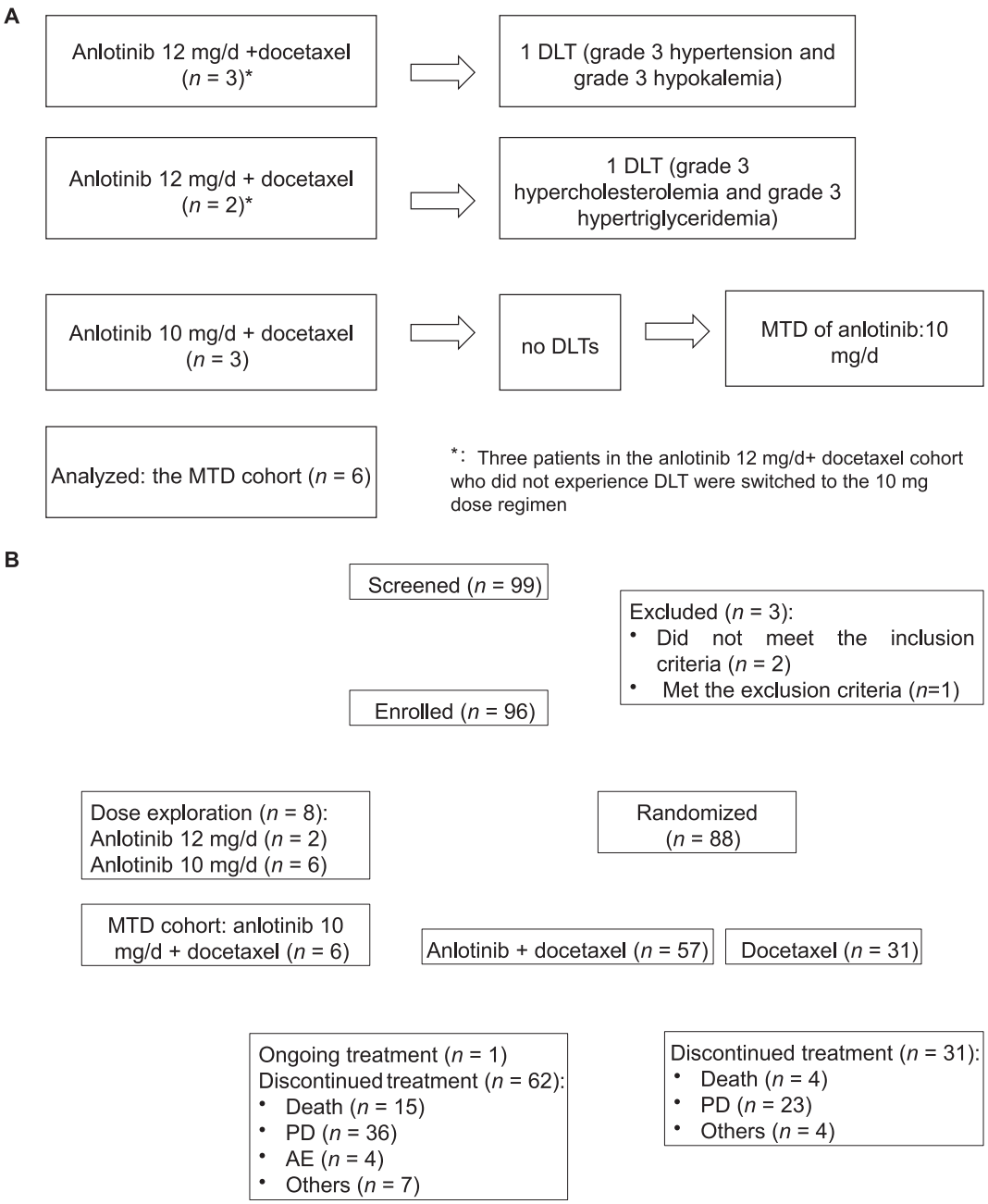

FIGURE 1 Study flowchart. (A) Dose exploration in the phase 1 trial. (B) Patient flowchart in the current phase 1/2 trial. AE indicates adverse event; DLT, dose-limiting toxicity; mg/d, milligrams per day; MTD, maximum tolerated dose; PD, progressive disease.

MTD of anlotinib combined with docetaxel

In the phase 1 trial, in total, eight patients were enrolled. At the 12-mg dose level of anlotinib, one of the initial three patients experienced grade 3 hypertension and grade 3 hypokalemia, and both were considered DLTs. Two additional patients were subsequently enrolled at the same dose, and one of them developed grade 3 hypercholesterolemia and grade 3 hypertriglyceridemia, which also classified as DLTs. Three patients who did not experience DLTs were switched to the 10-mg dose regimen, and no DLTs were observed. Then, three additional patients were treated with 10 mg of anlotinib in combination with docetaxel, and no DLTs were observed. Therefore, the MTD of anlotinib combined with docetaxel was determined to be 10 mg (Figure 1A).

Efficacy

As of February 28, 2023, the median follow-up duration was 16.164 months (interquartile range [IQR], 10.355–21.973 months). In the phase 2 study, the combination of anlotinib and docetaxel resulted in a significant improvement in PFS compared with docetaxel

TABLE 1 Baseline patient characteristics in the phase 2 study, $N = 57$.

Characteristic	Anlotinib plus docetaxel, No. (%)	Docetaxel ($n = 31$)
Age: Median [range], years	64 (31–74)	63 (40-75)
Sex		
Men	53 (92.98)	25 (80.65%)
Women	4 (7.02)	6 (19.35%)
ECOG performance status		
0	13 (22.81)	9 (29.03%)
1	44 (77.19)	22 (70.97%)
Smoking history		
Never	19 (33.33)	12 (38.71%)
Former	36 (63.12)	16 (51.61%)
Unknown	0 (0.00)	1 (3.23%)
Smoking	2 (3.51)	2 (6.45%)
Histologic subtype		
SCC	24 (42.11)	14 (45.16%)
LCC	1 (1.75)	1 (3.23%)
ADC	31 (54.39)	15 (48.39%)
Others	1 (1.75)	1 (3.23%)
Metastatic disease	52 (91.23)	30 (96.77%)
No. of metastatic organs		
≤2	36 (63.16)	24 (77.42%)
>2	21 (36.84)	7 (22.58%)
Brain metastasis		
Yes	7 (12.28)	3 (9.68%)
No	49 (85.96)	27 (87.10%)
Unknown	1 (1.75)	1 (3.23%)
Clinical stage		
IIIB	7 (12.28)	1 (3.23%)
IIIC	0 (0.00)	4 (12.90%)
IV	50 (87.72)	26 (83.87%)
Previous treatment		
Surgery	31 (54.39)	13 (41.94%)
Platinum-based doublet chemotherapy	57 (100.00)	29 (93.55%)
Radiotherapy	19 (33.33)	10 (32.26%)
Targeted therapy	8 (14.04)	5 (16.13%)
Immunotherapy	25 (43.86)	14 (45.16%)
Others	3 (5.26)	4 (12·90%)
Concomitant diseases or symptoms	48 (84.21)	29 (93.55%)

Abbreviations: ADC, adenocarcinoma; ECOG, Eastern Cooperative Oncology Group; LCC, large cell carcinoma; SCC, squamous cell carcinoma.

monotherapy, with a median PFS of 5.39 months (95% CI, 3.98–9.26 months) versus 2.56 months (95% CI, 1.41–3.71 months; HR, 0.36; 95% CI, 0.21–0.63; log-rank $p = .0002$; Figure 2A). The 6-month PFS rate was 49.17% (95% CI, 32.45%–63.90%) in the combination group compared with 24.77% (95% CI, 9.92%-43.04%) in the monotherapy group (see Table S3). The median OS was 16.82 months (95% CI, 9.63–20.40 months) in the anlotinib plus docetaxel group versus 9.86 months (95% CI, 4.90 months to not evaluable [NE]) in the docetaxel monotherapy group (HR, 0.89; 95% CI, 0.47–1.66; log-rank $p = .7114$; Figure 2B). The 12-month OS rates were 61.60% (95% CI, 46.90%–73.34%) and 49.86% (95% CI, 29.95%–66.92%) in the combination and monotherapy groups, respectively (see Table S5). Similar trends were observed in pooled data from the phase 1 and 2 trials (see Tables S4 and S6 and Figure S3).

The ORR was 26.32% (95% CI, 15.54%–39.66%) for anlotinib plus docetaxel compared with 6.45% (95% CI, 0.79%–21.42%) for docetaxel monotherapy; and the disease control rate was 84.21% (95% CI, 72.13%–92.52%) versus 51.61% (95% CI, 33.06%-69.85%), respectively (Table 2). The median duration of response was 5.85 months (95% CI, 1.41–9.89 months) for the combination treatment versus 1.58 months (95% CI, NE to NE) for monotherapy (HR, 0.57; 95% CI, 0.06–5.17; log-rank $p = .6108$). The combined efficacy results from both the phase 1 and phase 2 studies are presented in Table S2.

In the docetaxel monotherapy group, follow-up treatment information was collected on 13 patients after discontinuation. Among these, nine patients received crossover treatment with anlotinib. Specifically, three patients received anlotinib monotherapy, and six patients received anlotinib in combination with other therapies.

Subgroup analyses of efficacy

Subgroup analyses demonstrated that the combination of anlotinib and docetaxel significantly improved PFS compared with docetaxel monotherapy across various baseline characteristics (Figure 3A), with the most pronounced benefits observed in patients who had LCC/ADC, SCC, and those who previously failed on immunotherapy. In addition, the OS benefit of anlotinib plus docetaxel was comparable to that of docetaxel monotherapy across these patient subgroups (Figure 3B).

In patients who had LCC/ADC, the median PFS was significantly prolonged in the anlotinib plus docetaxel group compared with the monotherapy group (6.24 months [95% CI, 5.03–10.09 months] vs. 2.40 months [95% CI, 0.72–3.71 months]; HR, 0.40; 95% CI, 0.19–0.82; log-rank $p = .0096$). Similarly, in patients who had SCC, the median PFS was extended (5.13 months [95% CI, 3.52–9.26 months] vs. 3.55 months [95% CI, 1.41–6.28 months]; HR, 0.33; 95% CI, 0.13–0.85; log-rank $p = .0156$; see Figure S1A,B). The median OS for patients with LCC/ADC was 20.40 months (95% CI, 7.49 months to NE) in the anlotinib plus docetaxel group versus not reached (95% CI, 2.00 months to NE) in the docetaxel group (log-rank $p = .6504$). For patients with SCC, the median OS was 14.36 months (95% CI, 7.20–17.35 months) in the anlotinib group versus 9.86 months (95%

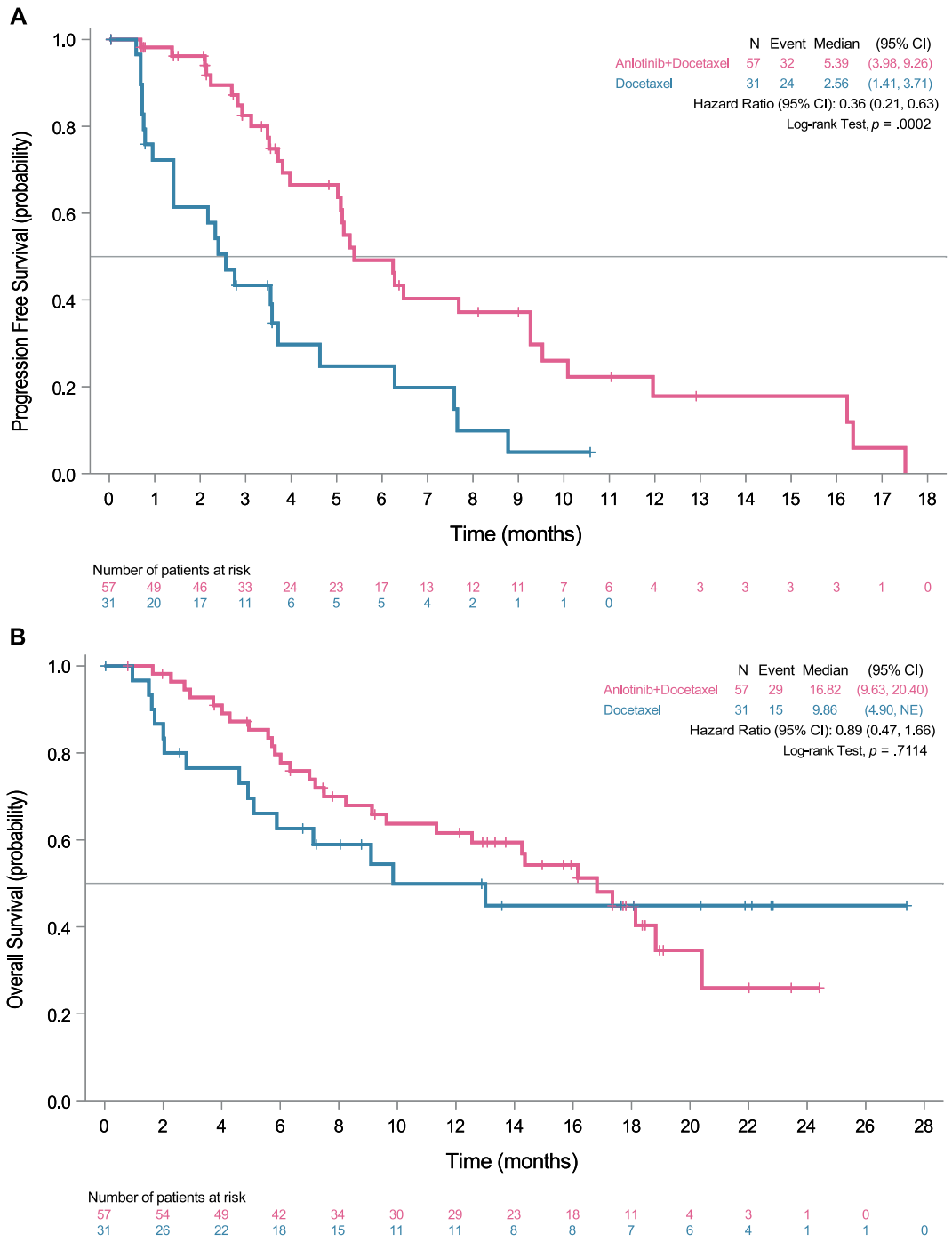

FIGURE 2 (A) Progression-free survival and (B) overall survival of patients with advanced nonsmall cell lung cancer in the phase 2 study. CI, confidence interval; HR, hazard ratio; NE, not evaluable.

CI, 4.60 months to NE) in the monotherapy group (see Figure S2A,2B).

Among patients who had previously failed immunotherapy, 25 participants in the anlotinib plus docetaxel group and 14 in the docetaxel group were analyzed. In this subgroup, anlotinib plus docetaxel significantly improved median PFS compared with docetaxel monotherapy (5.39 months [95% CI, 5.03–9.53 months] vs. 2.33 months [95% CI, 0.79–4.63 months]; HR, 0.12; 95% CI, 0.04–0.40; log-rank $p < .0001$; see Figure S1C). The median OS was 16.16 months (95% CI, 8.25 months to NE) in the combination group compared with 9.05 months (95% CI, 2.00 months to NE) in the docetaxel group (see Figure S2C).

For immunotherapy-naive patients, the anlotinib plus docetaxel group also demonstrated numerically a longer median PFS compared with the docetaxel group (6.24 months [95% CI, 3.48–10.09 months] vs. 3.55 months [95% CI, 0.76–7.59 months]; HR, 0.50; 95% CI, 0.24–1.04; log-rank $p = .0577$; see Figure S1D). In terms of OS, the anlotinib plus docetaxel group achieved a median OS of 17.35 months (95% CI, 7.49–NE) versus not reached (95% CI, 5.88 months to NE) in the docetaxel group (see Figure S2D).

TABLE 2 Tumor response as assessed by investigators according to Response Evaluation Criteria in Solid Tumors, version 1.1, in the phase 2 study.

	Total population		LCC/ADC		SCC	
Response	Anlotinib plus docetaxel, *n* = 57	Docetaxel, *n* = 31	Anlotinib plus docetaxel, *n* = 32	Docetaxel, *n* = 16	Anlotinib plus docetaxel, *n* = 24	Docetaxel, *n* = 14
Best overall response, no. (%)						
PR	15 (26.32)	2 (6.45)	8 (25.00)	1 (6.25)	6 (25.00)	1 (7.14)
SD	33 (57.89)	14 (45.16)	19 (59.38)	6 (37.50)	14 (58.33)	8 (57.14)
PD	7 (12.28)	12 (38.71)	3 (9.38)	7 (43.75)	4 (16.67)	4 (28.57)
NE	2 (3.51)	3 (9.68)	2 (6.25)	2 (12.50)	0 (0.0)	1 (7.14)
ORR [95% CI], %	26.32 [15.54–39.66]	6.45 [0.79–21.42]	25.00 [11.46–43.40]	6.25 [0.16–30.23]	25.00 [9.77–46.71]	7.14 [0.18–33.87]
DCR [95% CI], %	84.21 [72.13–92.52]	51.61 [33.06–69.85]	84.38 [67.21–94.72]	43.75 [19.75–70.12]	83.33 [62.62–95.26]	64.29 [35.14–87.24]

Abbreviations: ADC, adenocarcinoma; CI, confidence interval; DCR, disease control rate; LCC, large cell carcinoma; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SCC, squamous cell carcinoma; SD, stable disease.

Safety

In total, two patients in the anlotinib 12-mg plus docetaxel group, 63 in the anlotinib 10-mg plus docetaxel group, and 31 in the docetaxel monotherapy group were included in the safety set. TEAEs were observed in two of two (100%), 62 of 63 (98.41%), and 24 of 31 (77.42%) patients in the anlotinib 12-mg, anlotinib 10-mg, and docetaxel groups, respectively. Among these groups, grade ≥3 TEAEs were reported in two of two (100%), 34 of 63 (53.97%), and 10 of 31 (32.26%) patients, respectively (Table 3).

TRAEs occurred in two of two patients (100%) in the anlotinib 12-mg group, 59 of 63 (93.65%) in the anlotinib 10-mg group, and 19 of 31 (61.29%) in the docetaxel monotherapy group. Of these, two of two (100%), 30 of 63 (47.62%), and six of 31 (19.35%) patients, respectively, experienced grade ≥3 TRAEs. SAEs were documented in 13 of 63 patients (20.63%) in the anlotinib 10-mg group, in no patients (0%) in the anlotinib 12-mg group, and in seven of 31 patients (22.58%) in the docetaxel group. Discontinuation of treatment because of TEAEs occurred in four of 63 patients (6.35%) in the anlotinib 10-mg plus docetaxel group, and one TEAE-related death (3.23%) was reported in the docetaxel monotherapy group (Table 3).

The most frequently reported TEAEs included decreased neutrophil count (100% in the anlotinib 12-mg group, 46.03% in the anlotinib 10-mg group, and 32.26% in the docetaxel group) and decreased white blood cell count (100%, 42.86%, and 38.71%, respectively; Table 3).

DISCUSSION

The phase 1 study established the MTD of anlotinib at 10 mg in combination with docetaxel for patients with advanced NSCLC who had progressed after platinum-based chemotherapy. Although the standard first-line dose of docetaxel for NSCLC is 75 mg/m^2 every 3 weeks, a reduced dose of 60 mg/m^2 every 3 weeks was used in the current study because previous findings have demonstrated improved tolerability at this lower dose in Asian populations when used in the second-line setting.[22,23] The phase 2 trial demonstrated that anlotinib combined with docetaxel significantly prolonged PFS versus docetaxel monotherapy, with the combination regimen exhibiting a favorable safety and tolerability profile.

Anlotinib exerts its antitumor effects by inhibiting tumor angiogenesis, reducing cancer cell proliferation and migration, and modulating the tumor immune microenvironment toward a less immune-tolerant state.[12,24,25] The addition of anti-angiogenic agents to chemotherapy represents a promising therapeutic approach, enhancing the cytotoxic effects of chemotherapy on vulnerable tumor cells.[26] In this study, anlotinib plus docetaxel significantly improved PFS (median, 5.39 vs. 2.56 months) compared with docetaxel monotherapy in patients with advanced NSCLC who had failed platinum-based therapy. This outcome was either numerically superior or at least comparable to results from other second-line anti-angiogenic agents, such as ramucirumab plus docetaxel (median PFS, 4.5–5.22 months)[11,27] and nintedanib plus docetaxel (3.5 months),[21] as well as single-agent ICIs like tislelizumab (4.2 months),[4] sintilimab (4.3 months),[5] nivolumab (2.8 months),[6] and atezolizumab (2.8 months).[7] In addition, the ORR of 26.32% observed in this study was comparable to the ORRs reported in prior studies (range, 22.6%–28.9%).[4,5,11,27] Furthermore, the combination of anlotinib and docetaxel also yielded an improved median OS of 16.82 months, which is consistent with survival outcomes reported for ramucirumab plus docetaxel (median OS, 10.5–15.15 months),[11,27] nintedanib plus docetaxel (10.1 months),[21] and single-agent ICIs (11.79–16.9 months).[4–7] However, the observed crossover effect, in which initial OS discrimination was followed by a period of reduced difference, can be explained by several factors. First, after discontinuation, nine

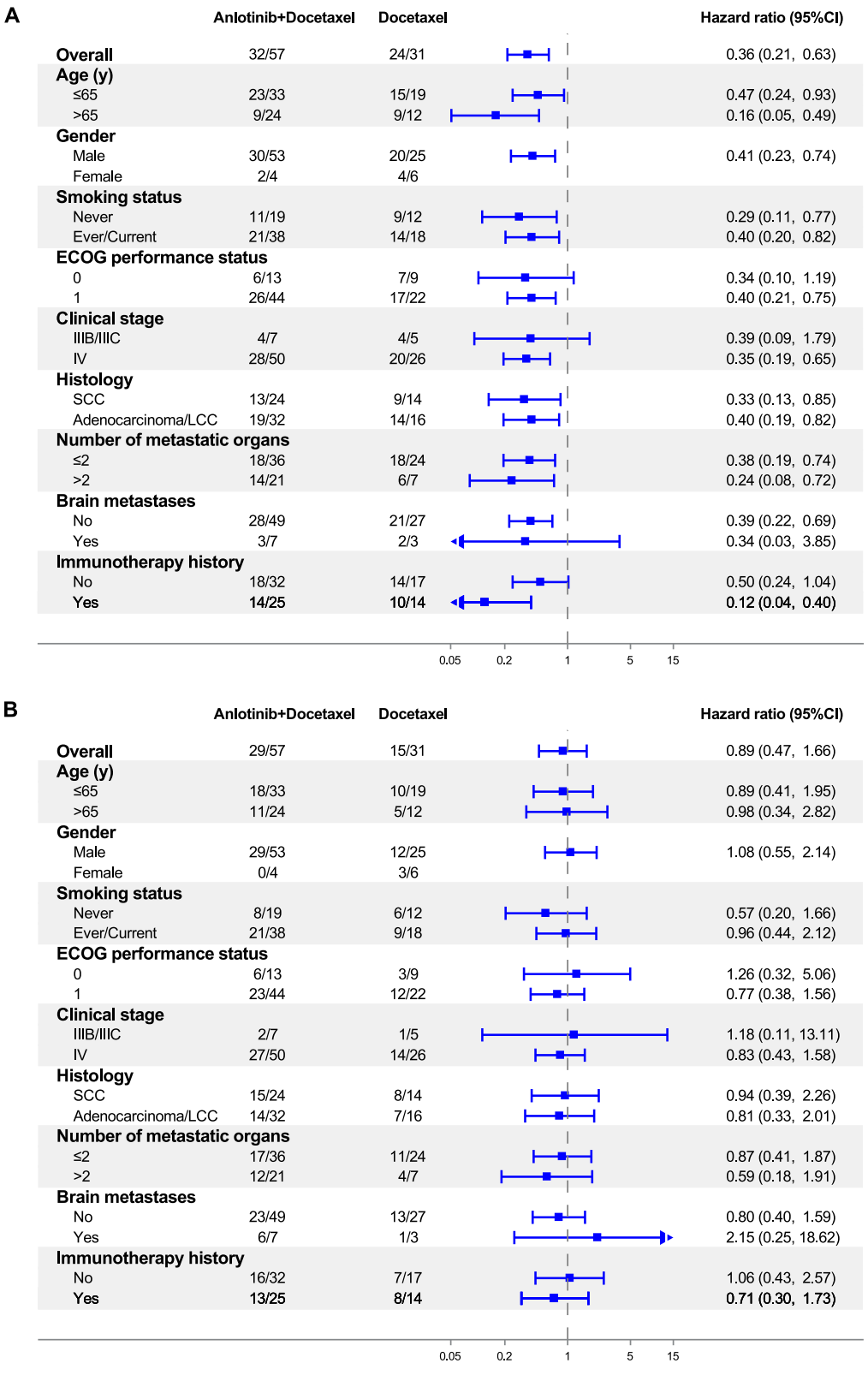

FIGURE 3 Subgroup analyses of (A) progression-free survival and (B) overall survival in the phase 2 study. CI indicates confidence interval; ECOG, Eastern Cooperative Oncology Group; SCC, squamous cell carcinoma.

of 13 patients in the control group received anlotinib as a crossover treatment. This crossover likely may contribute to the dilution of OS differences during certain time periods because patients in the control group derived a survival benefit from subsequent anlotinib therapy. Second, the relatively small sample size may have affected the consistency of OS discrimination throughout the study.

TABLE 3 Safety profile in the phase 1 (maximum tolerated dose cohort) and phase 2 studies.

	No. of events (%)			
	Anlotinib 10 mg plus docetaxel, $n = 63$		Docetaxel, $n = 31$	
Events	Any grade	Grade ≥3	Any grade	Grade ≥3
TEAE	62 (98.41)	34 (53.97)	24 (77.42)	10 (32.26)
TRAE	59 (93.65)	30 (47.62)	19 (61.29)	6 (19.35)
TEAE leading to dose reduction	12 (19.05)	—	1 (3.23)	—
TEAE leading to treatment discontinuation	4 (6.35)	—	0 (0.00)	0 (0.00)
SAE	13 (20.63)	—	7 (22.58)	—
TEAE leading to death	0 (0.00)	0 (0.00)	1 (3.23)	1 (3.23)
The most common TEAEs: >10% in either group)				
Neutrophil count decreased	29 (46.03)	18 (28.57)	10 (32.26)	4 (12.90)
White blood cell count decreased	27 (42.86)	11 (17.46)	12 (38.71)	4 (12.90)
Proteinuria	12 (19.05)	1 (1.59)	2 (6.45)	0 (0.00)
Anemia	12 (19.05)	0 (0.00)	5 (16.13)	0 (0.00)
Hand–foot syndrome	12 (19.05)	0 (0.00)	0 (0.00)	0 (0.00)
Hypertension	11 (17.46)	3 (4.76)	0 (0.00)	0 (0.00)
Diarrhea	10 (15.87)	1 (1.59)	0 (0.00)	0 (0.00)
Fatigue	10 (15.87)	1 (1.59)	3 (9.68)	0 (0.00)
Alopecia	10 (15.87)	0 (0.00)	1 (3.23)	0 (0.00)
Hypertriglyceridemia	9 (14.29)	1 (1.59)	1 (3.23)	0 (0.00)
Mucositis oral	9 (14.29)	2 (3.17)	0 (0.00)	0 (0.00)
Hypoalbuminemia	8 (12.70)	0 (0.00)	2 (6.45)	0 (0.00)
Hypokalemia	8 (12.70)	2 (3.17)	2 (6.45)	0 (0.0)
Cough	8 (12.70)	0 (0.00)	3 (9.68)	1 (3.23)
Sore throat	8 (12.70)	0 (0.00)	0 (0.00)	0 (0.00)
Abnormal liver function	7 (11.11)	0 (0.00)	1 (3.23)	0 (0.00)

Abbreviations: SAE, serious adverse event; TEAE: treatment-emergent adverse event; TRAE, treatment-related adverse event.

It is important to highlight that immunotherapy, either as monotherapy or in combination with chemotherapy, has become the standard first-line treatment for patients with advanced NSCLC who lack actionable driver mutations.[1,2] During the course of this study, as immunotherapy agents became more widely available and were covered by health insurance in China, more than 40% of the enrolled patients had received immunotherapy as their first-line treatment. Consequently, although our findings suggest that anlotinib combined with docetaxel demonstrates promising efficacy in advanced NSCLC and holds potential as a novel second-line treatment option, these results should be interpreted with caution. Further head-to-head clinical trials are necessary to substantiate this observation.

To account for this potential bias, we conducted a subgroup analysis focusing on patients who had previously received immunotherapy. The analysis revealed that anlotinib plus docetaxel extended median PFS (5.39 vs. 2.56 months) and OS (16.82 vs. 9.86 months) compared with docetaxel monotherapy, suggesting a beneficial survival advantage because of the synergistic antitumor effects of ICIs and tyrosine kinase inhibitors.[28,29] In the CONTACT-01 trial (ClinicalTrials.gov identifier NCT04471420), which included patients with advanced NSCLC who had previously received ICIs and chemotherapy and subsequently experienced disease progression, the median PFS was 4.6 months in the atezolizumab plus cabozantinib arm compared with 4.0 months in the docetaxel arm, with the median OS reported as 10.7 months and 10.5 months, respectively.[30] Similarly, in the SAPPHIRE trial (ClinicalTrials.gov identifier NCT03906071), sitravatinib plus nivolumab did not significantly improve PFS (4.4 vs. 5.4 months; $p = 0.452$) or OS (12.2 vs. 10.6 months; $p = 0.144$) compared with docetaxel monotherapy in patients with advanced nonsquamous NSCLC who had progressed after prior treatment with platinum-based chemotherapy and ICIs.[31] These studies underscore the limited efficacy of immunotherapy rechallenge as a second-line

option in advanced NSCLC. Moreover, our findings are consistent with previous studies evaluating second-line anti-angiogenic agents.[32–34] The median PFS in patients who received nintedanib or ramucirumab plus chemotherapy was reported as 5.5–5.9 months in those who progressed after platinum-based chemotherapy and/or ICIs.[32,33] Notably, the median OS with ramucirumab plus docetaxel was 19.8 months in patients who progressed after prior immunotherapy, which is comparable to the 16.16 months observed with anlotinib plus docetaxel in the current study.[33] These findings suggest that chemotherapy combined with targeted agents may be a viable therapeutic alternative in this patient population. This trend of survival benefit was also observed in immunotherapy-naive patients, in whom anlotinib plus docetaxel resulted in superior median PFS (6.24 vs. 3.55 months) compared with docetaxel alone. The HR for PFS in immunotherapy-naive patients was 0.50, which was higher than the HR of 0.12 observed in patients who had previously failed immunotherapy. This suggests that patients with prior immunotherapy exposure may derive greater PFS benefit from second-line anlotinib combined with docetaxel. However, the median PFS was 6.24 months in the immunotherapy-naive group compared with 5.39 months in the group that had received prior immunotherapy. This suggests that, in terms of absolute PFS time, the immunotherapy-naive group may have an advantage. However, these findings should be interpreted with caution. The sample size for the subgroup analysis was relatively small, which may affect the robustness of the results. In addition, there may be differences in baseline characteristics between the subgroups that could influence the comparison of treatment effects.

Recent studies have demonstrated that the combination of ICIs with anti-angiogenic agents or novel agents, such as datopotamab deruxtecan, may represent a promising second-line treatment option for patients with NSCLC who have failed first-line chemotherapy and/or immunotherapy.[35–37] In the MORPHEUS-Lung study (ClinicalTrials.gov identifier NCT03337698), atezolizumab combined with bevacizumab significantly improved PFS (7.0 vs. 4.6 months) and OS (13.7 vs. 9.6 months) compared with docetaxel in patients with NSCLC who progressed after prior platinum-based chemotherapy and anti–PD-L1/PD-1 therapy, whether administered concurrently or sequentially.[35] Similarly, the Lung-MAP S1800A trial (ClinicalTrials.gov identifier NCT03971474) demonstrated that ramucirumab plus pembrolizumab significantly improved OS (14.5 vs. 11.6 months) compared with the standard of care (including docetaxel/ramucirumab, docetaxel, gemcitabine, and pemetrexed) in patients with advanced NSCLC who progressed after prior anti–PD-L1/PD-1 therapy and/or platinum-based chemotherapy.[36] Consequently, for patients with advanced NSCLC who have failed prior immunotherapy, the combination of anlotinib with chemotherapy or ICIs as a second-line treatment warrants further investigation.

In addition, PFS benefits were observed across various subgroups that received with docetaxel plus anlotinib, in line with the primary analysis. Notably, both patients with SCC and those with LCC/ADC showed improved outcomes with the addition of anlotinib, consistent with the subgroup analysis from the ALTER 0303 trial.[38]

The observed median PFS for docetaxel in the current study (2.56 months) is consistent with the CheckMate 078 trial (ClinicalTrials.gov identifier NCT02613507),[6] which enrolled Chinese patients and reported a median PFS of 2.8 months for docetaxel. This also aligns with findings from other studies, including LUME-Lung 1 trial (ClinicalTrials.gov identifier NCT00805194; median PFS, 2.7 months),[21] ORIENT-3 (ClinicalTrials.gov identifier NCT03150875; median PFS, 2.79 months),[5] REVEL (median PFS, 3.0 months),[11] and a phase 3 trial comparing pemetrexed with docetaxel (median PFS, 2.9 months).[39] These results further support the appropriateness of using the PFS achieved with docetaxel as a benchmark for the control group in our study. Although trials like CheckMate 017 (ClinicalTrials.gov identifier NCT01642004)[40] and CheckMate 057 (ClinicalTrials.gov identifier NCT01673867)[41] reported higher median PFS values for docetaxel, the smaller sample size of our control group (31 patients) and the focus on a specific Chinese population likely contributed to the observed variation in the data.

The safety profile of the anlotinib plus docetaxel regimen in this study was comparable to that observed with other anti-angiogenic agents in combination with chemotherapy.[11,21,27] The incidence of TEAEs was similar (98.41% vs. 93.6%–100%), as was the rate of SAEs (20.63% vs. 28.9%–43%), with hematologic events being the most common TEAEs. No TEAEs leading to death were observed in the anlotinib plus docetaxel group, and the rate of TEAEs leading to treatment discontinuation was 6.35%, which was lower than the 22.7% reported with nintedanib plus docetaxel.[21] Thus anlotinib combined with docetaxel as a second-line therapy in NSCLC was generally well tolerated, with no new safety signals identified.[14,25]

However, this study has certain limitations. Despite being adequately powered, the sample size was relatively small, and the findings require validation in larger phase 3 clinical trials. Moreover, the study population was limited to Chinese patients, which may affect the generalizability of the results.

In conclusion, anlotinib plus docetaxel significantly improved PFS compared with docetaxel monotherapy in patients with advanced NSCLC who had failed prior platinum-based chemotherapy. The combination regimen demonstrated a favorable safety profile and could represent a potential second-line treatment option for these patients. Furthermore, for patients who have failed both immunotherapy and/or platinum-based chemotherapy, the combination of anlotinib with either chemotherapy or ICIs presents a viable avenue for exploration in future second-line treatment strategies.

AUTHOR CONTRIBUTIONS

Jiawei Shou: Conceptualization; methodology; writing—original draft; writing—review and editing; data curation. **Jun Chen**: Conceptualization; writing—original draft; writing—review and editing; data curation. **Qunyi Guo**: Data curation; writing—review and editing. **Wei Hong**: Data curation; writing—review and editing. **Yonghui Wang**: Data curation; writing—review and editing. **Chuangzhou Rao**: Data curation; writing—review and editing. **Liqin Lu**: Data curation; writing–review and editing. **Xinmei Yang**: Data curation; writing—

review and editing. **Dan Zhu**: Data curation; writing—review and editing. **Fen Lan**: Data curation; writing—review and editing. **Yong Fang**: Conceptualization; writing—original draft; writing—review and editing. **Hongming Pan**: Conceptualization; project administration; writing—original draft; writing—review and editing

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data collection form and extracted data can be made available upon request to the corresponding authors Yong Fang (Email: fangyong@zju.edu.cn.) and Hongming Pan (Email: panhongming@zju.edu.cn).

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REFERENCES

1. Guidelines Working Committee of the Chinese Society of Clinical Oncology. *Guidelines of Chinese Society of Clinical Oncology (CSCO): non-small-cell lung cancer*. People's medical publishing house co., Ltd.; 2023.
2. National Comprehensive Cancer Network (NCCN). *NCCN Guidelines: Non-Small Cell Lung Cancer Version 2.2024*. NCCN; 2024.
3. Wu L, Deng C, Zhang H, et al. Efficacy and safety of docetaxel and sodium cantharidinate combination vs. either agent alone as second-line treatment for advanced/metastatic NSCLC with wild-type or unknown EGFR status: an open-label, randomized controlled, prospective, multi-center phase III trial (Cando-L1). *Front Oncol*. 2021;11:769037. doi:10.3389/fonc.2021.769037
4. Zhou C, Huang D, Fan Y, et al. Tislelizumab versus docetaxel in patients with previously treated advanced NSCLC (RATIONALE-303): a phase 3, open-label, randomized controlled trial. *J Thorac Oncol*. 2023;18(1):93-105. doi:10.1016/j.jtho.2022.09.217
5. Shi Y, Wu L, Yu X, et al. Sintilimab versus docetaxel as second-line treatment in advanced or metastatic squamous non-small-cell lung cancer: an open-label, randomized controlled phase 3 trial (ORIENT-3). *Cancer Commun (Lond.)*. 2022;42(12):1314-1330. doi:10.1002/cac2.12385
6. Wu YL, Lu S, Cheng Y, 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(5):867-875. doi:10.1016/j.jtho.2019.01.006
7. 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(10066):255-265. doi:10.1016/s0140-6736(16)32517-x
8. Chen B, Zhao H, Huang J, et al. Efficacy of regorafenib combined with PD-1 inhibitors in elderly patients with advanced metastatic colorectal cancer. *BMC Geriatr*. 2022;22(1):987. doi:10.1186/s12877-022-03637-9
9. Liu J, Liao S, Huang Y, et al. PDGF-D improves drug delivery and efficacy via vascular normalization, but promotes lymphatic metastasis by activating CXCR4 in breast cancer. *Clin Cancer Res*. 2011;17(11):3638-3648. doi:10.1158/1078-0432.ccr-10-2456
10. Zhou Q, Gallo JM. Differential effect of sunitinib on the distribution of temozolomide in an orthotopic glioma model. *Neuro Oncol*. 2009;11(3):301-310. doi:10.1215/15228517-2008-088
11. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384(9944):665-673. doi:10.1016/s0140-6736(14)60845-x
12. Shen G, Zheng F, Ren D, et al. Anlotinib: a novel multi-targeting tyrosine kinase inhibitor in clinical development. *J Hematol Oncol*. 2018;11(1):120. doi:10.1186/s13045-018-0664-7
13. Han B, Li K, Wang Q, et al. Effect of anlotinib as a third-line or further treatment on overall survival of patients with advanced non-small cell lung cancer: the ALTER 0303 phase 3 randomized clinical trial. *JAMA Oncol*. 2018;4(11):1569-1575. doi:10.1001/jamaoncol.2018.3039
14. Xiang M, Yang X, Ren S, et al. Anlotinib combined with S-1 in third- or later-line stage IV non-small cell lung cancer treatment: a phase II clinical trial. *Oncologist*. 2021;26(12):e2130-e2135. doi:10.1002/onco.13950
15. Han B, Chu T, Zhang W, et al. First-line anlotinib-based combination treatment for patients with advanced non-small cell lung cancer: a three arms, prospective study [abstract]. *J Clin Oncol*. 2021;39(15 suppl):e21073. doi:10.1200/jco.2021.39.15_suppl.e21073
16. Chu T, Zhang W, Zhang B, et al. Efficacy and safety of first-line anlotinib-based combinations for advanced non-small cell lung cancer: a three-armed prospective study. *Transl Lung Cancer Res*. 2022;11(7):1394-1404. doi:10.21037/tlcr-22-438
17. Han B, Li K, Zhao Y, et al. Anlotinib as a third-line therapy in patients with refractory advanced non-small-cell lung cancer: a multicentre, randomised phase II trial (ALTER0302). *Br J Cancer*. 2018;118(5):654-661. doi:10.1038/bjc.2017.478
18. Djebbari F, Rampotas A, Vallance G, et al. Efficacy of isatuximab with pomalidomide and dexamethasone in relapsed myeloma: results of a UK-wide real-world dataset. *Hemasphere*. 2022;6:e738. doi:10.1097/hs9.0000000000000738
19. Chinese Medical Association; Oncology Society of Chinese Medical Association; Chinese Medical Association Publishing House. Chinese Medical Association guidelines for clinical diagnosis and treatment of lung cancer (edition 2018) [article in Chinese]. *Zhonghua Zhong Liu Za Zhi*. 2018;40(12):935-964. doi:10.3760/cma.j.issn.0253-3766.2018.12.012
20. Kawaguchi T, Ando M, Asami K, et al. Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small-cell lung cancer: Docetaxel and

Erlotinib Lung Cancer Trial (DELTA). *J Clin Oncol*. 2014;32(18):1902-1908. doi:10.1200/jco.2013.52.4694
21. Reck M, Kaiser R, Mellemgaard A, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. *Lancet Oncol*. 2014;15(2):143-155. doi:10.1016/s1470-2045(13)70586-2
22. Watanabe N, Niho S, Kirita K, et al. Second-line docetaxel for patients with platinum-refractory advanced non-small cell lung cancer and interstitial pneumonia. *Cancer Chemother Pharmacol*. 2015;76(1):69-74. doi:10.1007/s00280-015-2775-y
23. Seto T, Hirai F, Saka H, et al. Safety and tolerability of selumetinib as a monotherapy, or in combination with docetaxel as second-line therapy, in Japanese patients with advanced solid malignancies or non-small cell lung cancer. *Jpn J Clin Oncol*. 2018;48(1):31-42. doi:10.1093/jjco/hyx144
24. Song M, Wen J, Xiangfeng B, Jie T, Wenjie W, Jiayu L. Clinical application and efficacy evaluation of the mitral annuloplasty ring Carpentier–Edwards Physio II. *J Kunming Med Univ*. 2020;41:85-88.
25. Gao Y, Liu P, Shi R. Anlotinib as a molecular targeted therapy for tumors. *Oncol Lett*. 2020;20(2):1001-1014. doi:10.3892/ol.2020.11685
26. Daum S, Hagen H, Naismith E, Wolf D, Pircher A. The role of anti-angiogenesis in the treatment landscape of non-small cell lung cancer—new combinational approaches and strategies of neovessel inhibition. *Front Cell Dev Biol*. 2020;8:610903. doi:10.3389/fcell.2020.610903
27. Yoh K, Hosomi Y, Kasahara K, et al. A randomized, double-blind, phase II study of ramucirumab plus docetaxel vs placebo plus docetaxel in Japanese patients with stage IV non-small cell lung cancer after disease progression on platinum-based therapy. *Lung Cancer*. 2016;99:186-193. doi:10.1016/j.lungcan.2016.07.019
28. Sharma P, Goswami S, Raychaudhuri D, et al. Immune checkpoint therapy—current perspectives and future directions. *Cell*. 2023;186(8):1652-1669. doi:10.1016/j.cell.2023.03.006
29. Zhao Y, Guo S, Deng J, et al. VEGF/VEGFR-targeted therapy and immunotherapy in non-small cell lung cancer: targeting the tumor microenvironment. *Int J Biol Sci*. 2022;18(9):3845-3858. doi:10.7150/ijbs.70958
30. Neal J, Pavlakis N, Kim S, Lim S, Mountzios G, Fountzilas E. C60 CONTACT-01: Efficacy and safety from a phase III study of atezolizumab (atezo) + cabozantinib (cabo) vs docetaxel (doc) monotherapy in patients (pts) with metastatic NSCLC (mNSCLC) previously treated with checkpoint inhibitors and chemotherapy [abstract]. *J Thorac Oncol*. 2023;18(4 suppl):S39-S40. doi:10.1016/S1556-0864(23)00260-5
31. Borghaei H, Johnson ML, Garon EB, et al. LBA63 Phase III study of sitravatinib plus nivolumab versus docetaxel in patients with previously treated advanced non-squamous non-small cell lung cancer (NSCLC) [abstract]. *Ann Oncol*. 2023;34(suppl 2):S1308. doi:10.1016/j.annonc.2023.10.064
32. Grohe C, Gleiber W, Haas S, et al. Nintedanib plus docetaxel after progression on immune checkpoint inhibitor therapy: insights from VARGADO, a prospective study in patients with lung adenocarcinoma. *Future Oncol*. 2019;15(23):2699-2706. doi:10.2217/fon-2019-0262
33. Tozuka T, Kitazono S, Sakamoto H, et al. Addition of ramucirumab enhances docetaxel efficacy in patients who had received anti-PD-1/PD-L1 treatment. *Lung Cancer*. 2020;144:71-75. doi:10.1016/j.lungcan.2020.04.021
34. Grohé C, Blau W, Gleiber W, et al. Real-world efficacy of nintedanib plus docetaxel after progression on immune checkpoint inhibitors: results from the ongoing, non-interventional VARGADO study. *Clin Oncol (R Coll Radiol)*. 2022;34(7):459-468. doi:10.1016/j.clon.2021.12.010
35. Ghiringhelli F, Felip E, Zer A. et al. 1441P Atezolizumab and bevacizumab (atezo + bev) ± radiotherapy (RT) vs docetaxel (doc) in checkpoint inhibitor (CPI)–experienced metastatic NSCLC (mNSCLC): results from the phase Ib/II MORPHEUS-lung study [abstract]. *Ann Oncol*. 2023;34(suppl 2):S819-S820. doi:10.1016/j.annonc.2023.09.2472
36. Reckamp KL, Redman MW, Dragnev KH, et al. Phase II randomized study of ramucirumab and pembrolizumab versus standard of care in advanced non-small-cell lung cancer previously treated with immunotherapy—Lung-MAP S1800A. *J Clin Oncol*. 2022;40(21):2295-2306. doi:10.1200/jco.22.00912
37. Ahn MJ, Lisberg AE, Paz-Ares L, et al. 509MO Datopotamab deruxtecan (Dato-DXd) vs docetaxel in previously treated advanced/metastatic (adv/met) non-small cell lung cancer (NSCLC): results of the randomized phase III study TROPION-Lung01 [abstract]. *Ann Oncol*. 2023;34(suppl 4):S1305-S1306. doi:10.1016/j.annonc.2023.10.588
38. Cheng Y, Han B, Li K, et al. Effect of anlotinib as a third- or further-line therapy in advanced non-small cell lung cancer patients with different histologic types: subgroup analysis in the ALTER0303 trial. *Cancer Med*. 2020;9(8):2621-2630. doi:10.1002/cam4.2913
39. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol*. 2004;22(9):1589-1597. doi:10.1200/jco.2004.08.163
40. 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(2):123-135. doi:10.1056/nejmoa1504627
41. 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(17):1627-1639. doi:10.1056/nejmoa1507643

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