

ORIGINAL RESEARCH

## Safety and activity of alectinib plus bevacizumab in patients with advanced *ALK*-rearranged non-small-cell lung cancer: a phase I/II study

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**Background:** Alectinib, a second-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI), is highly effective in advanced *ALK*-rearranged non-small-cell lung cancer and represents a standard first-line therapy. New strategies are needed, however, to delay resistance. We conducted a phase I/II study to assess the safety and efficacy of combining alectinib with bevacizumab, a monoclonal antibody against vascular endothelial growth factor.

**Patients and methods:** Patients with advanced *ALK*-rearranged non-squamous non-small-cell lung cancer were enrolled. The phase I portion employed a dose de-escalation strategy with alectinib and bevacizumab starting at the individual standard doses. The primary objective was to determine the recommended phase II dose (RP2D). In phase II, the primary objective was to evaluate the safety of the combination at the RP2D; the secondary objective was to determine extracranial and intracranial efficacy.

**Results:** Eleven patients were enrolled between September 2015 and February 2020. Most patients (82%) had baseline brain metastases. Six patients (55%) were treatment-naïve; five (46%) had received prior ALK TKIs (crizotinib,  $n = 3$ ; ceritinib,  $n = 1$ ; crizotinib then brigatinib,  $n = 1$ ). No dose-limiting toxicities occurred. RP2D was determined as alectinib 600 mg orally twice daily plus bevacizumab 15 mg/kg intravenously every 3 weeks. Three patients experienced grade 3 treatment-related adverse events: pneumonitis related to alectinib, proteinuria related to bevacizumab, and hypertension related to bevacizumab. Treatment-related intracranial hemorrhage was not observed. Six (100%) of six treatment-naïve patients and three (60%) of five ALK TKI-pretreated patients had objective responses; median progression-free survival was not reached (95% confidence interval, 9.0 months-not reached) and 9.5 months (95% confidence interval, 4.3 months-not reached), respectively. Intracranial responses occurred in four (100%) of four treatment-naïve and three (60%) of five TKI-pretreated patients with baseline brain metastases. The study was stopped prematurely because of slow accrual.

**Conclusions:** Alectinib plus bevacizumab was well tolerated without unanticipated toxicities or dose-limiting toxicities.

**Key words:** alectinib, bevacizumab, anaplastic lymphoma kinase, non-small-cell lung cancer, targeted therapy

### INTRODUCTION

Anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) have significantly improved outcomes of patients with advanced *ALK*-rearranged non-small-cell

lung cancer (NSCLC). Crizotinib, a first-generation ALK TKI, became the initial standard first-line therapy for advanced *ALK*-rearranged NSCLC after demonstrating superior efficacy compared with platinum-pemetrexed chemotherapy.<sup>1</sup> Several randomized phase II trials have since demonstrated, however, that more potent and central nervous system (CNS)-active second-generation ALK TKIs (alectinib, brigatinib, and ensartinib) are superior to crizotinib in the first-line setting.<sup>2-4</sup> Alectinib in particular has been commonly used on the basis of the phase III global ALEX trial, which demonstrated significantly prolonged progression-free survival (PFS) compared with crizotinib with a median PFS of 25.7 months versus 10.4 months (by independent review committee assessment).<sup>2</sup> Despite this efficacy, drug resistance develops, and disease progression is inevitable in most patients.<sup>5-7</sup>

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As one approach to improve upon the efficacy of second-generation ALK inhibitors, a third-generation ALK TKI, lorlatinib, was evaluated in patients with untreated advanced ALK-rearranged NSCLC in the phase III CROWN study.<sup>8</sup> The comparator here, however, was crizotinib—rather than a second-generation ALK TKI—with markedly superior PFS in favor of lorlatinib. An alternative strategy being explored to delay resistance and disease progression is combination therapy, built upon the foundation of an ALK inhibitor. To date, various partners including anti-programmed cell death protein 1/programmed death-ligand 1 checkpoint inhibitors,<sup>9-12</sup> heat shock protein 90 inhibitors,<sup>13</sup> and inhibitors of MET,<sup>14,15</sup> MEK,<sup>16,17</sup> or SHP2<sup>18,19</sup> have been combined with an ALK TKI. A combination regimen that offers additive clinical benefit in advanced ALK-rearranged NSCLC is yet to be established.

Bevacizumab is an anti-angiogenic monoclonal antibody targeting the vascular endothelial growth factor (VEGF) signaling pathway, which has shown efficacy when combined with platinum-based chemotherapy in advanced non-squamous NSCLC.<sup>20</sup> Despite initial concerns related to the potential risk of intracranial hemorrhage limiting its use in patients with brain metastases, multiple studies have now demonstrated the safety and efficacy of bevacizumab in treating brain metastases in NSCLC when combined with either chemotherapy or targeted therapy.<sup>21-23</sup> This is particularly relevant in ALK-rearranged NSCLC given its propensity to form CNS metastases.<sup>24,25</sup> Furthermore, in advanced NSCLC harboring epidermal growth factor receptor (*EGFR*) gene mutations, a combination of erlotinib, a first-generation *EGFR* TKI, with bevacizumab significantly improved PFS compared with erlotinib alone.<sup>26-28</sup> The combination of bevacizumab and erlotinib was granted approval by the European Medicines Agency for the first-line treatment of patients with advanced *EGFR*-mutant NSCLC. More recently, in a phase I/II study, bevacizumab combined with osimertinib, a third-generation CNS-active *EGFR* inhibitor, was found to be well tolerated and met the study's prespecified endpoint for effectiveness,<sup>29</sup> providing the rationale for an ongoing phase III trial of osimertinib with or without bevacizumab in advanced untreated *EGFR*-mutant NSCLC ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04181060) identifier NCT04181060).

Here, we carried out a phase I/II trial to evaluate the safety and efficacy of bevacizumab plus alectinib in patients with advanced ALK-rearranged NSCLC.

## MATERIALS AND METHODS

### Study design and participants

This study was an investigator-initiated, single-institution, open-label, single-arm phase I/II clinical trial. Eligible patients had locally advanced or metastatic non-squamous NSCLC with ALK rearrangements as established using ALK FISH, immunohistochemistry, or next-generation sequencing. ALK FISH was considered positive if >15% of tumor cells demonstrated abnormal signals. Patients who were treatment-naïve in the advanced setting, as well as those who had disease progression on previous treatments

including ALK TKI(s), were permitted to enroll; however, prior alectinib or anti-angiogenic therapy was not permitted. While patients were initially required to have at least one measurable CNS lesion per modified RECIST version 1.1<sup>30</sup> in addition to measurable extracranial disease by RECIST version 1.1, the protocol was later amended to allow enrollment with or without measurable CNS disease. Other key eligibility criteria included age 18 years or older, Eastern Cooperative Oncology Group performance status of 0-2, and adequate end-organ function. Patients who had clinically stable or asymptomatic untreated, non-hemorrhagic CNS metastases were eligible.

Key exclusion criteria included: squamous cell or mixed, predominantly squamous adenosquamous histology; history of hemoptysis; tumor infiltrating into large vessels or proximal tracheobronchial network; intracranial hemorrhage; history of or genetic predisposition to a bleeding diathesis or coagulopathy; arterial or venous thromboembolic events within 6 months of enrollment; and poorly controlled arterial hypertension (systolic >150 mm Hg and/or diastolic > 100 mm Hg). The protocol was approved by the local Institutional Review Board, and all patients provided written informed consent before screening.

### Study procedures

In the phase I portion of the study, a 3 + 3 dose de-escalation design was used to determine the recommended phase II dose (RP2D) of alectinib and bevacizumab. Starting alectinib dose of 600 mg twice daily administered orally (p.o.) and bevacizumab dose of 15 mg/kg every 3 weeks administered intravenously (i.v.) were selected based on the individual RP2Ds for each medication and anticipation for minimal overlapping toxicities. If no dose-limiting toxicities (DLTs) were observed at the initial dose level, the cohort was expanded to a total of six patients to determine the final dose level established as RP2D. DLTs were defined as adverse events (AEs) occurring within the first cycle of treatment (21 days) attributed to the study drugs. The RP2D for the combination of alectinib and bevacizumab was defined as either (i) the highest dosage cohort in which less than a third of patients experienced a DLT, or (ii) alectinib at the previously defined RP2D as a single agent (600 mg twice daily) plus bevacizumab at the highest tolerated dose investigated for the indication (15 mg/kg every 21 days), whichever was the lower dose. In the phase II portion of the study, all patients received alectinib plus bevacizumab at the RP2D determined in the phase I portion.

Cycles were 21 days long. Treatment was continued until there was evidence of progressive disease, death, or unacceptable toxicity. Patients were allowed to continue study drugs beyond progression if deemed clinically beneficial at the investigator's discretion. Intra-patient dose modification of bevacizumab was not permitted. Dose holds and reductions of alectinib were permitted in the event of protocol-specified treatment-related AEs. Patients could remain on alectinib alone despite discontinuation of

bevacizumab, provided they were tolerating alectinib. Of note, this study period spanned the COVID-19 pandemic.<sup>31</sup> During the pandemic, the protocol was amended to allow bevacizumab infusions to be held in the absence of toxicity at the investigator's discretion, to minimize patient exposures.

Safety assessments were carried out in all patients at baseline, on day 1 and day 15 of the first cycle, and every 3 weeks thereafter. For patients who were holding or had permanently discontinued bevacizumab, safety assessments could be carried out every 6 weeks. AEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Computed tomography scans of the chest and abdomen (and pelvis if clinically indicated) and brain magnetic resonance imaging (MRI) scans were obtained at baseline, every 6 weeks for the first 10 cycles of study treatment, and every 12 weeks thereafter. Patients in the phase I portion who had no evidence of intracranial metastases on brain MRI screening were not required to undergo subsequent brain MRI. Response assessment was conducted according to the RECIST version 1.1. For patients with brain metastases, intracranial response was assessed using modified RECIST version 1.1.<sup>30</sup>

### Outcomes

The primary objectives of this study were to determine the RP2D of the combination of alectinib and bevacizumab (phase I) and to evaluate the safety and tolerability of alectinib and bevacizumab at the RP2D as assessed using the CTCAE version 4.0 (phase II). The secondary endpoints were safety, tolerability, and DLTs (in phase I); CNS objective response rate (ORR), CNS disease control rate (DCR; defined as the rate of complete response, partial response, and stable disease), CNS PFS, overall (intra- and extra-CNS) ORR, overall (intra- and extra-CNS) DCR, PFS, and patient-reported functioning and impact on disease/treatment-related symptoms of brain metastases and global QOL assessed using European Organisation for Research and Treatment of Cancer quality of life questionnaire (QLQ)-C30 and QLQ-BN20. PFS was measured as the time from the start of the study drug treatment until disease progression or death.

### Statistical analysis

For the dose-finding, phase I portion of the study, no hypothesis was pre-established, and sample size was not predefined. For the phase II portion of the study, the combination of alectinib and bevacizumab was to be deemed unsafe if two or more patients were observed to have grade 2 or higher CNS hemorrhagic events. We initially planned to enroll 20 patients, which would guarantee that the study treatment discontinuation rate was not higher than 28% based upon the upper bound of the 95% exact binomial confidence interval (CI). Because of slow accrual, however, the decision was made to stop the study prematurely in July 2021.

Safety data are summarized for all patients who received at least one dose of study treatment. Efficacy data are reported for all patients with a baseline scan and at least one post-treatment scan, or in patients who had a best overall response of progressive disease or death before the end of cycle 1. CNS and overall PFS rates were estimated using the Kaplan-Meier method. Data were pooled for the phase I and phase II cohorts. Statistical analyses were carried out using SAS version 9.4. This study is registered with [ClinicalTrials.gov](https://clinicaltrials.gov) (identifier NCT02521051).

## RESULTS

### Patient characteristics

Between September 2015 and February 2020, a total of 11 patients with advanced *ALK*-rearranged NSCLC were enrolled and received at least one dose of the study drugs. One additional patient initially provided consent but withdrew thereafter with the preference of starting commercial alectinib. Baseline demographics and disease characteristics for the 11 patients who received alectinib plus bevacizumab are presented in [Table 1](#). The data cut-off for these analyses was 31 July 2021. The median age at the time of study entry was 46 years (range, 25-66 years). Most patients were never smokers (72.7%), and all had adenocarcinoma. Most patients (81.8%) had active brain metastases at baseline. Two of the nine patients with baseline brain metastases had previously received brain radiation [either whole brain radiotherapy ( $n = 1$ ) completed 17.0 months before study start, or stereotactic radiosurgery ( $n = 1$ ) completed 3.5 months before study start], with definite evidence of subsequent CNS disease progression before study enrollment.

Six patients (54.5%) were treatment-naïve. The remaining 5 patients (45.5%) had received the following prior *ALK* TKI(s): crizotinib only ( $n = 3$ ), ceritinib only ( $n = 1$ ), or crizotinib followed by brigatinib ( $n = 1$ ). All patients discontinued their preceding *ALK* TKI because of disease progression (CNS and extra-CNS progression,  $n = 2$ ; CNS only,  $n = 2$ ; extra-CNS only,  $n = 1$ ). The median time interval between the last *ALK* TKI dose and the initiation of alectinib plus bevacizumab was 8 days (range, 5-10). None of the patients had received prior chemotherapy or immunotherapy.

### Safety and toxicity

All 11 patients were evaluated for toxicity. No DLTs were identified in the initial dosing cohort of six patients enrolled in the phase I portion of the study. Therefore, dosing de-escalation was not pursued, and RP2D was established as p.o. alectinib 600 mg twice a day plus i.v. bevacizumab 15 mg/kg every 21 days.

The most common treatment-related AEs occurring in more than one patient enrolled in phase I/II portions were: myalgia ( $n = 7$ ; 63.6%), fatigue ( $n = 5$ , 45.5%), diarrhea ( $n = 5$ , 45.5%), hypertension ( $n = 4$ , 36.4%), proteinuria ( $n = 4$ , 36.4%), edema of the limbs ( $n = 4$ , 36.4%), increased alanine aminotransferase ( $n = 4$ , 36.4%),

Baseline characteristic	<i>n</i> = 11
Age, years	
Median (range)	46 (25-66)
Sex, <i>n</i> (%)	
Male	5 (45.5)
Female	6 (54.5)
Race, <i>n</i> (%)	
White	8 (72.7)
Asian	2 (18.2)
Unknown	1 (9.1)
ECOG performance status, <i>n</i> (%)	
0	7 (63.6)
1	3 (27.3)
2	1 (9.1)
Smoking status, <i>n</i> (%)	
Never	8 (72.7)
Light (<10 pack-years)	3 (27.3)
Histology, <i>n</i> (%)	
Adenocarcinoma	11 (100)
Brain metastases, <i>n</i> (%)	
Present <sup>a</sup>	9 (81.8)
Absent	2 (18.2)
ALK testing, <i>n</i> (%)	
IHC	2 (18.2)
FISH	9 (81.8)
Line of therapy	
Median (range)	1 (1-3)
Prior ALK TKIs, <i>n</i> (%)	
Yes <sup>b</sup>	5 (45.5)
No	6 (54.5)

ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; TKI, tyrosine kinase inhibitor.

<sup>a</sup> Two patients had received prior brain radiation (whole brain radiotherapy, one; stereotactic radiosurgery, one) with subsequent progression in the central nervous system and active brain metastases before study enrollment.

<sup>b</sup> Three patients had received prior crizotinib; one had received prior ceritinib; and one had received prior crizotinib followed by brigatinib.

constipation (*n* = 4, 36.4%), increased creatine phosphokinase (CPK) (*n* = 3, 27.3%), increased aspartate aminotransferase (AST) (*n* = 3, 27.3%), epistaxis (*n* = 3, 27.3%), nausea (*n* = 3, 27.3%), hypophosphatemia (*n* = 3, 27.3%), increased bilirubin (*n* = 2, 18.2%), and maculopapular rash (*n* = 2, 18.2%) (Table 2). Three patients experienced grade 3 serious AEs that were deemed related to study treatment: pneumonitis related to alectinib (*n* = 1), proteinuria related to bevacizumab (*n* = 1), and hypertension related to bevacizumab (*n* = 1). No grade 4 or 5 AEs occurred. The patient who experienced grade 3 pneumonitis attributed to alectinib discontinued study treatment because of this toxicity. Seven patients (63.6%) discontinued bevacizumab early (but continued alectinib monotherapy on the study), after a median of 9 cycles of treatment (range, 4-48). A total of 4 patients (36.4%) stopped bevacizumab due to treatment-related AEs [proteinuria (*n* = 3), fatigue (*n* = 1)]. The remaining 3 patients discontinued bevacizumab following diverticular abscess not related to study treatment (*n* = 1), following radiation to a progressive disease site (*n* = 1), or per patient preference (after cycle 48 on the study without disease progression or toxicity, *n* = 1). All seven patients who discontinued bevacizumab early remained on the study and continued with alectinib monotherapy. Overall, treatment-naïve patients (*n* = 6) received a median of 17.5

Treatment-related adverse events, <i>n</i> (%)	Any grade	Grade 3/4
Myalgia	7 (64)	0
Fatigue	5 (46)	0
Diarrhea	5 (46)	0
Hypertension	4 (36)	1 (9)
Proteinuria	4 (36)	1 (9)
Edema limbs	4 (36)	0
ALT increased	4 (36)	0
Constipation	4 (36)	0
CPK increased	3 (27)	0
AST increased	3 (27)	0
Epistaxis	3 (27)	0
Nausea	3 (27)	0
Hypophosphatemia	3 (27)	0
Bilirubin increased	2 (18)	0
Rash, maculopapular	2 (18)	0
Pneumonitis	1 (9)	1 (9)
Anemia	1 (9)	0
Hemoptysis	1 (9)	0
Gingival bleeding	1 (9)	0
Hematoma	1 (9)	0
Tongue sensitivity	1 (9)	0
Headache	1 (9)	0
Dysgeusia	1 (9)	0
Bloating	1 (9)	0
Sinus congestion	1 (9)	0
Palpitations	1 (9)	0
Memory impairment	1 (9)	0
Influenza-like syndrome	1 (9)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase.

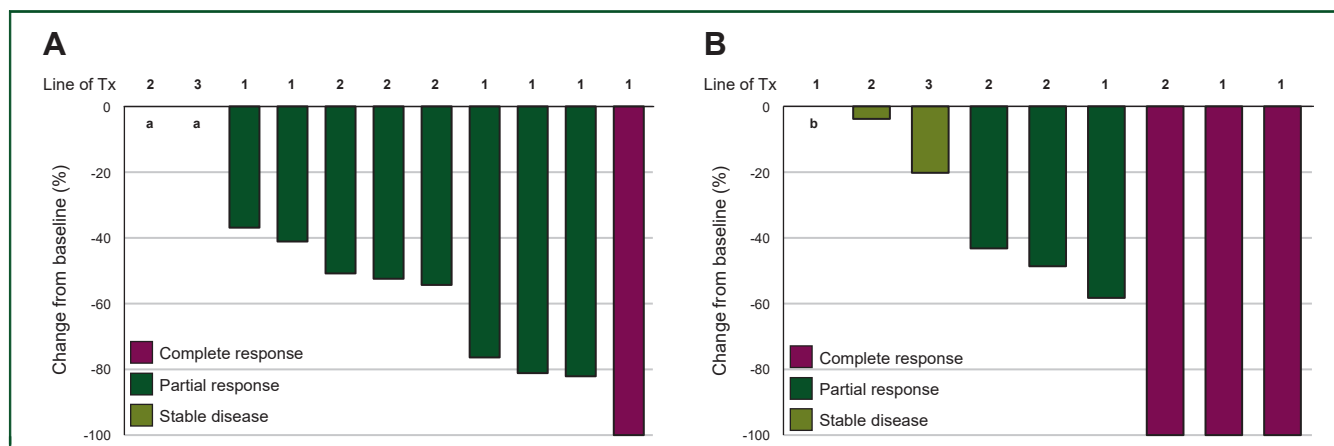
cycles of bevacizumab (range, 4-48), and patients with prior ALK TKI treatment (*n* = 5) received a median of 7 cycles of bevacizumab (range, 7-34). One patient required dose reductions of alectinib to 300 mg twice daily because of grade 2 fatigue possibly related to study treatment.

No treatment-related deaths were reported. Of note, although the majority of patients (81.8%) had untreated brain metastases at baseline, intracranial hemorrhagic events were not observed. One patient (9.1%) had grade 1 hemoptysis deemed possibly related to bevacizumab, and one patient (9.1%) had grade 1 hematoma related to bevacizumab. Serious or fatal hemorrhagic events did not occur in this study.

### Efficacy

All patients were included in the efficacy analysis. Overall, nine patients (81.8%) had confirmed objective responses, of which one (9.1%) was a complete response (Figure 1A). All had disease control (DCR 100%). The median PFS of the overall population was 19.1 months (95% CI 4.3 months-not reached) after a median follow-up of 34.9 months (median follow-up for patients still alive by the end of the study: 37 months) (Figure 2A).

Among treatment-naïve patients who received alectinib plus bevacizumab as initial treatment ('first-line cohort,' *n* = 6), the ORR and DCR were both 100% (6/6 confirmed objective responses), and the median PFS was not reached (95% CI 9.0 months-not reached) (Supplementary Figure S1A and Supplementary Table S1, available at



**Figure 1. Antitumor activity of alectinib plus bevacizumab in patients with advanced ALK-rearranged non-small-cell lung cancer.**

(A) Overall antitumor activity of alectinib plus bevacizumab as shown in the waterfall plot of best percentage change from baseline in the sum of longest tumor diameters. (B) Intracranial antitumor activity of alectinib plus bevacizumab in patients with measurable and non-measurable brain metastases at baseline ( $n = 9$ ).

Line of Tx, line of study treatment of advanced lung cancer.

<sup>a</sup> Patients who had stable disease with 0% tumor shrinkage as best response.

<sup>b</sup> Patients who had complete intracranial response with resolution of non-measurable baseline brain metastasis.

<https://doi.org/10.1016/j.esmooop.2021.100342>). Among patients who had received prior ALK TKI(s) ('ALK TKI-pretreated cohort,'  $n = 5$ ), the ORR was 60% (3/5), DCR 100% (5/5), and the median PFS 9.5 months (95% CI 4.3 months-not reached), respectively (Supplementary Figure S1A and Supplementary Table S1, available at <https://doi.org/10.1016/j.esmooop.2021.100342>). Of the three responders who had received prior ALK TKIs, two had experienced prior disease progression on crizotinib, whereas one patient had experienced prior CNS and extracranial disease progression on first-line ceritinib.

At data cut-off, four patients (36%) had died. The 2-year OS rate for the entire cohort was 63.6%.

### CNS efficacy

Among 9 patients with measurable or non-measurable CNS lesions at baseline, the CNS ORR was 77.8% (7/9) and CNS DCR was 100% (9/9) (Figure 1B; Supplementary Figure S2, available at <https://doi.org/10.1016/j.esmooop.2021.100342>). Of note, four patients (44.4%) had CNS complete responses. Among 8 patients with measurable CNS target lesions at baseline, the CNS ORR was 75.0% (6/8; 3 CNS complete responses) and CNS DCR was 100% (8/8). The median CNS PFS was not reached (95% CI 4.3 months-not reached) (Figure 2B).

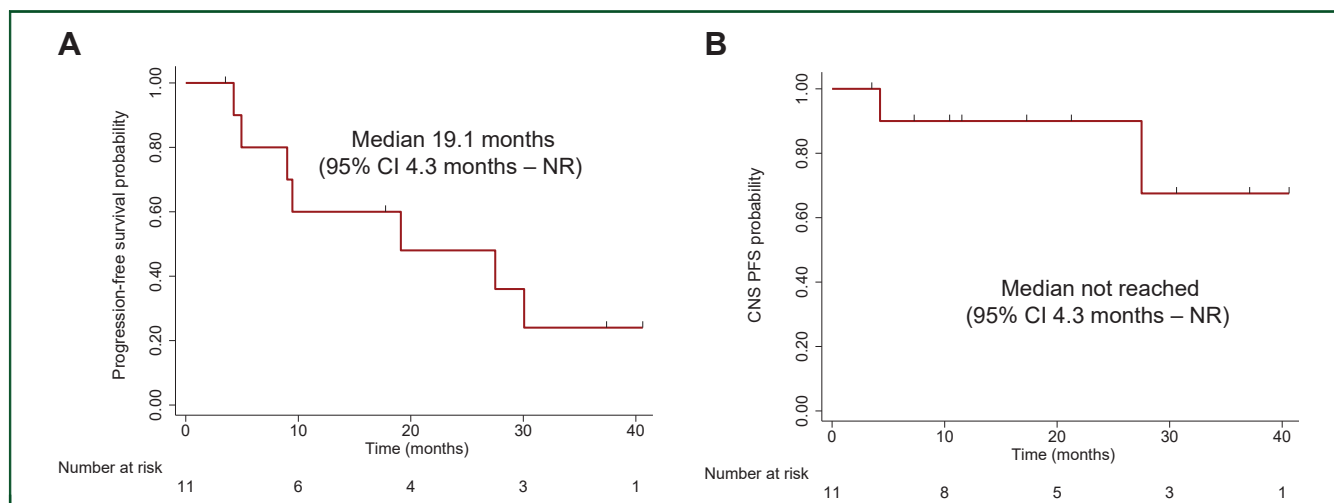
In the first-line cohort, the CNS ORR and CNS DCR among 4 patients with measurable or non-measurable baseline brain metastases were 100% (4 CNS responses, 3 of which were CNS complete responses) (Supplementary Figure S1B and Supplementary Table S1, available at <https://doi.org/10.1016/j.esmooop.2021.100342>). The median CNS PFS was not reached (95% CI 27.5 months-not reached). In the ALK TKI-pretreated cohort, among 5 patients, all of whom had measurable baseline brain metastases, the CNS ORR was 60% (3/5), CNS DCR was 100% (5/5), and the median CNS PFS was not reached (95% CI 4.3 months-not reached) (Supplementary Figure S1B and Supplementary Table S1, available at <https://doi.org/10.1016/j.esmooop.2021.100342>).

The three CNS responders in the ALK TKI-pretreated cohort included one crizotinib-pretreated patient with a CNS complete response, another crizotinib-pretreated patient with a CNS partial response, and a ceritinib-pretreated patient with prior CNS progression who then had CNS partial response to alectinib plus bevacizumab.

### DISCUSSION

To our knowledge, this is the first phase I/II trial to be published reporting on the safety and activity of adding the anti-VEGF inhibitor bevacizumab to alectinib in patients with advanced ALK-rearranged NSCLC. In this study, the combination was found to be tolerable with no new safety signals identified. Based on the safety assessment, p.o. alectinib 600 mg twice daily combined with i.v. bevacizumab 15 mg/kg every 3 weeks was determined to be the recommended phase II doses for the combination.

With five ALK inhibitors currently approved for first-line use in advanced ALK-rearranged NSCLC, anticipated toxicities influence the selection of first-line regimen. The most frequent treatment-related AEs of alectinib plus bevacizumab were highly concordant with the toxicities anticipated from each individual agent—such as myalgia, increased CPK, and edema associated with alectinib,<sup>2,32,33</sup> or hypertension, proteinuria, and epistaxis associated with bevacizumab.<sup>34,35</sup> The overall safety of combining bevacizumab with alectinib in this study is in line with a previously presented Japanese phase II study of alectinib plus bevacizumab in patients with ALK-rearranged NSCLC who had progressed on prior alectinib,<sup>36</sup> and with prior trials assessing tolerability of bevacizumab when combined with chemotherapy or with other targeted therapies such as crizotinib or EGFR TKIs erlotinib or osimertinib.<sup>20,21,26,29,37,38</sup> The rate of discontinuation of bevacizumab due to AEs is also comparable to that reported in prior studies, with proteinuria representing the most common treatment-related AE resulting in bevacizumab discontinuation which



**Figure 2. Progression-free survival and central nervous system (CNS) progression-free survival of patients treated with alectinib plus bevacizumab.**

Kaplan–Meier curves depicting (A) progression-free survival and (B) CNS progression-free survival of 11 patients enrolled in the study. CI, confidence interval; NR, not reached; PFS, progression-free survival.

likely reflects the dose-dependent effect of bevacizumab on the development of proteinuria and the long treatment of patients on combination regimen.<sup>28,34,35,39,40</sup> It is worth noting that despite the presence of brain metastases at baseline in the majority of patients enrolled in this study, intracranial hemorrhagic events did not occur. Whereas this finding supports the safety of using bevacizumab in patients with *ALK*-rearranged NSCLC who have known high incidence of brain metastases, further investigation is warranted given the small size of this study cohort.

In this study, the combination of alectinib plus bevacizumab was highly efficacious in both TKI-naïve and TKI-pretreated patients (ORR 100% and 60%, respectively; and DCR 100% and 100%, respectively), as anticipated on the basis of the known efficacy of alectinib alone in these patient populations.<sup>2,33</sup> The CNS ORR among treatment-naïve patients with measurable and non-measurable CNS metastases at baseline was 100% with a CNS complete response rate of 75% (compared with 59% and 45%, respectively, with alectinib monotherapy in the global ALEX trial<sup>2</sup>), although the number of patients was very small and further investigation of CNS and extracranial efficacy is required. It is possible that anti-angiogenic therapy with bevacizumab may improve TKI delivery and efficacy in the CNS through modulation of the tumor vasculature.<sup>41</sup> Furthermore, of note, bevacizumab has additionally demonstrated efficacy in treating brain radiation necrosis,<sup>42,43</sup> which is not uncommon in *ALK*-rearranged NSCLC given the frequency of CNS metastases which may require local therapies.

Our study raises several questions regarding the future clinical development of *ALK*-VEGF inhibitor combinations in *ALK*-rearranged NSCLC. First, could the combination of anti-VEGF therapy plus an *ALK* TKI augment efficacy beyond that achieved with an *ALK* TKI alone? Further studies are needed in order to provide the rationale for pursuing randomized trials. Second, what is the optimal line of therapy (i.e. first-line versus later-line) in which VEGF inhibition may be combined with an *ALK* TKI? Prior studies have demonstrated

at least some clinical benefit from the addition of bevacizumab to alectinib or lorlatinib after disease progression on *ALK* TKI monotherapy;<sup>36,44</sup> however, whether the combination is best pursued upfront versus following disease relapse on an *ALK* inhibitor remains undetermined. And third, in such studies focused on assessing the efficacy of *ALK*-VEGF inhibitor combinations, how do we select the best endpoint (PFS versus OS)? In the context of advanced, treatment-naïve *EGFR*-mutant NSCLC, the randomized phase III NEJ026 trial demonstrated that bevacizumab plus erlotinib significantly prolonged PFS compared with erlotinib monotherapy, but this did not translate into OS benefit.<sup>27,45</sup> The multicenter phase III ARTEMIS-CTONG1509 study in Chinese patients with untreated *EGFR*-mutant NSCLC similarly showed PFS benefit from the combination of bevacizumab plus erlotinib, and while the OS data remained immature, the mature 2-year and 3-year OS rates were not significantly different between the combination arm and the erlotinib monotherapy arm.<sup>26</sup> The potential benefit of adding bevacizumab to a more CNS-active and potent, third-generation *EGFR* TKI osimertinib, however, remains to be determined, and is currently being evaluated in an ongoing randomized phase III trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04181060) identifier NCT04181060). Furthermore, whether the observations made in the *EGFR*-mutant NSCLC patient population will be mirrored in *ALK*-rearranged NSCLC is unknown.

Finally, what is the optimal duration of bevacizumab when combining with an *ALK* inhibitor in patients with advanced *ALK*-rearranged lung cancer, who may continue on the same line of treatment for several years? Indeed, the median PFS with first-line treatment using second-generation *ALK* inhibitors including alectinib exceeds 2 years.<sup>2–4</sup> Whereas four patients (36%) in this study discontinued bevacizumab early due to treatment-related AEs, seven patients (63.6%) overall discontinued bevacizumab early due to either treatment-related AEs, per investigator discretion, or per patient preference, after a median of 9 cycles of bevacizumab (range, 4–48). Long-term addition

of an agent that must be administered i.v. and will inevitably increase toxicities is certainly a weighty consideration for patients who may otherwise be treated with an oral TKI alone, as is the added cost of such combination regimens. It will be important to consider these questions on the combination strategy of ALK TKI plus anti-VEGF therapy, in addition to other combination approaches (i.e. an ALK inhibitor plus chemotherapy), which collectively will provide the framework for informing potential avenues to augment efficacy and offer more durable disease control in patients with *ALK*-rearranged lung cancer.

This study had several limitations. As mentioned, the sample size was small owing to the slow accrual and premature closure of the study. Multiple factors likely contributed to the limited accrual. First, *ALK*-rearranged NSCLC remains a small subset of lung cancer overall. Second, although our institution is a major referral center for patients with *ALK*-rearranged lung cancers, the availability of multiple approved first-line ALK inhibitors meant that the majority of patients were not being referred for first-line clinical trial options. Third, this was a single-institution study, impacting access. Fourth, the trial regimen incorporated i.v. bevacizumab infusions, necessitating more frequent visits than would typically be required for patients receiving standard-of-care p.o. ALK TKIs—a difference further exacerbated when patients remain on treatment for years. Other contributors included the availability of other competing clinical trials and the COVID-19 pandemic which occurred during the study period.

Another limitation of our study was that the patient population enrolled in this study was heterogeneous and included both TKI-naïve and TKI-pretreated patients, as the primary objective of the study was to assess the safety and tolerability of the combination. Although the toxicity profile was overall reassuring without significant new safety signals in this analysis, there may not have been sufficient power to capture an increase in relatively rare events, which requires further study. Additionally, the efficacy assessment requires ongoing investigation. Some patients were remaining on the combination therapy and the PFS and OS data were immature; in this setting, it is not yet feasible to determine subsequent patient outcomes after disease progression. This study was also not designed to formally evaluate mechanisms of resistance to alectinib plus bevacizumab, given the small sample size and the non-randomized nature of the study (in terms of comparing with resistance mechanisms to alectinib alone).

### Conclusions

In summary, to the best of our knowledge, this study suggests that the combination of bevacizumab with a second-generation ALK inhibitor alectinib is safe and tolerable in patients with advanced *ALK*-rearranged NSCLC, including in patients with baseline brain metastases. Toxicities in line with those anticipated from each individual agent were observed from the combination. More broadly, this trial

raises important considerations for the design of future studies of ALK inhibitor combinations, particularly in the first-line setting. Multicentered clinical trials will help enhance patient access, and modifications to eligibility criteria—such as allowing the enrollment of patients who received up to a limited duration of single-agent ALK TKI without evidence of disease progression—may further provide flexibility for referrals and enrollment. An abbreviated course of the combination partner could be considered where appropriate (e.g. with an anti-angiogenic agent or chemotherapy). Finally, incorporation of telehealth into trial design could ameliorate the burden patients incur related to travel for on-site visits, although this may be more relevant and feasible for studies without i.v. infusion requirements.

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