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Phase Ib/II study of the pan-cyclin-dependent kinase inhibitor roniciclib in combination with chemotherapy in patients with extensive-disease small-cell lung cancer

Byoung Chul Cho[a,*], Grace K. Dy[b], Ramaswamy Govindan[c], Dong-Wan Kim[d], Nathan A. Pennell[e], Gerard Zalcman[f], Benjamin Besse[g], Joo-Hang Kim[h], Goekben Koca[i], Prabhu Rajagopalan[j], Simon Langer[k], Matthias Ocker[i], Hendrik Nogai[i], Fabrice Barlesi[l,m,n]

[a] Yonsei Cancer Center, Yonsei University College of Medicine, 50–1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
[b] Roswell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY 14263, USA
[c] Washington University in St. Louis, 1 Brookings Dr, St. Louis, MO 63130, USA
[d] Seoul National University Hospital, 101, Daehak-ro, Jongno-gu, Seoul 03080, Korea
[e] Cleveland Clinic Taussig Cancer Institute, 10201 Carnegie Ave, Cleveland, OH 4419, USA
[f] University Hospital, Clinical Research Center, Avenue de la Côte de Nacre, 14033 Caen, France
[g] Gustave Roussy, 114 Rue Edouard Vaillant, 94800 Villejuif, France
[h] CHA Bundang Medical Center, CHA University, 222 Yatap-dong, Bundang-gu, Seongnam-shi, Gyeongghi-do, Korea
[i] Bayer AG, Müllerstraße 178, 13353 Berlin, Germany
[j] Bayer HealthCare Pharmaceuticals, Inc., 100 Bayer Boulevard, PO Box 915, Whippany, NJ 07981, USA
[k] Chrestos Concept GmbH & Co. KG, Girardetstraße 1–5, 45131 Essen, Germany
[l] Aix Marseille University, Jardin du Pharo, 58, bd Charles Livon, 13284 Marseille, France
[m] Assistance Publique Hôpitaux de Marseille, 80, rue Brochier, 13005 Marseille, France
[n] Centre d'Essais Précoces en Cancérologie de Marseille (CLIP^2), Hôpital La Timone – Basement F, 1st Floor, 264, rue St Pierre, 13885 Marseille, France

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ABSTRACT

Objectives: This phase Ib/II study evaluated safety, pharmacokinetics, maximum tolerated dose (MTD), and efficacy of the pan-cyclin-dependent kinase inhibitor roniciclib with cisplatin-etoposide (CIS-ETOP) or carboplatin-etoposide (CARBO-ETOP) in patients with extensive-disease small-cell lung cancer (ED-SCLC).

Patients and methods: In this open-label, non-randomized study, patients with previously untreated ED-SCLC received roniciclib twice daily (BID) in a 3 days on/4 days off schedule. Cisplatin 75 mg/m^2 or carboplatin (AUC5) dose was administered on day 1, and etoposide 100 mg/m^2 on days 1–3, of 21-day cycles. Phase Ib used a dose-escalation design to define the MTD for phase II. Pharmacokinetics were assessed.

Results: Forty-three patients received treatment (roniciclib 2.5 mg BID [+ CARBO-ETOP, n = 4; + CIS-ETOP, n = 3] and roniciclib 5 mg BID [+ CARBO-ETOP, n = 24; + CIS-ETOP, n = 12]). The MTD of roniciclib was 5 mg BID with CARBO-ETOP or CIS-ETOP. Common adverse events were nausea (90.7%) and vomiting (69.8%). Roniciclib was readily absorbed following oral administration at the MTD (median t_{max} 0.5–1 h), with a 30–40% reduction in exposure when co-administered with CARBO-ETOP or CIS-ETOP; administration of roniciclib had no effect on etoposide or platinum pharmacokinetics. The response rate was 81.4% (35/43) overall and 86.1% (31/36) in the pooled roniciclib 5 mg BID population (all partial responses).

Conclusion: Roniciclib co-administered with chemotherapy in patients with ED-SCLC demonstrated tolerability, acceptable pharmacokinetics, and promising efficacy. An observed safety signal in a related phase II study resulted in discontinuation of the present study and termination of further roniciclib development.

Abbreviations: BID, twice daily; CARBO-ETOP, carboplatin-etoposide therapy; CDK, cyclin-dependent kinase; CI, confidence interval; CIS-ETOP, cisplatin-etoposide therapy; DCR, disease control rate; DLT, dose-limiting toxicity; DoR, duration of response; ED-SCLC, extensive-disease small-cell lung cancer; MTD, maximum tolerated dose; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RP2D, recommended phase II dose; SCLC, small-cell lung cancer; TEAE, treatment-emergent adverse event

* Corresponding author at: Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea.
E-mail addresses: cbc1971@yuhs.ac (B.C. Cho), grace.dy@roswellpark.org (G.K. Dy), rgovindan@wustl.edu (R. Govindan), kimdw@snu.ac.kr (D.-W. Kim), penneln@ccf.org (N.A. Pennell), zalcman-g@chu-caen.fr (G. Zalcman), benjamin.besse@gustaveroussy.fr (B. Besse), kim123@cha.ac.kr (J.-H. Kim), goekben.koca@bayer.com (G. Koca), prabhu.rajagopalan@bayer.com (P. Rajagopalan), simon.langer.ext@bayer.com (S. Langer), matthias.ocker@bayer.com (M. Ocker), hendrik.nogai@bayer.com (H. Nogai), fabrice.barlesi@ap-hm.fr (F. Barlesi).

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1. Introduction

Small-cell lung cancer (SCLC) affects approximately 30,000 patients yearly in the USA, with two-thirds of patients presenting with extensive-disease SCLC (ED-SCLC) [1–3]. SCLC is characterized by rapid cellular growth and aggressive metastases, and patients with ED-SCLC currently have no curative options and a median survival of about 10 months [4]. Platinum-based combination chemotherapy is the mainstay of therapy for ED-SCLC, with cisplatin- or carboplatin-based chemotherapy showing equivalent efficacy in randomized studies [3–5]. Most cases initially show response to treatment; however, almost all patients experience relapse and limited survival [6], emphasizing a need for better treatment options.

In tumor cells, deregulation of the cell cycle arises through overexpression or amplification of cell-cycle activators including cyclin-dependent kinases (CDKs; e.g. CDK4 and CDK6) and inactivation of cell-cycle inhibitors (e.g. p16 and Rb) [7]. Non-cell-cycle CDKs (e.g. CDK7 and CDK9) contribute to transcription initiation via phosphorylation of RNA polymerase II [7]. Inhibition of all CDKs leads to cell-cycle arrest and down-regulation of anti-apoptotic proteins, resulting in an induction of apoptosis and inhibition of tumor cell proliferation [8]. Therefore, CDK inhibitors are an attractive therapeutic target in cancer.

Roniciclib (Bayer AG, Leverkusen, Germany) is a novel, highly potent, orally active, small-molecule pan-CDK inhibitor [9] that has demonstrated more than additive efficacy in combination with cisplatin-etoposide therapy (CIS-ETOP) in preclinical SCLC xenograft models, without worsening toxicity [9]. In a phase I study of patients with advanced malignancies receiving single-agent roniciclib, the maximum tolerated dose (MTD) was determined to be 7.5 mg twice daily (BID), administered 3 days on/4 days off in a 21-day cycle, but the recommended phase II dose (RP2D) was reduced to 5 mg BID because of observed thromboembolic events [10]. An expansion cohort with roniciclib monotherapy in pretreated SCLC patients at the RP2D demonstrated an acceptable safety profile and a moderate disease control rate (DCR) of 17.4%, warranting further exploration as a treatment option in patients with advanced SCLC [10].

Here we describe the results of a phase Ib/II study of roniciclib in combination with CIS-ETOP or carboplatin-etoposide therapy (CARBO-ETOP) as first-line treatment in patients with ED-SCLC (NCT01573338).

2. Patients and methods

2.1. Study design

This open-label, non-randomized, multicenter study comprised two phases. The primary objective of phase Ib was to evaluate the safety, tolerability, pharmacokinetics (PK), and MTD of roniciclib in combination with CIS-ETOP or CARBO-ETOP in patients with ED-SCLC in two parallel cohorts. Secondary objectives included biomarker response, overall survival (OS), progression-free survival (PFS), response rate, duration of response (DoR), stable disease, and DCR.

The primary objective of phase II was to evaluate the response rate in patients with ED-SCLC receiving first-line CIS-ETOP or CARBO-ETOP in combination with roniciclib. The secondary objectives included tolerability, safety profile, biomarker response profile, OS, PFS, DoR, stable disease, and DCR for roniciclib in combination with chemotherapy and subsequent maintenance treatment with roniciclib.

2.2. Patients

Eligibility criteria included: aged ≥18 years with histologically or cytologically confirmed and previously untreated ED-SCLC; Eastern Cooperative Oncology Group performance status of 0 or 1; life expectancy ≥12 weeks; serum sodium ≥130 mmol/L; and adequate bone marrow, liver, and renal functions. At least one solid tumor lesion measurable according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was required for inclusion in phase II.

Exclusion criteria included: any prior systemic anticancer therapy or radiotherapy, or anticoagulation therapy; hepatic impairment of Child-Pugh class B or C; a history of cardiac disease or organ allograft; human immunodeficiency virus infection or chronic hepatitis B or C virus; symptomatic metastatic brain or meningeal tumors; or previous or co-existing cancer distinct in primary site or histology from the cancer evaluated in this study (excluding cervical cancer *in situ*, treated basal cell carcinoma, superficial bladder tumors, or any cancer curatively treated more than 3 years before study entry).

2.3. Treatment

Roniciclib was administered BID on a 3 days on/4 days off schedule in 21-day cycles (Supplementary Table 1). In patients with PK assessment, roniciclib was not administered on cycle 1, day 1, in order to determine the PK profile of chemotherapy without roniciclib. Cisplatin 75 mg/m^2 or carboplatin (dose determined by Calvert's formula to yield an area under the curve of 5 mg/mL*min) was administered intravenously on day 1 of each cycle. Platinum agent was at the investigator's discretion, and patients could switch treatments if they did not tolerate specific toxicities. Etoposide 100 mg/m^2 was administered intravenously on days 1–3 of each cycle. Chemotherapy continued for a maximum of six cycles or until tumor progression, unacceptable toxicity, or withdrawal from the study. Dosing of roniciclib continued until tumor progression, unacceptable toxicity, or study withdrawal.

In phase Ib, roniciclib was administered to three patients each at a starting dose of 2.5 mg BID in combination with CIS-ETOP or CARBO-ETOP, i.e. one dose level below the RP2D of single-agent roniciclib 5 mg BID [10], in two parallel, independent cohorts. Dosing progressed in a modified 3 + 3 dose-escalation/de-escalation design to a maximum roniciclib dose of 5 mg BID and a minimum dose of 2.5 mg once daily. If one of the three patients within a cohort at the starting dose experienced a dose-limiting toxicity (DLT) during cycle 1, a further three patients were enrolled to that cohort. A DLT was defined as any of the following occurring during cycle 1 and regarded to be related to roniciclib or the combination of roniciclib with chemotherapy: absolute neutrophil counts $< 0.5 \times 10^9$/L for ≥7 days; febrile neutropenia with absolute neutrophil counts $< 0.5 \times 10^9$/L and fever ≥38.5 °C; any grade 3–5 non-hematologic toxicity; or any grade 4 vomiting event or grade 3 nausea or vomiting lasting over 48 h. If two or more of three or two or more of six patients within a cohort experienced a DLT at the starting dose, enrollment to that cohort was discontinued and dosing was to be de-escalated to 2.5 mg once daily.

If none of three or one of six patients in either cohort experienced a DLT at the starting dose of roniciclib 2.5 mg BID in combination with chemotherapy, the roniciclib dose was escalated to 5 mg BID for six patients in each cohort. If one of six patients in each of the parallel cohorts experienced a DLT, then 5 mg BID was defined as the MTD in combination with chemotherapy; if two or more of three or two or more of six patients experienced a DLT within a cohort, then enrollment was to be discontinued. The tolerability of the starting dose of roniciclib 2.5 mg BID in combination with chemotherapy was then evaluated in six patients, with 2.5 mg BID defined as the MTD if one or more of six patients experienced a DLT.

The studies were conducted in accordance with the Declaration of Helsinki. The protocol was approved by the ethics committee at each participating center. All patients provided written, informed consent before enrollment.

2.4. Assessments

PK assessments were conducted in all patients in phase Ib and were planned in approximately six patients per chemotherapy regimen in phase II. Plasma samples for PK assessments were collected as follows: cycle 1, day 8 and cycle 2, day 1 at pre-dose, 0.5, 1, 2, 4, 6, and 8 h post-

dose for roniciclib and its metabolite M-1; cycle 1, day 1 and cycle 2, day 1 at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24, and 48 h after start of cisplatin or carboplatin infusion for total and free platinum; and cycle 1, day 1 and cycle 2, day 1 at pre-dose, 0.5, 1, 2, 3, 4, 5, 7, and 24 h after start of etoposide infusion for total etoposide. Plasma concentrations were measured using validated analytical methods, and PK parameters were calculated by non-compartmental analysis using WinNonlin® software (Certara USA, Inc., Princeton, NJ).

Tumors were assessed by computed tomography or magnetic resonance imaging using RECIST version 1.1 at baseline, then every two cycles. Confirmatory scans were performed ≥4 weeks following the observation of a tumor response. For patients without disease progression, follow-up evaluation was done until death, if possible. Patients treated at the MTD in phase Ib were included in the response evaluation of phase II.

Safety was assessed throughout the treatment period and approximately 14 and 30 days after discontinuing roniciclib. Safety variables included physical examinations, vital signs, concomitant medications, and adverse events recorded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

2.5. Statistical analysis

Summary statistics were calculated for the total study population and by cohort. Frequency tables were generated for qualitative data. Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). All patients who received one or more doses of roniciclib were included in the safety evaluation. Study sample size in phase Ib was dependent on the number of dose-escalation/de-escalation steps required for determination of the MTD. In phase II, a clinically meaningful improvement was defined as a 20% increase in response rate from 60% to 80%. A total of 36 evaluable patients was determined to be sufficient to detect a 20% difference in response rate with a significance level of 10% and power of 90%. Response rate was defined as the proportion of patients with a best tumor response of confirmed partial response or confirmed complete response achieved during or within 30 days after treatment. DCR was defined as the proportion of patients with a best tumor response of complete response, partial response, or stable disease during or within 30 days after treatment.

PK summary statistics were calculated for each sampling point. Means were calculated if at least two-thirds of the individual data were measured and were above the lower limit of quantification. For calculation of the mean value, a data point below the lower limit of quantification was substituted by one-half the lower limit. Individual and geometric mean concentration–time curves of roniciclib and its metabolite M-1, total and free platinum, and total etoposide (using the actual sampling times for individual plots and the planned sampling times for mean plots) were plotted by treatment.

PK parameters were calculated for total and free platinum, etoposide, and roniciclib and its metabolite M-1. To investigate PK interaction, an explorative analysis of variation was performed on the log-transformed values of PK parameters.

3. Results

3.1. Patient disposition, demographics, and baseline characteristics

In total, 58 patients were enrolled and 43 patients were eligible to receive treatment across four cohorts (roniciclib 2.5 mg BID [+ CARBO-ETOP, n = 4; + CIS-ETOP, n = 3] and roniciclib 5 mg BID [+ CARBO-ETOP, n = 24; + CIS-ETOP, n = 12]) (Table 1). Seven patients were enrolled to phase Ib. No DLTs were reported at the starting dose of roniciclib 2.5 mg BID; therefore, the dose was escalated to 5 mg BID. Thirty-six patients were enrolled to phase II; 12 patients were treated with roniciclib 5 mg BID + CIS-ETOP and 24 patients with roniciclib 5 mg BID + CARBO-ETOP. Five of the 12 patients receiving roniciclib 5 mg BID + CIS-ETOP switched to treatment with CARBO-ETOP during the study at the investigator's decision. Per protocol, these patients were considered part of the CIS-ETOP cohort for analyses. All patients assigned to treatment comprised the safety analysis set. Eighteen patients were valid for PK analysis. The primary reason for discontinuation was radiologic progression (62.8%).

Of the patients treated, 29 (67.4%) were male, median age was 60 years (range 43–76), and 26 (60.5%) had an Eastern Cooperative Oncology Group performance status of 1 (Table 1). Three patients (7.0%) had received any prior anticancer therapeutic procedure, while concurrent therapy included anticancer therapeutic procedures (six patients [14.0%]), radiotherapy (nine patients [20.9%]), and diagnostic procedures (four patients [9.3%]) (Table 1).

3.2. Exposure and dose escalation

The overall median duration of treatment was 23.6 weeks (range 2.4–142.4) and patients received a median of eight cycles (range 2–47), with roniciclib monotherapy continuing after a maximum of six chemotherapy cycles (Table 2). Most patients (62.8%) received treatment for 20–40 weeks. Twenty-five patients (89.3%) in the roniciclib + CARBO-ETOP cohorts received six cycles of chemotherapy, compared with only seven patients (46.7%) in the roniciclib + CIS-ETOP cohorts. Median treatment duration and median number of treatment cycles were comparable across dose levels and combinations (Table 2).

One patient receiving roniciclib 5 mg BID + CARBO-ETOP experienced hypokalemia and hypocalcemia, both reported as DLTs and assessed as related to roniciclib, carboplatin, and etoposide. One patient receiving roniciclib 5 mg BID + CIS-ETOP experienced hypotension, neutropenia, sepsis, febrile neutropenia, and decreased platelet count, all reported as DLTs and assessed as related to roniciclib, carboplatin, and etoposide. The roniciclib MTD was determined to be 5 mg BID administered 3 days on/4 days off in combination with CARBO-ETOP or CIS-ETOP and was the dose used for phase II.

3.3. Safety

At least one treatment-related adverse event (TEAE) was reported in all patients (100%); frequencies were generally similar across dose levels and combinations (Table 3). The most common TEAEs of any grade were nausea (90.7%), vomiting (69.8%), and anemia, decreased neutrophil count, and decreased platelet count (67.4% each) (Table 3). Standard anti-emetic therapy was used to manage nausea and vomiting. TEAEs of worst grade 3 were reported in 16 patients (37.2%), most commonly anemia (27.9%), hypomagnesemia and decreased white blood cell count (18.6% each), decreased neutrophil count (16.3%), and decreased platelet count (11.6%). TEAEs of worst grade 4 were reported in 22 patients (51.2%), most commonly decreased neutrophil count (39.5%), decreased platelet count (27.9%), and sepsis (4.7%). Grade 5 TEAEs occurred in two patients (4.7%) receiving roniciclib 5 mg BID; one with lung infection (associated with disease progression) and the other with hypercarbic respiratory failure (not associated with disease progression). One additional patient died within 30 days after treatment with roniciclib 5 mg BID + CIS-ETOP (associated with disease progression), but no adverse event was reported as associated with the death so no grade 5 event was reported. No deaths were assessed as roniciclib-related.

Roniciclib-related TEAEs were experienced by 42 patients (97.7%), most commonly nausea (88.4%) and vomiting (67.4%) (Supplementary Table 2). Worst grade 3 roniciclib-related TEAEs were experienced by 12 patients (27.9%), most commonly anemia and decreased white blood cell count (18.6% each), decreased neutrophil count (16.3%), and decreased platelet count and hypomagnesemia (11.6% each), and worst grade 4 roniciclib-related TEAEs were experienced by 16 patients (37.2%), most commonly decreased neutrophil count (27.9%) and

Table 1
Demographics and baseline characteristics (safety analysis set).

	Roniciclib 2.5 mg BID		Roniciclib 5 mg BID		Total (N = 43)
	CARBO-ETOP (n = 4)	CIS-ETOP (n = 3)	CARBO-ETOP (n = 24)	CIS-ETOP (n = 12)	
Male, n (%)	2 (50.0)	1 (33.3)	19 (79.2)	7 (58.3)	29 (67.4)
Median age, years (range)	71.5 (56–73)	58.0 (55–65)	60.5 (48–76)	59.5 (43–75)	60.0 (43–76)
Baseline ECOG PS, n (%)					
0	3 (75.0)	2 (66.7)	7 (29.2)	4 (33.3)[a]	16 (37.2)[a]
1	1 (25.0)	1 (33.3)	17 (70.8)	7 (58.3)	26 (60.5)
Median time since initial diagnosis, weeks (range)	3.6 (1–5)	3.7 (2–4)	2.1 (1–9)	2.8 (1–4)	2.6 (1–9)
Any prior anticancer therapeutic procedure, n (%)	0	1 (33.3)	1 (4.2)	1 (8.3)	3 (7.0)
Concurrent anticancer therapies, n (%)					
Any therapeutic procedure	1 (25.0)	2 (66.7)	2 (8.3)	1 (8.3)	6 (14.0)
Any radiotherapy	1 (25.0)	0	3 (12.5)	5 (41.7)	9 (20.9)
Any diagnostic procedure	0	0	2 (8.3)	2 (16.7)	4 (9.3)
Number of target lesions, n (%)					
1	1 (25.0)	0	5 (20.8)	0	6 (14.0)
2	2 (50.0)	1 (33.3)	6 (25.0)	1 (8.3)	10 (23.3)
≥3	1 (25.0)	2 (66.7)	13 (54.2)	11 (91.7)	27 (62.8)
Number of non-target lesions, n (%)					
0	0	0	3 (12.5)	2 (16.7)	5 (11.6)
1	0	1 (33.3)	5 (20.8)	2 (16.7)	8 (18.6)
2	1 (25.0)	0	8 (33.3)	2 (16.7)	11 (25.6)
≥3	3 (75.0)	2 (66.7)	8 (33.3)	6 (50.0)	19 (44.2)

BID = twice daily; CARBO-ETOP = carboplatin-etoposide therapy; CIS-ETOP = cisplatin-etoposide therapy; ECOG PS = Eastern Cooperative Oncology Group performance status.
[a] Value missing for one patient.

Table 2
Roniciclib duration of treatment (safety analysis set).

	Roniciclib 2.5 mg BID		Roniciclib 5 mg BID		Total (N = 43)
	CARBO-ETOP (n = 4)	CIS-ETOP (n = 3)	CARBO-ETOP (n = 24)	CIS-ETOP (n = 12)	
Median duration of treatment, weeks (range)	25.0 (18.3–34.7)	23.6 (3.4–142.4)	24.7 (3.0–49.6)	21.7 (2.4–35.3)	23.6 (2.4–142.4)
Median number of cycles (range)	8.5 (6.0–12.0)	8.0 (2.0–47.0)	8.0 (2.0–14.0)	8.0 (2.0–12.0)	8.0 (2.0–47.0)

BID = twice daily; CARBO-ETOP = carboplatin-etoposide therapy; CIS-ETOP = cisplatin-etoposide therapy.

decreased platelet count (20.9%).

Twenty-one patients (48.8%) experienced serious adverse events (Table 3). Serious adverse events reported in one or more patients included lung infection (4/43; 9.3%) and febrile neutropenia, decreased neutrophil count, decreased platelet count, sepsis, and vascular disorders (other) (2/43 each; 4.7%). The majority of serious adverse events were of worst grade 3 (23.3%) (Table 3). Serious adverse events were assessed as roniciclib-related in seven patients (16.3%): febrile neutropenia, decreased neutrophil count, and decreased platelet count (2/43 each; 4.7%), and fatigue, hyponatremia, hypotension, nausea, maculo-papular rash, sepsis, syncope, and vomiting (1/43 each; 2.3%).

Twenty-nine patients (67.4%) had one or more dose modifications of roniciclib (reduction or interruption) during the first six treatment cycles in combination with chemotherapy. TEAEs leading to dose modification were reported in 28 patients (65.1%) (Table 3); events were considered roniciclib-related in 23 patients (53.5%) (Supplementary Table 2). TEAEs led to permanent discontinuation of roniciclib in five patients (11.6%) (Table 3), in whom one event (2.3%) was considered roniciclib-related (Supplementary Table 2). Nine patients (20.9%) received whole-brain radiotherapy; dosing of roniciclib was interrupted during this period. Dose modifications were reported in 23 patients (65.1%) for carboplatin, six patients (14.0%) for cisplatin, and 30 patients (69.8%) for etoposide.

3.4. Pharmacokinetics

Roniciclib geometric mean plasma concentration–time profiles are shown in Figs. 1A and B. Following administration of roniciclib 5 mg alone, roniciclib was rapidly absorbed with median time to maximum drug concentration values of 0.5 and 0.75 h and displayed slightly delayed absorption when co-administered with CARBO-ETOP (Fig. 1). After administration of roniciclib 5 mg alone and co-administered with chemotherapy, mean plasma concentrations of the M-1 metabolite showed no significant change over 8 h. Mean plasma concentrations of M-1 were in the range of approximately 0.2–0.5 μg/L and 0.2–0.8 μg/L after administration of roniciclib 5 mg alone and when co-administered with CARBO-ETOP or CIS-ETOP therapy, respectively (data not shown). Similar PK characteristics were observed with roniciclib 2.5 mg (data not shown). PK parameters for roniciclib and roniciclib metabolite M-1 in plasma following administration of roniciclib 2.5 mg and 5 mg alone and with CIS-ETOP and CARBO-ETOP are shown in Supplementary Table 3.

When roniciclib 5 mg was co-administered with CARBO-ETOP or CIS-ETOP, no changes were observed in the geometric mean concentration–time profiles of free platinum, total platinum, or etoposide, as shown in Supplementary Fig. 1.

Roniciclib exposure was approximately 30–40% lower when co-administered with CARBO-ETOP or CIS-ETOP compared with roniciclib alone (Supplementary Table 3). Etoposide, free platinum, and total platinum concentrations were ≤20% different on average between cycles 1 and 2, indicating no clinically relevant effect of concomitant administration of roniciclib on etoposide or free platinum and total platinum PK parameters (Supplementary Fig. 1).

3.5. Efficacy

All patients who received treatment were evaluable for efficacy. Overall, no patient achieved a confirmed complete response and 35

Table 3
Summary of safety and incidence of treatment-emergent adverse events (by worst CTCAE grade) occurring in ≥10% of patients (safety analysis set).

n (%)	Roniciclib 2.5 mg BID		Roniciclib 5 mg BID		Total (N = 43)
	CARBO-ETOP (n = 4)	CIS-ETOP (n = 3)	CARBO-ETOP (n = 24)	CIS-ETOP (n = 12)	
Any TEAE[a]	4 (100)	3 (100)	24 (100)	12 (100)	43 (100)
Worst grade					
1	0	1 (33.3)	0	0	1 (2.3)
2	0	0	2 (8.3)	0	2 (4.7)
3	1 (25.0)	1 (33.3)	7 (29.2)	7 (58.3)	16 (37.2)
4	3 (75.0)	1 (33.3)	13 (54.2)	5 (41.7)	22 (51.2)
5 (death)	0	0	2 (8.3)	0[b]	2 (4.7)[b]
Serious adverse events	0	2 (66.7)	13 (54.2)	6 (50.0)	21 (48.8)
Worst grade					
1	0	0	0	0	0
2	0	0	2 (8.3)	2 (16.7)	4 (9.3)
3	0	2 (66.7)	5 (20.8)	3 (25.0)	10 (23.3)
4	0	0	4 (16.7)	1 (8.3)	5 (11.6)
5 (death)	0	0	2 (8.3)	0[b]	2 (4.7)[b]
Patients with TEAEs leading to dose modification[c]	3 (75.0)	1 (33.3)	18 (75.0)	6 (50.0)	28 (65.1)
Patients with TEAEs leading to permanent discontinuation of study drug	1 (25.0)	0	3 (12.5)	1 (8.3)	5 (11.6)
Incidence of TEAEs (any grade) occurring in ≥10% of the total population					
Nausea	3 (75.0)	2 (66.7)	23 (95.8)	11 (91.7)	39 (90.7)
Vomiting	4 (100)	1 (33.3)	15 (62.5)	10 (83.3)	30 (69.8)
Anemia	4 (100)	2 (66.7)	15 (62.5)	8 (66.7)	29 (67.4)
Decreased neutrophil count	3 (75.0)	2 (66.7)	17 (70.8)	7 (58.3)	29 (67.4)
Decreased platelet count	4 (100)	1 (33.3)	18 (75.0)	6 (50.0)	29 (67.4)
Diarrhea	3 (75.0)	1 (33.3)	14 (58.3)	10 (83.3)	28 (65.1)
Anorexia	1 (25.0)	2 (66.7)	10 (41.7)	11 (91.7)	24 (55.8)
Alopecia	4 (100)	2 (66.7)	12 (50.0)	6 (50.0)	24 (55.8)
Fatigue	2 (50.0)	2 (66.7)	10 (41.7)	8 (66.7)	22 (51.2)
Headache	1 (25.0)	0	12 (50.0)	6 (50.0)	19 (44.2)
Hypomagnesemia	1 (25.0)	1 (33.3)	7 (29.2)	7 (58.3)	16 (37.2)
Decreased white blood cell count	2 (50.0)	1 (33.3)	8 (33.3)	4 (33.3)	15 (34.9)
Constipation	1 (25.0)	0	7 (29.2)	5 (41.7)	13 (30.2)
Dizziness	2 (50.0)	2 (66.7)	3 (12.5)	5 (41.7)	12 (27.9)
Hypokalemia	1 (25.0)	1 (33.3)	7 (29.2)	2 (16.7)	11 (25.6)
Hyponatremia	1 (25.0)	1 (33.3)	6 (25.0)	3 (25.0)	11 (25.6)
Insomnia	0	1 (33.3)	6 (25.0)	4 (33.3)	11 (25.6)
Cough	1 (25.0)	1 (33.3)	5 (20.8)	4 (33.3)	11 (25.6)
Limb edema	1 (25.0)	0	4 (16.7)	4 (33.3)	9 (20.9)
Upper respiratory infection	0	0	7 (29.2)	2 (16.7)	9 (20.9)
Dyspnea	0	0	6 (25.0)	3 (25.0)	9 (20.9)
Pain	0	2 (66.7)	5 (20.8)	1 (8.3)	8 (18.6)
Myalgia	0	1 (33.3)	5 (20.8)	2 (16.7)	8 (18.6)
Tinnitus	1 (25.0)	1 (33.3)	0	5 (41.7)	7 (16.3)
Increased alanine aminotransferase	1 (25.0)	1 (33.3)	3 (12.5)	2 (16.7)	7 (16.3)
Generalized muscle weakness	0	0	3 (12.5)	4 (33.3)	7 (16.3)
Fever	0	0	4 (16.7)	2 (16.7)	6 (14.0)
Lung infection	0	0	5 (20.8)	1 (8.3)	6 (14.0)
Urinary tract infection	0	1 (33.3)	3 (12.5)	2 (16.7)	6 (14.0)
Gastrointestinal disorders – other	1 (25.0)	1 (33.3)	1 (4.2)	2 (16.7)	5 (11.6)
General disorders and administration site conditions – other	1 (25.0)	1 (33.3)	2 (8.3)	1 (8.3)	5 (11.6)
Infective rhinitis	1 (25.0)	0	0	4 (33.3)	5 (11.6)
Increased aspartate aminotransferase	1 (25.0)	1 (33.3)	2 (8.3)	1 (8.3)	5 (11.6)
Hyperglycemia	1 (25.0)	0	2 (8.3)	2 (16.7)	5 (11.6)
Hypoalbuminemia	0	1 (33.3)	3 (12.5)	1 (8.3)	5 (11.6)
Hypocalcemia	0	1 (33.3)	2 (8.3)	2 (16.7)	5 (11.6)
Dysgeusia	1 (25.0)	0	0	4 (33.3)	5 (11.6)
Hypertension	0	1 (33.3)	1 (4.2)	3 (25.0)	5 (11.6)

BID = twice daily; CARBO-ETOP = carboplatin-etoposide therapy; CIS-ETOP = cisplatin-etoposide therapy; CTCAE = Common Terminology Criteria for Adverse Events version 4.0; TEAE = treatment-emergent adverse event.

[a] Number (%) of patients with the specified event starting or worsening between the start of treatment and 30 days after the end of treatment.

[b] In the roniciclib 5 mg BID + CIS-ETOP cohort, one patient died within 30 days after treatment but did not have a reported adverse event that was associated with the death; therefore, there is no grade 5 event representing this death.

[c] Dose modifications included delays, interruptions, and reductions.

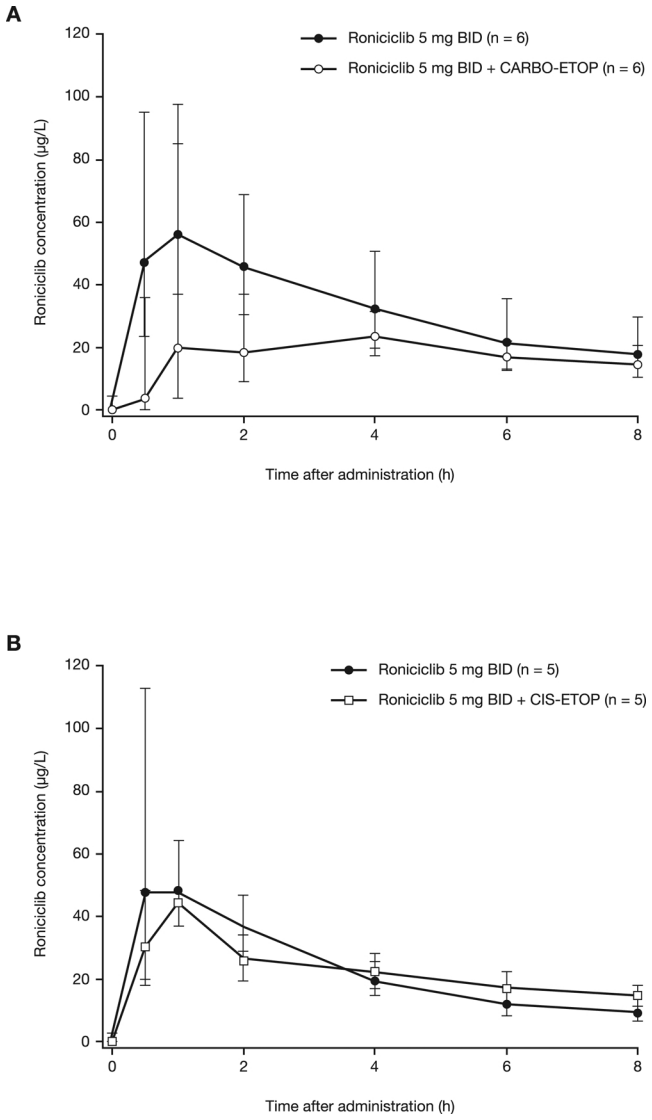

Fig. 1. Geometric mean plasma concentration–time profiles for roniciclib after oral administration of roniciclib 5 mg BID alone and after co-administration with CARBO-ETOP (A) and after oral administration of roniciclib 5 mg BID alone and after co-administration with CIS-ETOP (B). Pharmacokinetic analysis set. BID = twice daily; CARBO-ETOP = carboplatin-etoposide therapy; CIS-ETOP = cisplatin-etoposide therapy.

patients (81.4%) achieved a confirmed partial response, resulting in a response rate of 81.4% (Table 4). Five patients (11.6%) had stable disease, two patients (4.7%) had disease progression, and one patient (2.3%) had a missing evaluation (Table 4). The response rate was similar in the pooled roniciclib 5 mg BID population (86.1%; n = 31) (Table 4). The DCR was 93.0% in the overall population and 94.4% in the pooled roniciclib 5 mg BID population (Table 4).

Median OS was 12.6 months overall (95% confidence interval [CI] 9.8–17.2) and 13.4 months (95% CI 9.6–8.2) in the pooled roniciclib 5 mg BID population, with little difference between the chemotherapy groups: CARBO-ETOP, 14.1 months; CIS-ETOP, 11.2 months. Median PFS was 6.7 months overall and in the pooled roniciclib 5 mg BID population (95% CI 5.5–7.6), and was 7.2 and 6.2 months for roniciclib 5 mg BID with CARBO-ETOP or CIS-ETOP, respectively. Median time to progression was 6.7 months (95% CI 5.4–7.6) in both the overall population and the pooled roniciclib 5 mg BID population (CARBO-ETOP, 7.5 months; CIS-ETOP, 5.7 months). Median DoR was 5.6 months overall (95% CI 4.3–6.4) and 5.8 months (95% CI 4.3–7.0) in the pooled roniciclib 5 mg BID population (6.3 and 5.1 months for CARBO-ETOP or CIS-ETOP, respectively). For the roniciclib 2.5 mg BID CARBO-ETOP and CIS-ETOP groups, median OS was 12.6 and 11.4 months, respectively; median PFS and median time to progression were 6.7 and 5.4 months, respectively, and median DoR was 5.6 and 4.2 months, respectively.

Given the very limited number of tissue samples available, the exploratory biomarker analysis was not pursued due to the insufficient clinical significance expected.

4. Discussion

This phase Ib/II study evaluated the safety, PK, MTD, and efficacy of roniciclib in combination with platinum-based chemotherapy in patients with ED-SCLC. The MTD was roniciclib 5 mg BID administered orally in a 3 days on/4 days off regimen in combination with standard CARBO-ETOP or CIS-ETOP, consistent with the RP2D for roniciclib monotherapy reported in the first-in-human phase I study [10]. Overall, roniciclib was tolerated in combination with chemotherapy in patients with ED-SCLC.

The most frequently observed TEAEs of any grade across all cohorts were nausea, vomiting, anemia, decreased neutrophil count, and decreased platelet count, while the most common roniciclib-related TEAEs were nausea and vomiting. In general, TEAEs were as anticipated given the underlying poor condition of patients and the TEAEs expected for roniciclib (nausea, fatigue, diarrhea, and vomiting) [10] and for platinum-based chemotherapy (anemia, neutropenia, thrombocytopenia, and leukopenia) [11]. The frequencies of TEAEs were generally similar across cohorts; however, comparisons should be made with caution because of the small sample size of the roniciclib 2.5 mg BID cohorts.

Serious adverse events were reported in 21 patients, most of which correspond to those typically reported in an SCLC population treated with chemotherapy, including hepatotoxicity, infections, and respiratory failure [12,13]. Three deaths (lung infection, respiratory failure, and unknown cause) were reported during this study. Pulmonary events are common in the treated patient population and the

Table 4
Response evaluation according to RECIST version 1.1 (safety analysis set).

n (%)	Roniciclib 2.5 mg BID		Roniciclib 5 mg BID			Total (N = 43)
	CARBO-ETOP (n = 4)	CIS-ETOP (n = 3)	CARBO-ETOP (n = 24)	CIS-ETOP (n = 12)	Pooled roniciclib 5 mg BID (n = 36)	
Best overall response						
Partial response	3 (75.0)	1 (33.3)	21 (87.5)	10 (83.3)	31 (86.1)	35 (81.4)
Stable disease	1 (25.0)	1 (33.3)	2 (8.3)	1 (8.3)	3 (8.3)	5 (11.6)
Disease progression	0	1 (33.3)	0	1 (8.3)	1 (2.8)	2 (4.7)
Missing	0	0	1 (4.2)[a]	0	1 (2.8)	1 (2.3)
Objective tumor response rate	3 (75.0)	1 (33.3)	21 (87.5)	10 (83.3)	31 (86.1)	35 (81.4)
Disease control rate	4 (100)	2 (66.7)	23 (95.8)	11 (91.7)	34 (94.4)	40 (93.0)

BID = twice daily; CARBO-ETOP = carboplatin-etoposide therapy; CIS-ETOP = cisplatin-etoposide therapy; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Death caused by hypercarbic respiratory failure occurred after one cycle of treatment but before the cycle 2 response assessment.

deaths were assessed as unrelated to roniciclib.

No clinically relevant PK interaction was observed upon concomitant administration of roniciclib and CARBO-ETOP or CIS-ETOP. Exposures of etoposide, total platinum, and free platinum were not affected; however, roniciclib exposure (maximum drug concentration and area under the curve) was observed to be lower when administered with CARBO-ETOP or CIS-ETOP compared with administration as a single agent. As there is no known mechanistic basis for PK interaction, lower roniciclib exposure may be attributed, in part, to limited absorption as a result of increased gastrointestinal adverse events observed after repeated administration of roniciclib.

Efficacy results were promising in this study; 81.4% of patients achieved a confirmed partial response and 11.6% of patients achieved stable disease. The overall response rate was 81.4%, with a response rate of 86.1% at the MTD of roniciclib 5 mg. These results are consistent with response rates typically seen with standard chemotherapy in patients with ED-SCLC (70–85%) [14]. At the roniciclib MTD, median OS was 13.4 months, median PFS was 6.7 months, median time to progression was 6.7 months, and median DoR was 5.8 months. The OS of approximately 13 months was similar to previously reported treatment strategies in ED-SCLC [14]. Response rates were also similar between CARBO-ETOP and CIS-ETOP for patients receiving roniciclib 5 mg BID (87.5% and 83.3%, respectively). A meta-analysis comparing the efficacy of cisplatin versus carboplatin as first-line treatment of SCLC also demonstrated comparable response; median OS of 9.6 months and 9.4 months, median PFS of 5.5 and 5.3 months, and response rates of 67.1% and 66.0% for cisplatin and carboplatin, respectively [5].

While our efficacy data appear favorable, these data should be interpreted with caution, particularly results with roniciclib 2.5 mg BID plus chemotherapy, for which patient numbers are too low to provide meaningful clinical interpretation. In this study, no complete responses were observed, contrasting with previous studies of standard chemotherapy [14,15]. However, in 46.5% of patients receiving roniciclib + CARBO-ETOP or CIS-ETOP, the dose of etoposide had to be reduced because of adverse events, potentially affecting anti-tumor response [15]. Overall, the sample size in this study was too small for definite conclusions regarding efficacy.

The chemotherapy regimens in this study are commonly used and have been widely accepted for more than four decades [16–18], although median survival for patients with ED-SCLC remains low, with virtually every patient relapsing following response [14]. Thus far, the addition of thalidomide, bevacizumab, pemetrexed, and oblimersen to first-line chemotherapy treatment in patients with ED-SCLC has resulted in negative phase II and III studies [19]. Promising *in vivo* tumor growth inhibition with roniciclib in combination with cisplatin and/or etoposide in SCLC tumor models [9], coupled with an acceptable safety profile and moderate DCR in a phase I study of roniciclib monotherapy [10], suggested a potential for roniciclib to improve first-line treatment outcomes in patients with ED-SCLC in combination with standard chemotherapy.

In this study, the addition of roniciclib to standard chemotherapy for the treatment of ED-SCLC showed a safety profile similar to that seen previously for roniciclib and for the chemotherapy combinations, and no new safety signals were identified. Although occurrences of thromboembolic events resulted in a reduction of the RP2D in the first-in-human study [10], only two patients (4.7%) experienced thromboembolic events with the combination of roniciclib with chemotherapy. No clinically relevant PK interactions were observed, and efficacy results were potentially promising with a response rate of 81.4%. Nevertheless, when one patient on the present study had been stable for over 40 cycles and was still receiving treatment with roniciclib 2.5 mg BID, a safety signal was observed in a related phase II, placebo-controlled study evaluating the efficacy and safety of roniciclib in combination with CARBO-ETOP or CIS-ETOP as first-line therapy in patients with ED-SCLC (NCT02161419). Preliminary safety and efficacy data from that phase II study demonstrated an unfavorable benefit/risk balance for patients receiving roniciclib in combination with CARBO-ETOP or CIS-ETOP [20]. As a result, treatment with roniciclib in the present study was discontinued and further clinical development has been terminated.

Source

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Conflicts of interest

Byoung Chul Cho, MD, PhD reports grants from Novartis, AstraZeneca, Yuhan, Dong-A, Ono/Bristol-Myers Squibb, and Merck Sharp and Dohme; and personal fees from Novartis, AstraZeneca, Yuhan, Ono/Bristol-Myers Squibb, Merck Sharp and Dohme, Boehringer Ingelheim, Roche, and Ignyta outside the submitted work. Grace K. Dy, MD reports research fees to Roswell Park Cancer Institute from Bayer, Roche, GlaxoSmithKline, Boehringer Ingelheim, AbbVie, Merck, Genentech, Novartis, ARIAD, Bristol-Myers Squibb, Pfizer, Celgene, and AstraZeneca; and consultant fees from Novartis and AstraZeneca outside the submitted work. Nathan A. Pennell, MD, PhD reports personal fees from Eli Lilly, AstraZeneca, and Regeneron outside the submitted work. Gerard Zalcman, MD, PhD reports personal fees from Roche, Bristol-Myers Squibb, Merck Sharp and Dohme, and Boehringer Ingelheim; and meeting attendance for AstraZeneca outside the submitted work. Simon Langer, MSc reports personal fees from Bayer outside the submitted work. Fabrice Barlesi, MD, PhD reports personal fees from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Clovis Oncology, Eli Lilly Oncology, F. Hoffmann-La Roche, Novartis, Merck, Merck Sharp and Dohme, Pierre Fabre, and Pfizer outside the submitted work. Goekben Koca, MD, Prabhu Rajagopalan, PhD, Matthias Ocker, MD, and Hendrik Nogai, MD are employees of Bayer. Prabhu Rajagopalan, PhD and Matthias Ocker, MD report stocks in Bayer. The remaining authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.lungcan.2018.04.022.

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