ORIGINAL ARTICLE

Phase II Study of Roniciclib in Combination with Cisplatin/Etoposide or Carboplatin/Etoposide as First-Line Therapy in Patients with Extensive-Disease Small Cell Lung Cancer

Martin Reck, MD, PhD,[a,*] Leora Horn, MD, MSc,[b] Silvia Novello, MD, PhD,[c] Fabrice Barlesi, MD, PhD,[d] István Albert, MD,[e] Erzsébet Juhász, MD,[f] Dariusz Kowalski, MD,[g] Gilles Robinet, MD,[h] Jacques Cadranel, MD, PhD,[i] Paolo Bidoli, MD,[j] John Chung, PhD,[k] Arno Fritsch, PhD,[l] Uta Drews, PhD,[m] Andrea Wagner, MD,[m] Ramaswamy Govindan, MD[n]

[a]*LungenClinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany*
[b]*Vanderbilt University Medical Center, Nashville, Tennessee*
[c]*Department of Oncology, University of Turin, Orbassano, Turin, Italy*
[d]*Aix-Marseille University, Marseille, France; Assistance Publique-Hôpitaux de Marseille, Marseille, France*
[e]*Pulmonary Department, Mátraháza Hospital, Mátraháza, Hungary*
[f]*Korányi National Institute for Pulmonology, Budapest, Hungary*
[g]*Maria Sklodowska-Curie Institute of Oncology, Warsaw, Poland*
[h]*University Hospital Brest, Brest, France*
[i]*Assistance Publique-Hôpitaux de Paris, Paris, France*
[j]*San Gerardo Hospital, Monza, Italy*
[k]*Bayer HealthCare Pharmaceuticals, Inc., Whippany, New Jersey*
[l]*Bayer AG, Wuppertal, Germany*
[m]*Bayer AG, Berlin, Germany*
[n]*Washington University School of Medicine, St. Louis, Missouri*

Received 29 August 2018; revised 21 December 2018; accepted 9 January 2019
Available online - 21 January 2019

ABSTRACT

Introduction: This phase II study evaluated the efficacy and safety of the pan-cyclin–dependent kinase inhibitor roniciclib with platinum-based chemotherapy in patients with extensive-disease SCLC.

Methods: In this randomized, double-blind study, unselected patients with previously untreated extensive-disease SCLC received roniciclib, 5 mg, or placebo twice daily according to a 3 days–on, 4 days–off schedule in 21-day cycles, with concomitant cisplatin or carboplatin on day 1 and etoposide on days 1 to 3. The primary end point was progression-free survival. Other end points included overall survival, objective response rate, and safety.

Results: A total of 140 patients received treatment: 70 with roniciclib plus chemotherapy and 70 with placebo plus chemotherapy. Median progression-free survival times was 4.9 months (95% confidence interval [CI]: 4.2–5.5) with roniciclib plus chemotherapy and 5.5 months (95% CI: 4.6–5.6) with placebo plus chemotherapy (hazard ratio

*Corresponding author.

Disclosure: Dr. Reck has received honoraria for lectures and consultancy from AbbVie, AstraZeneca, BMS, Celgene, Eli Lilly, Merck, MSD, Novartis, Pfizer, and Roche. Dr. Horn provides consulting for AbbVie, AstraZeneca, Eli Lilly, EMD Serono, Genentech, Incyte, and Merck. Dr. Novello has received personal fees for speaker bureau participation with AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, MSD, Roche, and Takeda. Dr. Barlesi has received honoraria from AstraZeneca, Boehringer Ingelheim, BMS, Clovis Oncology, Eli Lilly Oncology, F. Hoffmann-La Roche Ltd, Merck, Novartis, Pfizer, and Takeda. Dr. Chung is employed by Bayer HealthCare Pharmaceuticals, Inc. Dr. Fritsch, Dr. Drews, and Dr. Wagner are employed by Bayer AG. Dr. Govindan is an advisory board member for Adaptimmune, BMS, Celgene, Genentech, GSK, Merck, Nektar, NeoHealth, Pfizer, and Phillips Gilmore, and provides consulting for Genentech. The remaining authors declare no conflict of interest.

Trial registration: Roniciclib/Placebo in Combination with Chemotherapy in Small Cell Lung Cancer (CONCEPT-SCLC). NCT-02161419.

Address for correspondence: Martin Reck, MD, PhD, LungenClinic Grosshansdorf, Wöhrendamm 80, 22927 Grosshansdorf, Germany. E-mail: dr.martin.reck@web.de

ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2019.01.010

[HR] = 1.242, 95% CI: 0.820–1.881, $p = 0.8653$). Median overall survival times was 9.7 months (95% CI: 7.9–11.1) with roniciclib plus chemotherapy and 10.3 months (95% CI: 8.7–11.9) with placebo plus chemotherapy (HR = 1.281, 95% CI: 0.776–1.912, $p = 0.7858$). The objective response rates were 60.6% with roniciclib plus chemotherapy and 74.6% with placebo plus chemotherapy. Common treatment-emergent adverse events in both groups included nausea, vomiting, and fatigue. Serious treatment-emergent adverse events were more common with roniciclib plus chemotherapy (57.1%) than with placebo plus chemotherapy (38.6%).

Conclusions: Roniciclib combined with chemotherapy demonstrated an unfavorable risk-benefit profile in patients with extensive-disease SCLC, and the study was prematurely terminated.

Keywords: Roniciclib; Extensive-disease small cell lung cancer; Cisplatin; Carboplatin; Etoposide; CDK inhibitor

Introduction

SCLC is an aggressive neuroendocrine cancer, accounting for approximately 15% of lung cancer cases.[1] Approximately two-thirds of patients with SCLC have extensive disease (ED) at diagnosis and a median overall survival (OS) of less than 10 months.[2] Platinum-based combination chemotherapy is the standard-of-care first-line treatment for SCLC[2,3] and can provide modest improvements in survival.[3–5] However, almost all patients relapse within a few months and, despite receiving subsequent chemotherapy treatment (e.g., topotecan), they will eventually die.[6,7]

Cyclin-dependent kinases (CDKs) are critical regulators of the cell cycle, and different isoforms regulate specific cell-cycle phases: CDK4 and CDK6 regulate cell-cycle progression at the G1 checkpoint, and CDK2 and CDK1 are required for S, G2, and M phase progression.[8,9] However, uncontrolled activity of CDKs can lead to sustained proliferation in tumor cells, making CDK inhibition an attractive therapeutic option in cancer.[10,11]

Roniciclib (BAY 1000394 [Bayer AG, Leverkusen, Germany]) is an orally active, highly potent, small-molecule pan-CDK inhibitor with low nanomolar activity against CDKs 1, 2, 4, and 6.[12] In preclinical SCLC xenograft models, roniciclib has demonstrated significant efficacy in combination with cisplatin plus etoposide (CIS-ETOP) without worsening toxicity.[12] A first-in-human phase I study in patients with advanced malignancies determined the recommended phase II dose of roniciclib monotherapy as 5 mg twice daily, administered according to a 3 days–on, 4 days–off schedule in a 21-day cycle.[13] In a phase I expansion cohort, roniciclib monotherapy at the recommended phase II dose demonstrated an acceptable safety profile and a moderate disease control rate of 17.4%.[13]

In a related phase Ib/II study of roniciclib in combination with carboplatin plus etoposide (CARBO-ETOP) or CIS-ETOP, the maximum tolerated dose was confirmed to be 5 mg of roniciclib twice daily in combination, with acceptable tolerability and pharmaokinetics.[14] In that phase Ib study, roniciclib in combination with CARBO-ETOP or CIS-ETOP showed promising preliminary efficacy, with a median progression-free survival (PFS), OS, time to progression, and duration of response of 6.7, 13.4, 6.7, and 5.8 months, respectively, and a response rate of 86.1% in a cohort of 11 patients with ED-SCLC.[14]

This phase II, randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of roniciclib in combination with CARBO-ETOP or CIS-ETOP as a first-line therapy in patients with ED-SCLC.

Materials and Methods

The protocol was approved by the institutional review board or independent ethics committee at each study site. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines as outlined by the International Conference on Harmonisation.

Study Design and Objectives

This multicenter study comprised a chemotherapy combination phase with roniciclib or placebo plus chemotherapy (CARBO-ETOP or CIS-ETOP) followed by a monotherapy maintenance phase with roniciclib or placebo. The primary objective was to evaluate PFS in patients with ED-SCLC treated with first-line CARBO-ETOP or CIS-ETOP in combination with roniciclib (roniciclib plus chemotherapy) or placebo (placebo plus chemotherapy). Secondary objectives included evaluation of OS, time to progression, and objective response rate (ORR). Additional objectives included evaluation of the exploratory end point of duration of response, and tolerability and safety.

Patients

All patients provided written, informed consent. The inclusion criteria included: histologically or cytologically confirmed ED-SCLC indicated for treatment with either CARBO-ETOP or CIS-ETOP; at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors, version 1.1; an Eastern Cooperative Oncology Group performance status of 0 or 1; a serum sodium level of at least 120 mmol/L; life expectancy of at least 12 weeks; and adequate bone marrow, liver, and

renal functions. Asymptomatic brain metastases could be included if previously treated with radiotherapy and/or at least 2 weeks of steroid therapy with no new signs and symptoms after treatment. Key exclusion criteria included: any prior systemic anticancer therapy for SCLC; known hypersensitivity to study treatments; deep vein thrombosis within the past 6 months; any previous arterial thrombotic events or pulmonary embolism; history of New York Heart Association class III or IV congestive heart failure; angina within the past 6 months; any prior myocardial infarction; history of cardiac arrhythmias requiring antiarrhythmic therapy; known human immunodeficiency virus infection or hepatitis B or C infection; any clinically serious infections evaluated as higher than grade 2; or symptomatic metastatic brain or meningeal tumors, including carcinomatous meningitis or leptomeningeal carcinomatosis.

Treatment

After randomization, patients entered the chemotherapy combination phase, during which they received roniciclib, 5 mg, twice daily (administered orally as two [2.5-mg] tablets) or matching placebo (administered orally as two tablets) (Supplementary Fig. 1*A*). Roniciclib or placebo was administered according to a 3 days–on, 4 days–off schedule in 21-day cycles with concomitant chemotherapy, starting on day 1 of each cycle (Supplementary Fig. 1*B*). Cisplatin, 75 mg/m^2, or carboplatin (dose determined by the Calvert formula to yield an area under the curve of 5 mg/mL $\times$ min) was administered intravenously on day 1 of each cycle. The choice of the platinum agent was at the investigator's discretion and patients could switch the agents in the event of unacceptable toxicities. Etoposide, 100 mg/m^2, was administered intravenously on days 1 to 3 of each cycle. The chemotherapy combination phase continued for a maximum of six cycles or until tumor progression, unacceptable toxicity, or study withdrawal. Roniciclib or placebo was continued after six cycles in the monotherapy maintenance phase until tumor progression, unacceptable toxicity, or withdrawal from the study (see Supplementary Fig. 1*A*).

Assessments

Safety was evaluated at screening, at the beginning of each cycle, and during the safety follow-up visit performed approximately 1 month after treatment discontinuation. Safety assessments included physical examinations, clinical laboratory investigations, concomitant medications, medical procedures, and adverse events (AEs). AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Efficacy was evaluated by computed tomography or magnetic resonance imaging at screening and then every 6 weeks until progressive disease or until another antitumor therapy had been started. Response was assessed by the investigator using the Response Evaluation Criteria in Solid Tumors, version 1.1. Survival follow-up was performed approximately every 2 months after discontinuation of the study treatment until death, loss to follow-up, withdrawal of consent, or study termination.

Statistical Analysis

All randomized patients were included in the full analysis set for efficacy analysis. The primary efficacy variable was PFS. Assuming a type I error rate (α) equal to 5%, a power of 90%, a 100% increase in median PFS time, and a treatment group allocation ratio of 1:1, 71 PFS events were required for the primary analysis. Assuming a median time to PFS of 5 months in the control group, it was determined that 140 patients needed to be enrolled to observe 71 events after approximately 17 months (the primary completion date). The treatment groups were compared by using a one-sided stratified log-rank test with the null hypothesis assuming that both treatment arms had the same PFS distribution and a hazard ratio (HR) of 1, being tested against the alternative hypothesis of an HR less than 1, favoring roniciclib, with a type I error rate (α) equal to 5%. Kaplan-Meier estimates of median PFS with 95% confidence intervals (CIs), as well as the HR with its CI derived by using a Cox proportional hazards model, were generated for each treatment group.

All secondary efficacy end points were tested at a type I error rate (α) of 5% for one-sided tests and 10% for two-sided tests. Analyses of all secondary end points were to be completed at the primary completion date. Analysis of OS was performed with use of the same stratified log-rank test as for PFS, and was planned to be performed when approximately 94 deaths had occurred (after approximately 2.5 years). Time to progression was analyzed by using the same stratified log-rank test as for PFS. Cochran-Mantel-Haenszel tests were used to analyze ORR, with estimates and CIs computed for the treatment groups and the differences in ORR between the groups. Duration of response was analyzed descriptively, and Kaplan-Meier estimates and distribution curves were generated for each treatment group.

All patients who received at least one dose of a study drug (roniciclib or placebo) were included in the safety analysis set.

Results

Patient Disposition, Demographics, and Baseline Characteristics

Overall, 172 patients were enrolled across 32 centers in nine countries, of whom 142 were assigned to treatment and included in the full analysis set (Fig. 1). A total of 140 patients received treatment, 70 in each treatment arm (roniciclib plus chemotherapy and placebo plus chemotherapy). In all, 33 patients receiving roniciclib plus chemotherapy (47.1%) and 46 receiving placebo plus chemotherapy (65.7%) discontinued treatment because of radiologic disease progression, which was the most common reason for treatment discontinuation (see Fig. 1). Other reasons for treatment discontinuation included AEs not associated with disease progression in 10 patients (14.3%) and three patients (4.3%), withdrawal in six patients (8.6%) and three patients (4.3%), and death in six patients (8.6%) and 1 patient (1.4%), respectively.

Of the 142 patients assigned to treatment, 87 (61.3%) were male; their median age was 63 years (range 40–83) (Table 1). Ninety-seven patients (68.3%) had a baseline Eastern Cooperative Oncology Group performance status of 1, and 126 patients (88.7%) had a serum lactate dehydrogenase level less than or equal to 2.5 times upper limit of normal.

Treatment

The median durations of treatment (including dose interruptions) for the overall study (chemotherapy combination phase and monotherapy phase) were 14.9 weeks (range 0–63) in the roniciclib plus chemotherapy group and 20.4 weeks (range 1–59) in the placebo plus chemotherapy group; the median numbers of treatment cycles received were 5.0 (range 1–20) and 6.0 (range 1–20), respectively.

In cycle 1, 44 patients (62.0%) started with CARBO + ETOP and 26 (36.6%) started with CIS + ETOP in each treatment group (see Table 1). Four patients in each treatment group switched from cisplatin to carboplatin during the study.

Fifty-nine patients (84.3%) in the roniciclib plus chemotherapy group and 58 (82.9%) in the placebo plus chemotherapy group required modifications of the dose of either agent (roniciclib or placebo), with similar proportions observed during the chemotherapy combination phase (with 80.0% [56 of 70] receiving roniciclib plus chemotherapy and 78.6% [55 of 70] receiving placebo plus chemotherapy) and slightly lower proportions observed during the monotherapy phase (67.9% [19 of 28] and 42.5% [17 of 40], respectively). Does interruptions were reported in 51 patients (72.9%) in the roniciclib plus chemotherapy group and

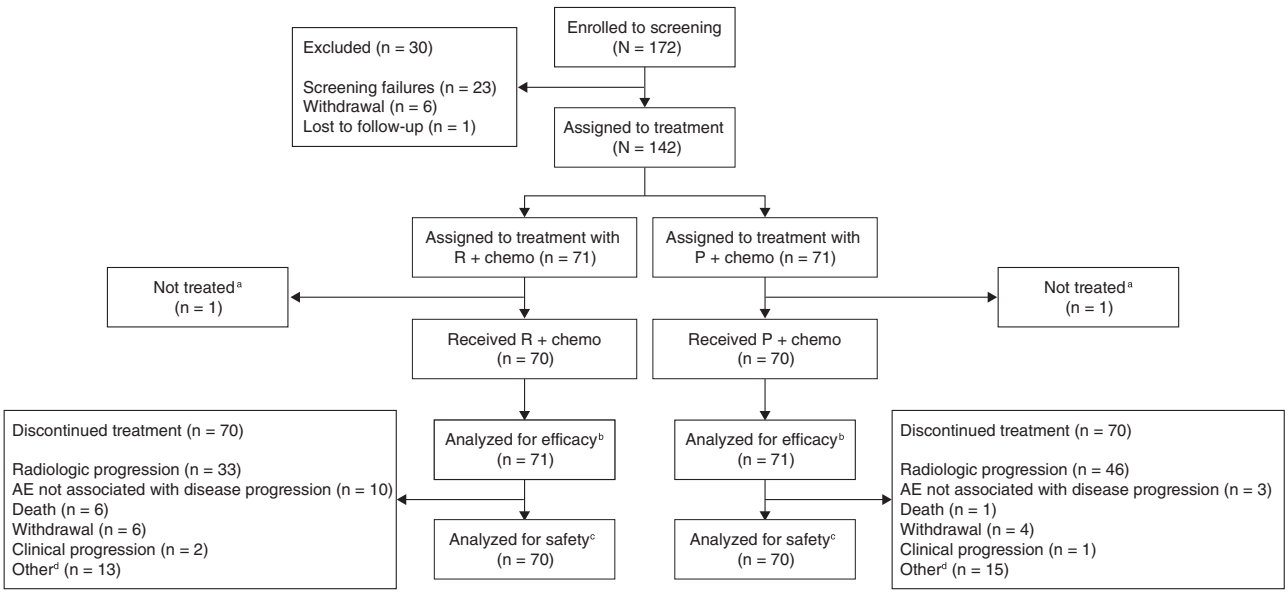


Figure 1. Patient disposition. [a]One patient in each treatment group did not receive treatment because of major protocol deviations (classed as treatment deviations), and each patient was excluded from the safety analysis. [b]Efficacy analyses were performed in the full analysis set, including all patients assigned to treatment (N = 142). [c]Safety analyses were performed in the safety analysis set, including all patients who received at least one dose of study treatment (n = 140). [d]Other includes protocol violation, loss to follow-up, study terminated by sponsor, physician's decision, adverse event (AE) associated with clinical disease progression, switching to the other therapy, protocol-driven decision, deterioration of general condition, and intolerance. R, roniciclib; P, placebo; chemo, chemotherapy. AE, adverse event.

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	Roniciclib + Chemotherapy (n = 71)	Placebo + Chemotherapy (n = 71)	Total (N = 142)
Sex, n (%)			
Male	43 (60.6)	44 (62.0)	87 (61.3)
Female	28 (39.4)	27 (38.0)	55 (38.7)
Median age, y (range)	62 (40-82)	63 (44-83)	63 (40-83)
Race, n (%)[a]			
White	57 (80.3)	53 (74.6)	110 (77.5)
Asian	5 (7.0)	8 (11.3)	13 (9.2)
Black	1 (1.4)	1 (1.4)	2 (1.4)
ECOG PS, n (%)			
0	25 (35.2)	20 (28.2)	45 (31.7)
1	46 (64.8)	51 (71.8)	97 (68.3)
Serum LDH, n (%)			
≤2.5 × ULN	63 (88.7)	63 (88.7)	126 (88.7)
>2.5 × ULN	8 (11.3)	8 (11.3)	16 (11.3)
Median time from initial diagnosis to start of study treatment, wk (range)	2.8 (1-9)[b]	2.7 (1-9)[c]	2.7 (1-9)[d]
Type of chemotherapy combination in cycle 1, n (%)[e]			
Carboplatin plus etoposide	44 (62.0)	44 (62.0)	88 (62.0)
Cisplatin plus etoposide	26 (36.6)	26 (36.6)	52 (36.6)

[a]Data missing or not reported for eight patients in the roniciclib plus chemotherapy group and nine patients in the placebo plus chemotherapy group.
[b]n = 70.
[c]n = 68.
[d]n = 138.
[e]One patient each in the roniciclib plus chemotherapy and placebo plus chemotherapy groups did not receive treatment.
ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal.

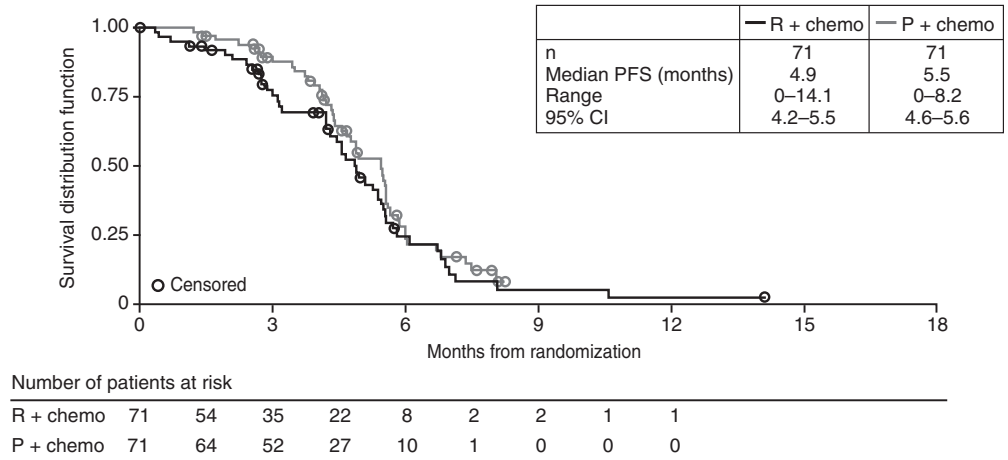
in 55 patients (78.6%) in the placebo plus chemotherapy group, with median durations of the dose interruptions or delays of 15.0 days (range 1–109) and 16.0 days (range 1–45), respectively. Reductions of the dose of roniciclib or placebo were reported in 40 patients (57.1%) in the roniciclib plus chemotherapy group and in 29 patients (41.4%) in the placebo plus chemotherapy group.

Efficacy

The study primary completion date was December 31, 2015. The analysis of PFS included all 142 patients assigned to treatment (full analysis set). A PFS event was experienced by 45 patients (63.4%) in the roniciclib plus chemotherapy group and 47 patients (66.2%) in the placebo plus chemotherapy group; median duration PFS was 4.9 months (95% CI: 4.2–5.5, range 0–14.1) and 5.5 months (95% CI: 4.6–5.6, range 0–8.2), respectively (Fig. 2). Treatment with roniciclib plus chemotherapy did not show a statistically significant difference in PFS compared with placebo plus chemotherapy, as shown by an HR of 1.242 (95% CI: 0.820–1.881, $p = 0.8653$). The PFS rates at 3 months were 77.5% (95% CI: 66.6–88.3) in the roniciclib plus chemotherapy group and 89.3% (95% CI: 81.9–96.8) in the placebo plus chemotherapy group, suggesting that more PFS events occurred early in the roniciclib plus chemotherapy group compared with the placebo plus chemotherapy group. However, this difference was less pronounced at 6 months, with PFS rates of 24.7% (95% CI: 12.0–37.4) and 28.2% (95% CI: 15.8–40.7) in the roniciclib plus chemotherapy and placebo plus chemotherapy groups, respectively.

The database cutoff date for the final analysis of OS was April 20, 2016. OS was numerically worse in patients receiving roniciclib plus chemotherapy compared with those receiving placebo plus chemotherapy: median OS was 9.7 months (95% CI: 7.9–11.1, range 0.1–18.3) in the roniciclib plus chemotherapy group and 10.3 months (95% CI: 8.7–11.9, range 0–17.0) in the placebo plus chemotherapy group, with an HR of 1.218 (95% CI: 0.776–1.912, $p = 0.7858$) (Fig. 3*A*). The greatest difference in OS rates was observed at 6 months, favoring placebo (76.9% for roniciclib plus chemotherapy [95% CI: 67.0–86.8] and 89.6% for placebo plus chemotherapy [95% CI: 82.3–96.9]).

Median time to progression was 5.4 months (95% CI: 4.6–5.7, range 0–14.1) in the roniciclib plus chemotherapy group and 5.5 months (95% CI: 4.8–5.6, range 0–8.2) in the placebo plus chemotherapy group, with an HR of 1.047 (95% CI: 0.665–1.648, $p = 0.5900$) (Fig. 3*B*).



	R + chemo	P + chemo
n	71	71
Median PFS (months)	4.9	5.5
Range	0–14.1	0–8.2
95% CI	4.2–5.5	4.6–5.6

Figure 2. Kaplan-Meier curves of progression-free survival (PFS) (full analysis set). chemo, chemotherapy; CI, confidence interval; P, placebo; R, roniciclib.

Similar time to progression rates were observed between the treatment groups at 3 and 6 months.

In the roniciclib plus chemotherapy group, one patient (1.4%) had a complete response, 42 (59.2%) had a partial response, nine (12.7%) had stable disease, and three (4.2%) had progressive disease as their best response; the ORR was 60.6% (95% CI: 48.3–72.0) (Table 2). In the placebo plus chemotherapy group, no patient had a complete response, 53 (74.6%) had a partial response, 11 (15.5%) had stable disease, and four (5.6%) had progressive disease as their best response; the ORR was 74.6% (95% CI: 62.9–84.2). The one-sided stratified Cochran-Mantel-Haenszel test for difference in ORR between the treatment groups gave a p value of 0.9685 (see Table 2).

The median durations of response were 4.2 months (95% CI: 3.0–4.6, range 0–13.0) in the roniciclib plus chemotherapy group and 4.2 months (95% CI: 3.2–4.3, range 0–6.9) in the placebo plus chemotherapy group (Fig. 3*C*), with similar duration of response rates observed at 3 and 6 months for both groups.

Safety

The safety analysis set included 140 patients, and the safety database cutoff date was April 20, 2016. All 140 patients had at least one treatment-emergent AE (TEAE) (Table 3). Overall, the most frequently reported TEAEs of any grade included nausea, vomiting, fatigue, and decreased neutrophil count. TEAEs with a worst grade of 3 were reported in 27.1% and 38.6% of patients in the roniciclib plus chemotherapy and placebo plus chemotherapy groups, respectively, and TEAEs with a worst grade of 4 were reported in 44.3% and 40.0%, respectively (see Table 3). The most common TEAEs with worst grades of 3 and 4 in both treatment groups included decreased neutrophil count, decreased platelet count, and anemia. Grade 5 (lethal) TEAEs occurred in nine patients (12.9%) receiving roniciclib plus chemotherapy and in three patients (4.3%) receiving placebo plus chemotherapy (see Table 3); two of these events (2.9%), which occurred in the roniciclib plus chemotherapy group, were considered drug-related (sepsis and bronchopulmonary hemorrhage) (Supplementary Table 1).

Drug-related TEAEs (considered related to roniciclib/placebo or chemotherapy) were reported in 64 patients (91.4%) in the roniciclib plus chemotherapy group and 45 patients (64.3%) in the placebo plus chemotherapy group (see Supplementary Table 1). The most common drug-related TEAEs of any grade overall included nausea and vomiting, which were generally more frequent in the roniciclib plus chemotherapy group.

The occurrence of serious TEAEs was higher in the roniciclib plus chemotherapy group than in the placebo plus chemotherapy group (57.1% versus 38.6%) (see Table 3). Serious drug-related TEAEs were observed in 15 patients (21.4%) in the roniciclib plus chemotherapy group and five patients (7.1%) in the placebo plus chemotherapy group (see Supplementary Table 1). The most common drug-related serious TEAEs were febrile neutropenia in three patients (4.3%) and anemia, sepsis, and a thromboembolic event in two patients each (2.9%) in the roniciclib plus chemotherapy group and hyponatremia in two patients (2.9%) in the placebo plus chemotherapy group. Differences in serious TEAEs, regardless of causality, between the treatment groups were mostly observed during the chemotherapy combination phase compared with the monotherapy phase of the study, with a higher incidence in the roniciclib plus chemotherapy group.

TEAEs leading to reductions of the dose of roniciclib or placebo were reported in 44.3% of patients in the

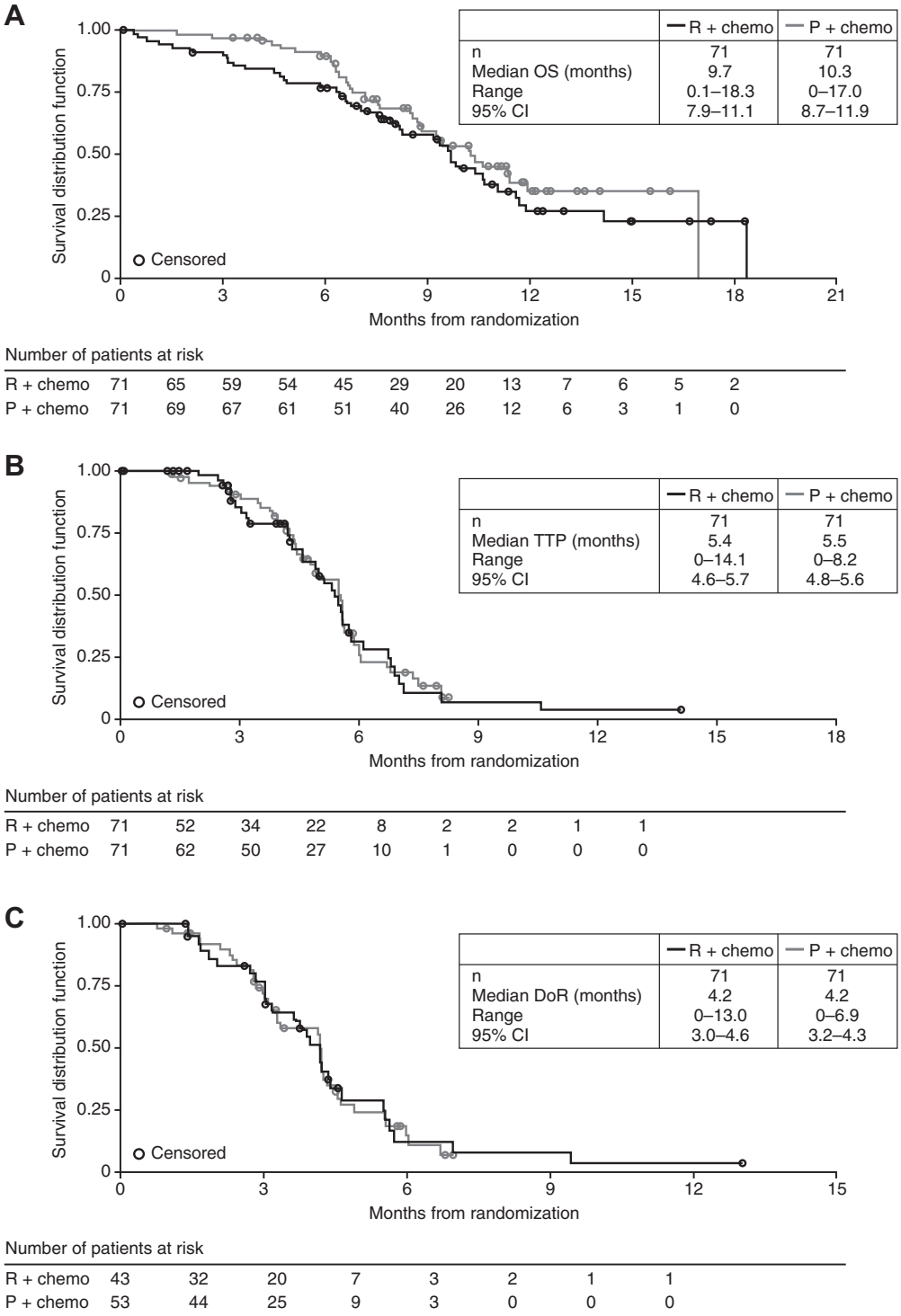


Figure 3. Kaplan-Meier curves of overall survival (OS) (*A*), time to progression (TTP) (*B*), and duration of response (DoR) (*C*) (full analysis set). chemo, chemotherapy; CI, confidence interval; P, placebo; R, roniciclib.

roniciclib plus chemotherapy group and 12.9% in the placebo plus chemotherapy group. Of these, the most common TEAEs (occurring in ≥10% of patients in either group) in the roniciclib plus chemotherapy and placebo plus chemotherapy groups included nausea (in 22.9% [16 of 70] and 1.4% [one of 70] of patients, respectively) and vomiting (in 17.1% [12 of 70] and 1.4% [one of 70], respectively). TEAEs leading to interruptions of the dose of roniciclib or placebo were reported in 64.3% and 60.0% of patients in the roniciclib plus chemotherapy and placebo plus chemotherapy groups, respectively. Of these, the most common TEAEs (occurring in ≥10% of

Table 2. Best Overall Tumor Response (Full Analysis Set)

Response	Roniciclib + Chemotherapy (n = 71)	Placebo + Chemotherapy (n = 71)
Best response, n (%) (95% CI)		
Complete response	1 (1.4) (0.0-7.6)	0
Partial response	42 (59.2) (46.8-70.7)	53 (74.6) (62.9-84.2)
Stable disease	9 (12.7) (6.0-22.7)	11 (15.5) (8.0-26.0)
Progressive disease	3 (4.2) (0.9-11.9)	4 (5.6) (1.6-13.8)
Not evaluable[a]	16 (22.5) (13.5-34.0)	3 (4.2) (0.9-11.9)
ORR, n (%) (95% CI)[b]	43 (60.6) (48.3-72.0)	53 (74.6) (62.9-84.2)
Difference in ORR, % (95% CI)	−14.37 (−29.34 to 0.60)	
One-sided *p* value	0.9685	

[a]Not evaluable refers to patients who discontinued treatment without any postbaseline tumor scan because of death or starting a different subsequent therapy.
[b]ORR includes patients with complete or partial response as their best response.
CI, confidence interval; ORR, objective response rate.

patients in either group) in the roniciclib plus chemotherapy and placebo plus chemotherapy groups were nausea (17.1% [12 of 70] and none), vomiting (12.9% [nine of 70] and 1.4% [one of 70]), decreased neutrophil count (18.6% [13 of 70] and 32.9% [23 of 70]), and decreased platelet count (10.0% [seven of 70] and 2.9% [two of 70]), respectively. Treatment discontinuation because of TEAEs was reported in 24.3% of patients in the roniciclib plus chemotherapy group and in 8.6% of those in the placebo plus chemotherapy group. The most commonly reported TEAEs leading to discontinuation of roniciclib or placebo were nausea in the roniciclib plus chemotherapy group (5.7% [four of 70]) and fatigue in the placebo plus chemotherapy group (2.9% [two of 70]).

Discussion

This phase II, randomized, double-blind study evaluated the efficacy and safety of roniciclib plus chemotherapy compared with placebo plus chemotherapy as a first-line treatment option in patients with ED-SCLC. Overall, roniciclib plus chemotherapy did not show a favorable efficacy and safety profile compared with placebo plus chemotherapy, and the study was prematurely terminated because of the negative risk-benefit ratio observed in the roniciclib plus chemotherapy group.

At the completion of the primary efficacy analysis, the study did not meet its primary end point of improved PFS for patients receiving roniciclib plus chemotherapy versus for those receiving placebo plus chemotherapy, with median PFS of 4.9 and 5.5 months, respectively. Analysis of the PFS rates at 3 and 6 months indicated that more PFS events occurred early in the roniciclib plus chemotherapy group compared with the placebo plus chemotherapy group, although this difference was less pronounced at 6 months. Additional efficacy analyses demonstrated that OS was shorter in the roniciclib plus chemotherapy group at 3 and 6 months, with OS remaining similar between treatment groups thereafter; there was a numerical difference but no statistically significant difference in OS between patients receiving roniciclib plus chemotherapy versus those receiving placebo plus chemotherapy (median OS of 9.7 versus 10.3 months, respectively, $p = 0.7858$). No treatment differences were observed with regard to median time to progression (5.4 versus 5.5 months) or median duration of response (4.2 versus 4.2 months).

Furthermore, a lower ORR was observed with roniciclib plus chemotherapy than with placebo plus chemotherapy (60.6% versus 74.6%), and a lower proportion of roniciclib-treated patients had a partial response compared with those receiving placebo (59.2% versus 74.6%), despite one complete response observed in a patient in the roniciclib plus chemotherapy group. However, the difference in ORR may be partly explained by a higher percentage of nonevaluable patients, mostly owing to a lack of postbaseline tumor assessments in the roniciclib plus chemotherapy group (22.5%) compared with the placebo plus chemotherapy group (4.2%). The response rate was lower than that reported in the roniciclib phase Ib/II study and lower than what is generally seen with standard chemotherapy alone in patients with ED-SCLC (70%–85%).[14,15] Collectively, these results are in contrast to those of the previous uncontrolled phase Ib/II study (NCT01573338), in which roniciclib demonstrated efficacy when administered in combination with standard chemotherapy.[14]

Overall, the incidence of all-grade TEAEs was generally higher in the roniciclib plus chemotherapy group than in the placebo plus chemotherapy group, particularly for vomiting, diarrhea, decreased platelet count, and hypomagnesemia. Similarly, the incidence of serious TEAEs was higher in the roniciclib plus chemotherapy group compared with the placebo plus

Table 3. Safety Summary and Incidence of Most Common TEAEs (Occurring in ≥10% of Patients) (Safety Analysis Set)

Variable, n (%)	Roniciclib + Chemotherapy (n = 70)			Placebo + Chemotherapy (n = 70)		
Any TEAE	70 (100)			70 (100)		
Worst grade						
1	4 (5.7)			4 (5.7)		
2	7 (10.0)			8 (11.4)		
3	19 (27.1)			27 (38.6)		
4	31 (44.3)			28 (40.0)		
5 (death)	9 (12.9)			3 (4.3)		
Any serious TEAE	40 (57.1)			27 (38.6)		
TEAE leading to dose reductions of roniciclib or placebo	31 (44.3)			9 (12.9)		
TEAE leading to dose interruptions of roniciclib or placebo	45 (64.3)			42 (60.0)		
TEAE leading to permanent discontinuation of roniciclib or placebo	17 (24.3)			6 (8.6)		
TEAEs occurring in ≥10% of patients in any treatment group						
Grade	Any	3	4	Any	3	4
Nausea	46 (65.7)	5 (7.1)	0	34 (48.6)	2 (2.9)	0
Vomiting	44 (62.9)	7 (10.0)	0	15 (21.4)	1 (1.4)	0
Fatigue	39 (55.7)	2 (2.9)	1 (1.4)	29 (41.4)	4 (5.7)	0
Decreased neutrophil count	38 (54.3)	13 (18.6)	22 (31.4)	46 (65.7)	18 (25.7)	23 (32.9)
Anemia	34 (48.6)	13 (18.6)	1 (1.4)	27 (38.6)	13 (18.6)	0
Decreased platelet count	34 (48.6)	16 (22.9)	5 (7.1)	16 (22.9)	4 (5.7)	8 (11.4)
Diarrhea	31 (44.3)	4 (5.7)	0	12 (17.1)	1 (1.4)	0
Hypomagnesemia	24 (34.3)	8 (11.4)	4 (5.7)	10 (14.3)	0	0
Anorexia	21 (30.0)	1 (1.4)	0	16 (22.9)	1 (1.4)	0
Alopecia	20 (28.6)	0	0	23 (32.9)	0	0
Headache	17 (24.3)	0	0	6 (8.6)	0	0
Limb edema	16 (22.9)	0	0	3 (4.3)	0	0
Dyspnea	15 (21.4)	2 (2.9)	0	6 (8.6)	1 (1.4)	0
Decreased white blood cell count	14 (20.0)	3 (4.3)	4 (5.7)	6 (8.6)	3 (4.3)	1 (1.4)
Pain	13 (18.6)	1 (1.4)	0	13 (18.6)	1 (1.4)	0
Hypotension	12 (17.1)	2 (2.9)	0	1 (1.4)	0	0
Insomnia	12 (17.1)	0	0	3 (4.3)	0	0
Back pain	10 (14.3)	2 (2.9)	0	6 (8.6)	1 (1.4)	0
Dizziness	10 (14.3)	0	0	6 (8.6)	0	0
Pain in extremity	10 (14.3)	0	0	4 (5.7)	0	0
Constipation	9 (12.9)	0	0	17 (24.3)	2 (2.9)	0
Hypokalemia	8 (11.4)	3 (4.3)	2 (2.9)	6 (8.6)	2 (2.9)	0
Thromboembolic event	8 (11.4)	2 (2.9)	0	2 (2.9)	2 (2.9)	0
Acute kidney injury	7 (10.0)	3 (4.3)	1 (1.4)	1 (1.4)	0	0
Febrile neutropenia	7 (10.0)	3 (4.3)	4 (5.7)	3 (4.3)	3 (4.3)	0
Fever	7 (10.0)	0	0	11 (15.7)	0	0
Paresthesia	7 (10.0)	0	0	6 (8.6)	0	0
Hyponatremia	6 (8.6)	4 (5.7)	1 (1.4)	8 (11.4)	2 (2.9)	5 (7.1)
Noncardiac chest pain	6 (8.6)	0	0	10 (14.3)	2 (2.9)	0
Oral mucositis	6 (8.6)	0	0	10 (14.3)	0	0
Peripheral sensory neuropathy	5 (7.1)	1 (1.4)	0	7 (10.0)	0	0
Hypertension	3 (4.3)	2 (2.9)	0	7 (10.0)	3 (4.3)	0

TEAE, treatment-emergent adverse event.

chemotherapy group (this included higher incidences of thromboembolic event, febrile neutropenia, anemia, sepsis, and acute kidney injury than with placebo plus chemotherapy). Of the 12 patients who died during the study, nine were in the roniciclib plus chemotherapy group, in which two deaths were due to drug-related TEAEs of bronchopulmonary hemorrhage and sepsis in one patient each. None of the three deaths in the placebo plus chemotherapy group were considered drug related.

Pan-CDK inhibitors have been extensively studied as a promising therapeutic option to disrupt the cell cycle in highly proliferative tumors,[11,16] and three selective CDK4/6 inhibitors have recently been approved by the U.S. Food and Drug Administration for the treatment of human EGFR2-negative advanced metastatic breast cancer.[17–19] The toxic effects of CDK inhibitors on normal cells, particularly myeloid cells and cells in gastrointestinal linings,[20] can lead to gastrointestinal and hematologic toxicities such as nausea and vomiting as observed in this study, and similar gastrointestinal toxicities have been reported in other clinical studies.[21,22] In this study, there was a higher incidence of fatal TEAEs as well as an increase in clinically important AEs, including sepsis, acute kidney injury, and thromboembolic events, in the roniciclib plus chemotherapy group than in the placebo plus chemotherapy group. However, detailed review of these AEs did not reveal an etiology or pathological mechanism that was clearly associated with roniciclib; most of the events could be explained by underlying disease, complications of disease progression, or cytotoxic chemotherapy treatment. Other CDK4/6 inhibitors such as trilaciclib have shown more manageable toxicity with preserved immune cell function and evidence of antitumor activity when administered in combination with chemotherapy versus chemotherapy plus placebo.[23,24]

TEAEs leading to reduction of the dose of roniciclib or placebo were more frequent in the roniciclib plus chemotherapy group than in the placebo plus chemotherapy group (44.3% versus 12.9%) and most commonly included nausea and vomiting, irrespective of treatment group. TEAEs leading to permanent treatment discontinuation of roniciclib or placebo occurred more frequently in roniciclib-treated patients than in those who received placebo (24.3% versus 8.6%, respectively), with nausea being the most common such TEAE. The incidence of TEAEs leading to interruptions or delays of the dose of roniciclib or placebo was similar between the treatment groups (64.3% in the roniciclib plus chemotherapy group versus 60.0% in the placebo plus chemotherapy group).

In conclusion, in this phase II study, roniciclib in combination with standard-of-care chemotherapy demonstrated an unfavorable risk-benefit profile in patients with ED-SCLC, and the study was prematurely terminated after the analysis at primary completion. All ongoing patients had their treatment discontinued. Future work to identify factors predictive of the clinical activity of CDK inhibitors would be beneficial to improve patient outcomes in ED-SCLC. Additionally, alternative therapeutic combinations, such as immunotherapy and standard chemotherapy, have shown promise in patients with ED-SCLC compared with chemotherapy alone.[25]

Acknowledgments

This study was supported by Bayer AG. Dr. Chung, Dr. Fritsch, Dr. Drews, and Dr. Wagner, who are employed by Bayer AG, were involved in the study design, data collection, analysis and interpretation, and writing of the article. All authors approved the final submitted article. Medical writing assistance was provided by Madeeha Aqil, PhD, at Complete HealthVizion (Chicago, IL) on the basis of detailed discussion and feedback from all the authors; this assistance was funded by Bayer AG.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.01.010.

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