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Phase Ib/II study of ceritinib in combination with ribociclib in patients with *ALK*-rearranged non–small cell lung cancer

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ABSTRACT

Background: Preclinical data show that the combination of an ALK inhibitor (ALKi) with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) may act synergistically to overcome drug resistance mechanisms. Here, we assessed the safety, tolerability, and preliminary clinical activity of ceritinib, an ALKi in combination with ribociclib, a CDK4/6i, in patients with *ALK*-rearranged non–small cell lung cancer (NSCLC).
Methods: This was a multicenter, open-label, phase Ib/II dose-escalation study to determine the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D) for ceritinib plus ribociclib therapy.
Results: Twenty-seven adult patients with *ALK*-rearranged advanced NSCLC with an ECOG PS ≤ 2 were enrolled into five cohorts to receive various dose combinations of ceritinib (range, 300–450 mg/day) and ribociclib (range, 100–300 mg/day). Median age of patients was 57 years. MTDs were not reached in this study. Enrollment into phase Ib was terminated early and phase II was not opened due to changes in the *ALK*-rearranged NSCLC treatment landscape. Ceritinib 300 mg/day and ribociclib 200 mg/day (3-weeks-on/1-week-off schedule) was identified as the RP2D. Among the 27 evaluable patients, the overall response rate (ORR) was 37.0% (95% CI, 19.4–57.6) and median progression-free survival (mPFS) was 21.5 months (95% CI, 5.5–25.0). At RP2D, the ORR was 50.0%, disease control rate was 75%, and mPFS was 24.8 months (95% CI, 5.5–25.1). Safety profile of the combination therapy was consistent with single-agent safety data.
Conclusion: Combination of ceritinib and ribociclib showed clinical activity with a manageable safety profile in patients with advanced *ALK*-rearranged NSCLC.

1. Introduction

Non–small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases [1]. Rearrangements in the anaplastic lymphoma kinase (*ALK*) gene are recognized oncogenic drivers and are detected in approximately 2% to 7% of NSCLC cases [2,3]. Therapies targeting the

Abbreviations: ALK, anaplastic lymphoma kinase; CDK4/6, cyclin-dependent kinases 4 and 6; ECOG PS, Eastern Cooperative Oncology Group performance status; MTD, maximum tolerated dose; NSCLC, non–small cell lung cancer; RP2D, recommended phase II dose; WHO, World Health Organization.

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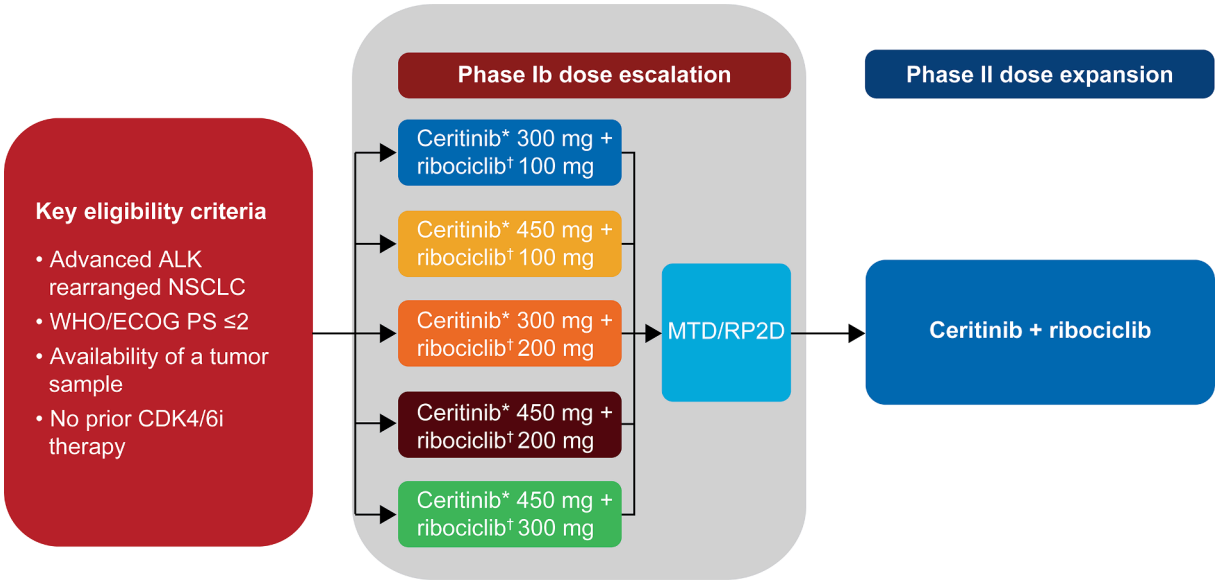

Fig. 1. Study design.

ALK protein in patients with *ALK*-rearranged NSCLC have shown clinically meaningful and durable responses with a manageable toxicity profile [4–6]. The ALK inhibitor (ALKi) ceritinib is an effective and safe treatment option for patients with NSCLC tumors that harbor *ALK* rearrangements [7–9]. However, the efficacy of ceritinib is limited by the development of acquired drug resistance [10]. Delaying *de novo* resistance mechanisms to ALKi or restoring dependence on ALK signaling in resistant tumor cells is a central focus of clinical investigation.

Simultaneous inhibition of ALK and an alternative pro-tumorigenic pathway is a key strategy to improve outcomes in patients who develop resistance to ALKi therapies. Preclinical evidence suggests that cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) may prevent or delay the emergence of resistance to ALKi, and a combination of an ALKi with a CDK4/6i may offer synergistic antitumor activity [11]. Ribociclib is an orally bioavailable, highly selective, small-molecule inhibitor of CDK4/6 [12]. Since CDK4/6 kinases are key downstream effectors of both PI3K and MAPK signaling, ribociclib may overcome resistance to ALK inhibition that emerges secondary to bypass track activation [11,13]. Therefore, a combination therapy with ceritinib and ribociclib may be able to overcome two primary resistance pathways associated with relapse in patients treated with ALKi.

This study aimed to evaluate the safety, tolerability, maximum tolerated dose (MTD), recommended phase II dose (RP2D), and efficacy of ceritinib in combination with ribociclib in patients with *ALK*-rearranged NSCLC.

2. Methods

2.1. Study design

This was a multicenter, open-label study to determine the safety and tolerability of ceritinib and ribociclib given as combination treatment in patients with advanced *ALK*-rearranged NSCLC (Fig. 1). This study was initiated on 14 May 2015 and terminated on 26 September 2018. In the phase Ib dose-escalation part of the study, adult patients with advanced *ALK*-rearranged NSCLC received ceritinib (starting dose: 300 mg, once daily [QD]) in combination with ribociclib (starting dose: 100 mg QD, 3-weeks-on/1-week-off schedule) under fed conditions (low-calorie, low-fat meal). The starting doses for the combination were selected based on SimCYP modeling of drug-drug interactions (DDIs) as well as the observed pharmacokinetics (PK) in patients and healthy volunteers. Patients were treated until disease progression, development of unacceptable toxicity, or withdrawal of informed consent. Data on the requirements for dose reductions/interruptions are described in the Supplementary Appendix.

The co-primary endpoints of phase Ib were to determine the incidence rate of dose–limiting toxicities (DLTs) during the first cycle of treatment and evaluate exposure to study drugs measured by PK parameters (area under the curve $[AUC]_{0-24h}$ at cycle 1 day 15). Secondary endpoints were to determine the overall response rate (ORR), progression-free survival using Kaplan-Meier estimation, disease control rate (DCR), time to response, duration of response, and overall survival. Safety was assessed as the incidence of adverse events (AEs) and changes in laboratory values and electrocardiograms (ECGs). Tolerability was assessed as the frequency of dose interruptions and dose reductions. After the confirmation of the RP2D for study drugs, patients were to be enrolled in the phase II study.

3. Patients

Adult patients with *ALK*-rearranged advanced NSCLC with an Eastern Cooperative Oncology Group performance status ≤ 2 were included in this study. Details of diagnostic methods used for the confirmation of ALK status are provided in the Supplementary Appendix. Patients who had neurologically unstable symptomatic central nervous system metastases or those who were previously treated with CDK4/6i therapy were excluded. Furthermore, patients with long QT syndrome, family history of idiopathic sudden death, or congenital long QT syndrome were excluded.

This study was conducted in accordance with the Good Clinical Practice guidelines of the International Conference on Harmonisation and the principles of the Declaration of Helsinki, and applicable local health authority regulations. The study protocol and all amendments were approved by the independent ethics committee or institutional review board. Informed consent was obtained from each patient.

3.1. Assessments

Safety was assessed as the incidence of AEs according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03. A DLT was defined as an AE or abnormal laboratory value assessed as unrelated to disease, disease progression, intercurrent illness, or concomitant medications that occurred within the first 28 days of treatment with

Table 1
Patient demographics and disease characteristics.

	Ceritinib 300 mg + ribociclib 100 mg n = 4	Ceritinib 450 mg + ribociclib 100 mg n = 7	Ceritinib 300 mg + ribociclib 200 mg n = 4	Ceritinib 450 mg + ribociclib 200 mg n = 7	Ceritinib 450 mg + ribociclib 300 mg n = 5	All patients N = 27
Age, median (range), years	54.5 (41.0–61.0)	64.0 (43.0–76.0)	58.0 (32.0–64.0)	49.0 (31.0–67.0)	58.0 (38.0–76.0)	57.0 (31.0–76.0)
Sex, n (%)						
Female	1 (25.0)	4 (57.1)	4 (100.0)	4 (57.1)	3 (60.0)	16 (59.3)
Male	3 (75.0)	3 (42.9)	0	3 (42.9)	2 (40.0)	11 (40.7)
Race, n (%)						
Asian	1 (25.0)	4 (57.1)	1 (25.0)	1 (14.3)	2 (40.0)	9 (33.3)
Caucasian	3 (75.0)	3 (42.9)	3 (75.0)	4 (57.1)	3 (60.0)	16 (59.3)
Other	0	0	0	1 (14.3)	0	1 (3.7)
Unknown	0	0	0	1 (14.3)	0	1 (3.7)
WHO/ECOG PS, n (%)						
0	4 (100.0)	5 (71.4)	2 (50.0)	4 (57.1)	3 (60.0)	18 (66.7)
1	0	2 (28.6)	2 (50.0)	3 (42.9)	2 (40.0)	9 (33.3)
Tumor histology, n (%)						
Adenocarcinoma	4 (100.0)	7 (100.0)	4 (100.0)	7 (100.0)	5 (100.0)	27 (100.0)
Presence of brain metastasis at screening, n (%)	1 (25)	2 (28.6)	2 (50.0)	4 (57.1)	2 (40.0)	11 (40.7)
Prior antineoplastic therapy, n (%)						
No prior ALK inhibitors	3 (75)	2 (28.6)	1 (25)	1 (14.3)	1 (20.0)	8 (29.6)
Crizotinib[a]	1 (25.0)	4 (57.1)	2 (50.0)	5 (71.4)	2 (40.0)	14 (51.9)
Next-generation ALK inhibitors	0	1 (14.3)	1 (25.0)	1 (14.3)	2 (40.0)	5 (18.5)
Median number of prior lines of antineoplastic therapy (range)[b]	1.0 (1.0–1.0)	3.5 (2.0–8.0)	2.0 (2.0–5.0)	2.0 (1.0–6.0)	2 (1.0–3.0)	2.0 (1.0–8.0)

Abbreviations: ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; max, maximum; min, minimum; WHO, World Health Organization.
[a] Patients who received crizotinib only as ALK inhibitor.
[b] Median (min–max) represents the number of prior regimens received by an individual patient.

ribociclib and ceritinib and met pre-specified criteria as per the protocol. ECG assessments were performed on days 1, 8, and 15 of cycle 1; days 1 and 15 of cycle 2; day 1 of cycle 3 to 6; and thereafter on day 1 of every third cycle and at the end of treatment. Additional ECGs were performed on day 1 of every subsequent cycle for patients with a Fridericia-corrected QT interval (QTcF) of ≥ 481 ms at any time prior to cycle 7, day 1. Tumor response was assessed every 8 weeks for the first 6 months and every 12 weeks thereafter, as per the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Blood samples for PK analyses were collected on days 1, 8, 15, and 21 of cycle 1; days 1 and 15 of cycle 2; and day 1 of cycle 3 to 6. Additional samples were collected in patients with a QTcF of ≥ 501 ms. Plasma samples from all patients were assayed for ceritinib and ribociclib concentrations using a validated liquid chromatography-tandem mass spectrometry assay. PK parameters were determined for all PK-evaluable patients using non-compartmental method(s) using Phoenix WinNonlin (Pharsight, Mountain View, CA).

3.2. Statistical analysis

In the dose-escalation phase, three to six patients were planned to be enrolled in each cohort, with six or more patients at the MTD/RP2D level. An adaptive Bayesian logistic regression model (BLRM) with escalation with overdose control (EWOC) guiding the dose escalation was to be used to determine the MTD(s) and/or RP2D(s) and continued until the MTD(s) and/or RP2D(s) of the combination was identified. The MTD was the highest dose or combination of doses estimated to have less than 25% risk of causing a DLT during the DLT evaluation period in more than 33% of treated patients and RP2D(s) represented the doses and schedules of study treatments that were below or equal to MTDs and believed to have the most appropriate benefit-risk ratio as assessed by the review of the safety, tolerability, pharmacokinetics, pharmacodynamic effects, and preliminary efficacy. A minimum of 20 patients were required in the dose-escalation phase to ascertain the MTD/RP2D. Data were summarized using descriptive statistics and/or contingency tables for demographic and baseline characteristics, efficacy parameters, safety measurements, and PK/pharmacodynamics. The full analysis set (FAS) comprised all patients who received ≥ 1 full or partial dose of the assigned combination of study drugs. The safety set included all patients from the FAS who had received ≥ 1 dose of ribociclib or ceritinib and had ≥ 1 valid postbaseline safety assessment. The dose-determining set comprised all patients from the safety set in the dose-escalation phase who either met the minimum exposure criterion and had sufficient safety evaluations or had experienced a DLT during cycle 1 (first 28 days of treatment). Details of the minimum exposure criteria are provided in the Supplementary Appendix.

4. Results

4.1. Patient disposition

A total of 27 adult patients were enrolled into the following five dose cohorts: ceritinib 300 mg + ribociclib 100 mg (n = 4); ceritinib 450 mg + ribociclib 100 mg (n = 7); ceritinib 300 mg + ribociclib 200 mg (n = 4); ceritinib 450 mg + ribociclib 200 mg (n = 7); and ceritinib 450 mg + ribociclib 300 mg (n = 5). All patients had discontinued treatment at data cutoff. Disease progression reported in 14 patients (51.9%) was the primary reason for treatment discontinuation.

5. Demographics and baseline characteristics

Patient characteristics for all dose cohorts are described in Table 1. The median age of the patients was 57 years (range, 31–76 years) and most patients were female (n = 16, 59.3%). A majority of the patients were Caucasians (n = 16, 59.3%). The ECOG PS was 0 and 1 in 18

Table 2
AEs suspected to be related to study treatment (any grade, ≥15% in all patients).

n (%)	Ceritinib 300 mg + ribociclib 100 mg n = 4		Ceritinib 450 mg + ribociclib 100 mg n = 7		Ceritinib 300 mg + ribociclib 200 mg n = 4		Ceritinib 450 mg + ribociclib 200 mg n = 7		Ceritinib 450 mg + ribociclib 300 mg n = 5		All patients N = 27	
Grade	Any	3/4	Any	3/4	Any	3/4	Any	3/4	Any	3/4	Any	3/4
Total	4 (100)	2 (50.0)	7 (100)	5 (71.4)	4 (100)	1 (25.0)	7 (100)	4 (57.1)	4 (80.0)	4 (80.0)	26 (96.3)	16 (59.3)
Diarrhea	4 (100)	0	4 (57.1)	0	4 (100)	0	5 (71.4)	0	4 (80.0)	0	21 (77.8)	0
Vomiting	0	0	5 (71.4)	0	1 (25.0)	0	3 (42.9)	0	3 (60.0)	0	12 (44.4)	0
ALT increased	1 (25.0)	0	3 (42.9)	2 (28.6)	1 (25.0)	0	3 (42.9)	3 (42.9)	2 (40.0)	0	10 (37.0)	5 (18.5)
AST increased	1 (25.0)	0	3 (42.9)	2 (28.6)	1 (25.0)	0	3 (42.9)	3 (42.9)	2 (40.0)	1 (20.0)	10 (37.0)	6 (22.2)
Nausea	0	0	3 (42.9)	0	3 (75.0)	0	1 (14.3)	0	2 (40.0)	0	9 (33.3)	0
Neutrophil count decreased	0	0	2 (28.6)	1 (14.3)	0	0	4 (57.1)	2 (28.6)	3 (60.0)	3 (60.0)	9 (33.3)	6 (22.2)
Blood creatinine increased	1 (25.0)	0	2 (28.6)	0	1 (25.0)	0	2 (28.6)	0	2 (40.0)	0	8 (29.6)	0
Neutropenia	2 (50.0)	1 (25)	1 (14.3)	0	1 (25.0)	0	3 (42.9)	0	0	0	7 (25.9)	1 (3.7)
Decreased appetite	0	0	3 (42.9)	0	0	0	2 (28.6)	1 (14.3)	1 (20.0)	0	6 (22.2)	1 (3.7)
Asthenia	1 (25.0)	0	0	0	2 (50.0)	0	1 (14.3)	1 (14.3)	1 (20.0)	1 (20.0)	5 (18.5)	2 (7.4)
GGT increased	0	0	2 (28.6)	1 (14.3)	1 (25.0)	1 (25.0)	2 (28.6)	0	0	0	5 (18.5)	2 (7.4)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase.
A patient with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment.
A patient with multiple AEs was counted only once in the total row.

(66.7%) and 9 (33.3%) patients, respectively. Most patients were heavily pretreated; 88.9% of patients had received a median of two lines of anticancer therapy. A total of 8 patients were ALKi naive, 14 had received prior crizotinib only, and 5 had received prior next-generation ALKi therapy. A list of next-generation ALKi is provided in the Supplementary Appendix. Patients with prior ALKi exposure had received a median of 1 (range, 1–2) prior lines of ALKi therapy. The median duration of exposure to study treatment was 9.92 months (range, 0.6–38.7 months). Ten patients (37%) were exposed to study drugs for a period of ≥ 18 months.

5.1. Determination of MTD/RP2D and DLTs

Of the 25 patients who were evaluable for the determination of MTD and/or RP2D, one patient (4.0%) in the ribociclib 100 mg + ceritinib 450 mg dose cohort experienced a DLT (grade 2 increase in serum creatinine ≥ 7 consecutive days). This patient began study treatment on 25-Sep-2015 and experienced grade 2 increase in serum creatinine on study day 8 which reduced to grade 1 on study day 32. The event was suspected to be related to study treatment. The ribociclib 300 mg + ceritinib 450 mg dose was not tolerated (four of five patients had dose reductions; two of five patients had AEs that nearly met the neutropenia DLT criteria (grade 4 neutropenia lasting > 4 days). In the ribociclib 200 mg + ceritinib 300 mg dose cohort, three of six patients experienced grade 3 increase in aspartate aminotransferase/alanine aminotransferase (AST/ALT). Therefore, no additional patients were enrolled, and the MTD was not reached. Subsequently, after consideration of the BLRM, safety, tolerability, PK, and pharmacodynamic factors, ribociclib 200 mg QD (3-weeks-on/1-week-off schedule) + ceritinib 300 mg QD was declared as the RP2D. The phase II part of the study was not opened, and enrollment in the phase Ib part was terminated early based on the changes in the treatment landscape for *ALK*-rearranged NSCLC.

5.2. Safety

Dose reductions due to AEs suspected to be related to one of the study drugs were more frequent with ceritinib versus ribociclib (33.3% vs 22.2%), whereas the frequency of dose interruptions was higher with ribociclib versus ceritinib (92.6% vs 77.8%). All patients in phase Ib experienced ≥ 1 AE regardless of the relationship with study drugs. The

Table 3
Summary of best overall response.

	Ceritinib 300 mg + ribociclib 100 mg n = 4	Ceritinib 450 mg + ribociclib 100 mg n = 7	Ceritinib 300 mg + ribociclib 200 mg n = 4	Ceritinib 450 mg + ribociclib 200 mg n = 7	Ceritinib 450 mg + ribociclib 300 mg n = 5	All patients N = 27
Best overall response, n (%)						
CR	1 (25)	0	0	0	0	1 (3.7)
PR	2 (50)	2 (29)	2 (50)	2 (29)	1 (20)	9 (33)
SD	1 (25)	3 (43)	1 (25)	3 (43)	3 (60)	11 (40)
PD	0	0	0	0	1 (20)	1 (4)
Unknown	0	2 (29)	1 (25)	2 (29)	0	5 (19)
ORR,[a] n (%) [95% CI]	3 (75) [19.4–99.4]	2 (29) [3.7–71.0]	2 (50.0) [6.8–93.2]	2 (29) [3.7–71.0]	1 (20) [0.5–71.6]	10 (37) [19.4–57.6]
No prior ALK inhibitor, n	3	2	1	1	1	8
ORR,[a] n (%) [95% CI]	3 (100) [29.2–100]	1 (50) [1.3–98.7]	0 [0.0–97.5]	1 (100) [2.5–100]	0 [0.0–97.5]	5 (62.5) [24.5–91.5]
Only prior crizotinib, n	1	4	2	5	2	14
ORR,[a] n (%) [95% CI]	0 [0.0–97.5]	1 (25) [0.6–80.6]	2 (100) [15.8–100]	1 (20) [0.5–71.6]	1 (50) [1.3–98.7]	5 (36) [12.8–64.9]
Prior next generation ALK inhibitor, n	-	1	1	1	2	5
ORR,[a] n (%) [95% CI]	-	0 [0.0–97.5]	0 [0.0–97.5]	0 [0.0–97.5]	0 [0–84.2]	0 [0–52.2]

Abbreviations: ALK, anaplastic lymphoma kinase; CI, confidence interval; CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a] ORR = CR + PR.

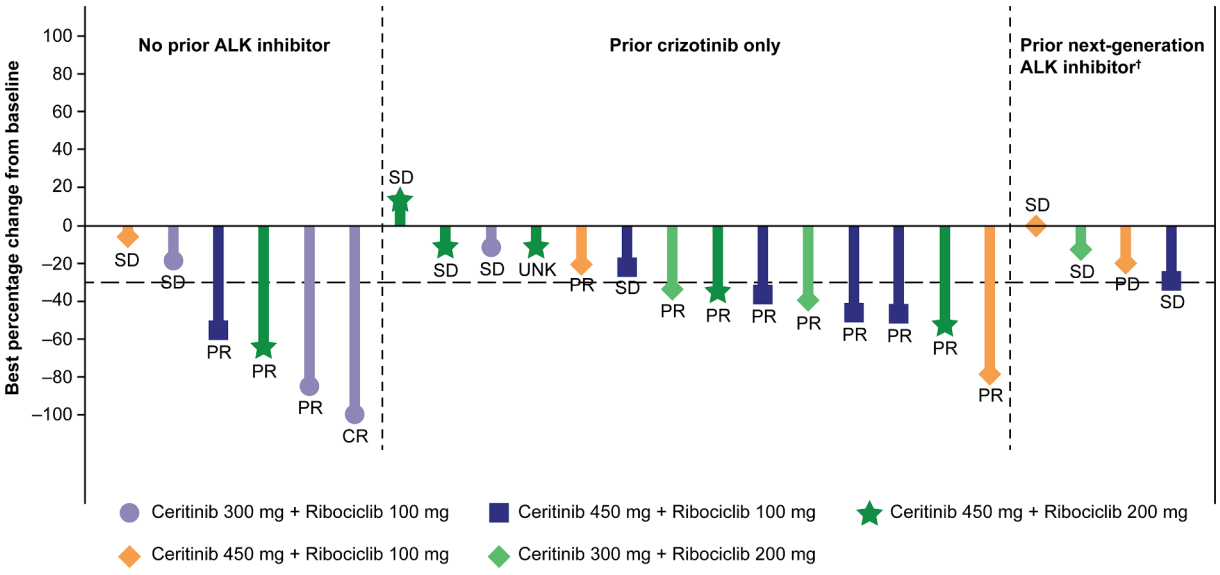

Fig. 2. Best percentage changes from baseline and best overall response*.

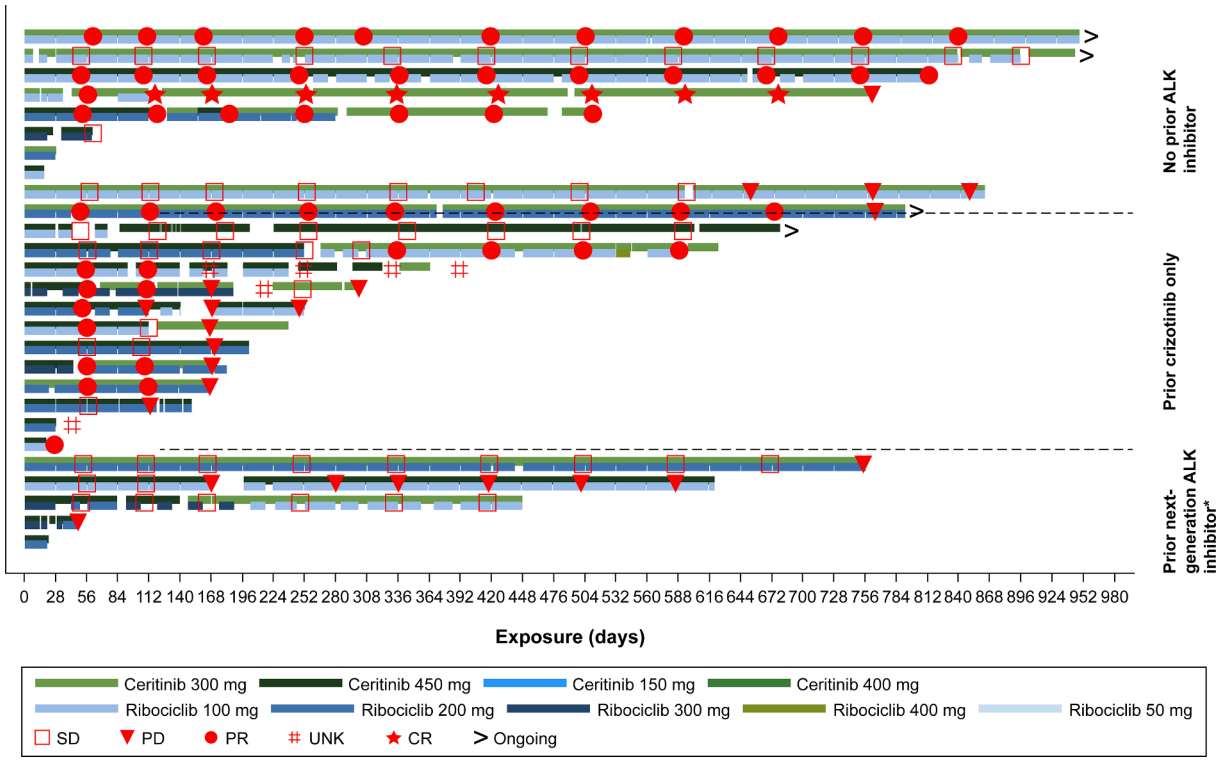

Fig. 3. Ceritinib and ribociclib exposure and overall response.

most common any-grade AEs (≥30% of all patients) were diarrhea (85.2%), vomiting (63%), increased ALT and AST (44.4% each), decreased neutrophil count (40.7%), and asthenia, nausea, decreased appetite, and increased blood creatinine (33.3% each). The most common grade 3/4 AEs (≥10% of all patients) were decreased neutrophil count and increased ALT and AST. AEs suspected to be related to study treatment are shown in Table 2. Compared with baseline, 11 patients (42.31%) had a worsening of QTcF of ≥ 450 ms and 1 patient had worsening of QTcF of ≥ 500 ms. This patient also had grade 3 ECG QT prolonged, which was suspected to be treatment related, and led to permanent drug discontinuation. The only serious AE that occurred in ≥ 1 patient was dyspnea (n = 2 [7.4%]).

Across all dose cohorts, seven patients (25.9%) discontinued treatment due to AEs. AEs were the most frequent reason for dose reductions of both ribociclib (22.2%) and ceritinib (29.6%). The most common AEs that led to dose reductions were grade 3/4 neutropenia and elevated liver enzymes. Dose interruptions occurred in 18 (66.7%) and 16 (59.3%) patients for ribociclib and ceritinib, respectively. On-treatment deaths were reported in three patients; two patients had died due to study indication and one patient died due to suspected myocardial infarction.

Table 4
Pharmacokinetic parameters for ceritinib and ribociclib.

Treatment	Day	T_{max} (h), Median [range]	C_{max} (ng/mL), Mean (SD)	AUC_{0-24h} (h·ng/mL), Mean (SD)
Ceritinib				
Ceritinib 300 mg + ribociclib 100 mg (n = 4)	Cycle 1 day 1	4.08 [4.00–6.00]	171 (17.0)	2388 (473)
	Cycle 1 day 15	6.00 [4.08–6.00]	482 (191)	9792 (4742)
Ceritinib 450 mg + ribociclib 100 mg (n = 7)	Cycle 1 day 1	5.95 [4.00–8.05]	283 (145)	4495 (2518)
	Cycle 1 day 15	6.00 [4.00–8.05]	1063 (339)	21592 (8182)
Ceritinib 300 mg + ribociclib 200 mg (n = 4)	Cycle 1 day 1	5.83 [4.00–6.00]	180 (15.8)	2874 (238)
	Cycle 1 day 15	7.64 [6.00–8.22]	694 (65.7)	13887 (2042)
Ceritinib 450 mg + ribociclib 200 mg (n = 7)	Cycle 1 day 1	5.92 [4.00–8.08]	368 (368)	6703 (7169)
	Cycle 1 day 15	5.97 [2.08–7.50]	973 (190)	20559 (3869)
Ceritinib 450 mg + ribociclib 300 mg (n = 5)	Cycle 1 day 1	6.83 [4.05–24.0]	182 (57.8)	3578 (1225)
	Cycle 1 day 15	6.00 [2.25–8.08]	936 (210)	19,777 (4092)
Ribociclib				
Ceritinib 300 mg + ribociclib 100 mg (n = 4)	Cycle 1 day 1	2.00 [1.87–4.00]	231 (138)	2152 (903)
	Cycle 1 day 15	4.00 [2.00–4.08]	198 (29.8)	3198 (650)
Ceritinib 450 mg + ribociclib 100 mg (n = 7)	Cycle 1 day 1	3.97 [2.00–5.97]	217 (97.5)	2510 (1120)
	Cycle 1 day 15	4.13 [1.92–7.62]	333 (78.3)	5998 (1654)
Ceritinib 300 mg + ribociclib 200 mg (n = 4)	Cycle 1 day 1	3.03 [2.00–4.05]	983 (574)	8780 (4414)
	Cycle 1 day 15	2.03 [1.97–4.00]	967 (475)	15299 (9491)
Ceritinib 450 mg +ribociclib 200 mg (n = 7)	Cycle 1 day 1	2.13 [1.12–4.00]	409 (211)	4625 (2833)
	Cycle 1 day 15	4.00 [2.07–6.00]	795 (318)	13613 (4973)
Ceritinib 450 mg + ribociclib 300 mg (n = 5)	Cycle 1 day 1	2.00 [1.25–4.50]	473 (97.6)	6240 (1613)
	Cycle 1 day 15	4.10 [4.00–8.08]	1095 (322)	18303 (7165)

Abbreviations: AUC_{0-24h}, area under the curve between 0 and 24 hours; C_{max}, maximum plasma concentration; SD, standard deviation; T_{max}, time to reach maximum plasma concentration.

5.3. Efficacy

Preliminary clinical activity was observed in patients treated with ceritinib in combination with ribociclib (Table 3; Figs. 2 and 3). Clinical response was observed in 10 of 27 evaluable patients, with an ORR of 37.0% (95% confidence interval [CI], 19.40–57.63). The ORR was 62.5% (5/8 patients) in ALKi-naive patients and 35.7% (5/14 patients) in patients who had received prior crizotinib therapy. No clinical response (either complete response or partial response) was observed in patients (0/5) who had received prior treatment with next-generation ALKi. At the RP2D of ribociclib 200 mg + ceritinib 300 mg, the ORR was 50.0% (2/4 patients; 95% CI, 6.8–93.2) and the DCR was 75% (3/4 patients; 95% CI, 19.4–99.4). Detailed information on secondary efficacy endpoints are described in the Supplementary Appendix.

5.4. Pharmacokinetics

Primary PK parameters for ceritinib and ribociclib, summarized by treatment group, are presented in Table 4. Following an oral dose of ribociclib in combination with ceritinib 300 mg or 450 mg, the median time to reach the peak plasma concentrations (T_{max}) ranged between 2 and 4 h post dose. On cycle 1 day 15, treatment with ribociclib 100 mg resulted in numerically higher mean ribociclib exposure (maximum plasma concentration [C_{max}] and AUC) with overlapping ranges in patients treated with ceritinib 450 mg versus those on ceritinib 300 mg; however, the exposure was comparable when treated with ribociclib 200 mg in combination with ceritinib 300 mg or 450 mg. Following an oral dose of ceritinib in combination with ribociclib, the median T_{max} ranged between 4.0 and 7.6 h post dose. Ceritinib exposure (C_{max} and AUC) on cycle 1 day 15 was comparable following administration of the same ceritinib dose in combination with ribociclib 100, 200, or 300 mg (Table 4). The mean plasma concentration-time profiles for ceritinib and ribociclib are shown in Fig. 4A and B. At steady state, ceritinib and ribociclib exposure (AUC from time zero to the 24 h [AUC_{0-24h}]) both increased by ~ 1.5- to 2-fold when administered in combination under fed conditions compared with ceritinib and ribociclib single-agent exposures under fasted conditions at equivalent doses. These data should be interpreted with caution due to large variability and limited patient numbers.

6. Discussion

The objective of this study was to assess safety and tolerability of ceritinib in combination with ribociclib for the treatment of patients with *ALK*-rearranged NSCLC. Furthermore, we aimed to assess the antitumor activity in ALKi-naive and ALKi-resistant patients with *ALK*-rearranged NSCLC. The MTDs of ribociclib (900 mg QD with a 3-weeks-on/1-week-off schedule) and ceritinib (750 mg QD) when assessed as monotherapies have been previously reported in phase I studies [14,15].

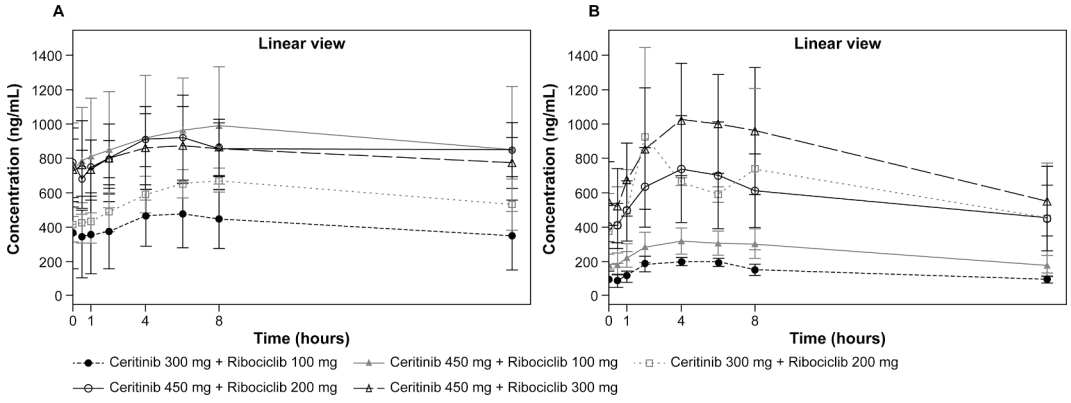

Fig. 4. Steady-state* arithmetic mean (±SD) plasma concentration–time profiles for (A) ceritinib and (B) ribociclib.

Since this was the first study evaluating ceritinib in combination with ribociclib, DDIs were anticipated.

At the starting dose of ceritinib 300 mg QD and ribociclib 100 mg QD 3 weeks on/1 week off, the ceritinib exposure was approximately similar to the exposure of ceritinib monotherapy at 600 mg QD [15] and 60% lesser than that of ribociclib monotherapy at the RP2D. In this study, the MTDs for ceritinib and ribociclib were not reached; however, the RP2D was declared as ceritinib 300 mg with ribociclib 200 mg. At the RP2D, both study drugs had exposures in the active range. Due to changes in the treatment landscape for *ALK*-rearranged NSCLC, specifically with development of next-generation ALKi, the enrollment for phase II was not opened and was terminated early in phase Ib of the study.

One patient who received ceritinib 450 mg with ribociclib 100 mg experienced a DLT during cycle 1 (grade 2 increase in serum creatinine for $\geq$ 7 consecutive days). At the RP2D, clinical response was noted in 50% of the evaluable patients. It is possible that the limited clinical activity noted at the RP2D in this study may be because of low individual doses of ceritinib and ribociclib in this combination compared with RP2D doses reported in monotherapy studies [14,15]. Although data are limited, overcoming of ALKi resistance through CDK4/6 inhibition in patients pretreated with next-generation ALKi appears to be minimal. Lack of predictive biomarkers for the efficacy of ribociclib is a limitation of this study.

Overall, the safety findings in the study were consistent with the known safety profile of ribociclib and ceritinib monotherapies, and no new safety signals were identified. The safety results were as expected in a population of patients in an advanced oncology setting.

7. Conclusions

Ceritinib 300 mg QD and ribociclib 200 mg QD (3-weeks-on/1-week-off schedule) was determined as the RP2D for the combination treatment in patients with *ALK*-rearranged NSCLC. Clinical activity, albeit limited, was noted with this combination at the RP2D. The overall safety of the combination was generally consistent with that observed in clinical trials of ribociclib or ceritinib as single agents.

8. Data availability

Novartis is committed to data sharing with qualified external researchers, providing access to patient-level data, and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on https://www.clinicalstudydatarequest.com.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Armando Santoro serves on the advisory board of Bristol-Myers-Squib, Servier, Gilead, Pfizer, Eisai, Bayer and Merck Sharp & Dohme. He is a consultant for Arqule and Sanofi. He also serves on the Speaker's bureau for Takeda, Bristol-Myers-Squib, Roche, AbbVie, Amgen, Celgene, Servier, Gilead, AstraZeneca, Pfizer, Arqule, Lilly, Sandoz, Eisai, Novartis, Bayer and Merck Sharp & Dohme. Alejandro Navarro is a consultant for AstraZeneca, Boehringer Ingelheim, Bristol-Myers-Squib, Pfizer and Roche. He has provided expert testimony to Oryzon and MedSIR. He has received travel support from Boehringer Ingelheim, Pfizer and Roche. James CH Yang serves as an advisor and consultant and also received personal fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers. He received grant support from AstraZeneca. Andrea Ardizzoni has received personal fees and serves on the advisory board of AstraZeneca, Bayer, Lilly, Merck Sharp & Dohme, Roche and Takeda. He was an invited speaker for Bristol-Myers-Squib. Fabrice Barlesi reports receiving personal fees from Astra-Zeneca, Bayer, Bristol-Myers Squibb, Boehringer–Ingelheim, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Novartis, Merck, Mirati, MSD, Pierre Fabre, Pfizer, Seattle Genetics and Takeda. Jin Hyoung Kang. Enriqueta Felip reports personal fees from AbbVie, personal fees from Amgen, AstraZeneca, Bayer, Blue Print Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Glaxo Smith-Kline, Janssen, Medscape, Merck KGaA, Merck Sharp & Dohme, Novartis, Peervoice, Pfizer, priME oncology, Puma Biotechnology, Roche, Sanofi Genzyme, Springer, Takeda, Touchmedical, CME Outfitters, Beigene, Medical Trends, Peptomyc, Regeneron, Syneos Health outside the submitted work, grants from Grant for Oncology Innovation (GOI), grants from Fundacion Merck Salud, and served as an independent member of the board for Grifols. Sarah DiDominick and Xueying Chen are employees of Novartis. Xueying Chen currently owns Novartis stocks. Uz Stammberger and Ahmed Abdelhady were employees of Novartis during the conduct of the study and preparation of this manuscript. Wu-Chou Su, Jin Hyoung Kang and Matteo Simonelli have nothing to declare.

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Appendix A. Supplementary data

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