

Phase I study of single-agent ribociclib in Japanese patients with advanced solid tumors

Toshihiko Doi¹ | Becker Hewes² | Tomoyuki Kakizume³ | Takeshi Tajima³ |
Norifumi Ishikawa³ | Yasuhide Yamada^{4,5}

¹National Cancer Center Hospital East, Kashiwa, Japan

²Torque Therapeutics, Inc., Cambridge, MA, USA

³Novartis Pharma K.K., Tokyo, Japan

⁴National Cancer Center Hospital, Tokyo, Japan

⁵National Center for Global Health and Medicine, Tokyo, Japan

Correspondence

Yasuhide Yamada, National Center for Global Health and Medicine, Shinjuku-ku, Tokyo, Japan.

Email: yayamada@hosp.ncgm.go.jp

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The cyclin D-CDK4/6-INK4-Rb pathway is frequently dysregulated in cancers. Ribociclib, an orally available, selective CDK4/6 inhibitor, showed preliminary clinical activity in a phase I study in the USA and Europe for patients with solid tumors and lymphomas. The present study aimed to determine the single-agent maximum tolerated dose (MTD) and recommended dose for expansion (RDE) in Japanese patients with advanced solid tumors. Ribociclib safety, tolerability, pharmacokinetic profile, and preliminary antitumor activity were also assessed. Japanese patients with solid tumors that had progressed on prior therapies received escalating doses of single-agent ribociclib on a 3-weeks-on/1-week-off schedule. Treatment continued until the development of toxicity or disease progression. A dose escalation was planned for patients with esophageal cancer. In the dose-escalation phase, 4 patients received 400 mg ribociclib and 13 patients received 600 mg ribociclib. Four patients experienced dose-limiting toxicities, 3 of whom were in the 600 mg group. The RDE was declared to be 600 mg, and the MTD was not determined. The most frequent adverse events were hematologic and gastrointestinal. Four patients achieved stable disease at the 600 mg dose; no patients achieved complete or partial response. All patients discontinued the study, the majority due to disease progression. No patients discontinued due to adverse events. Dose escalation was not pursued due to lack of observed efficacy in esophageal cancer. At the RDE of 600 mg/d on a 3-weeks-on/1-week-off schedule, ribociclib showed acceptable safety and tolerability profiles in Japanese patients with advanced solid tumors.

KEYWORDS

advanced solid tumors, dose escalation, Japanese patients, phase 1, ribociclib

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC_{0-24 h}, area under the concentration–time curve from time 0 to 24 h; BLRM, Bayesian Logistic Regression Model; CDK, cyclin-dependent kinase; CR, complete response; CYP3A4, cytochrome P450 3A4; DLT, dose-limiting toxicity; ESCC, esophageal squamous cell carcinoma; EWOC, escalation with overdose control; MTD, maximum tolerated dose; PK, pharmacokinetics; PR, partial response; pRb, retinoblastoma protein; Rb, retinoblastoma; Rb+, retinoblastoma-expressing; RDE, recommended dose for expansion; SD, stable disease; ULN, upper limit of normal.

This trial is registered with ClinicalTrials.gov (no. NCT01898845).

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1 | INTRODUCTION

Cancer incidence and mortality are expected to increase dramatically in Asia over the next 15 years, and patterns of diagnosis and treatment vary across this heterogeneous and populous region.¹ Although recent years have seen a consistent emphasis on increasing cancer prevention screenings and effectively planning treatment programs, there is a need for effective new strategies to manage the rapidly growing disease burden of Asian patients with advanced cancers, especially esophageal and head and neck squamous cell cancer.^{1,2}

Cyclin D-CDKs are enzyme complexes that serve as key regulators of cell cycle progression.³ In cancers, the cyclin D-CDK4/6-INK4-Rb pathway is often altered, leading to dysregulated cell cycle progression.^{3,4} This dysregulation, which leads to increased cyclin D-CDK4/6 activity, may be the result of overexpression of cyclin D1, overexpression and mutation of CDK4, or loss of regulatory proteins such as p16.^{3,5} The expression of phosphorylated pRb, a canonical tumor suppressor, is maintained in the vast majority of cancers.^{5,6} Retinoblastoma-expressing tumor cells with dysregulation in the CDK4/6 pathway show particular sensitivity to CDK4/6 inhibition.⁶

Ribociclib (LEE011) is an orally bioavailable, selective, small-molecule inhibitor of CDK4/6.⁷ Preclinical studies of ribociclib reported cell cycle arrest and tumor growth inhibition in both in vivo and in vitro models in a variety of Rb+ solid tumor types.^{8,9} A phase I study of single-agent ribociclib in patients from the USA and Europe with Rb+ advanced solid tumors and lymphomas (NCT01237236) confirmed ribociclib safety and tolerability at the RDE (600 mg/d, 3-weeks-on/1-week-off) and showed preliminary signs of clinical activity.⁴ The objective of the present study (NCT01898845) was to determine the MTD and RDE of single-agent ribociclib in Japanese patients with Rb+ advanced solid tumors that have progressed on prior therapy. The safety, tolerability, PK, and preliminary antitumor activity for single-agent ribociclib were also assessed.

2 | METHODS

2.1 | Study design and treatment

In this phase I, multicenter, single-arm, open-label study, Japanese patients with Rb+ advanced solid tumors were treated with single-agent ribociclib. Patients' Rb+ status was determined by testing of tumor samples by molecular screening at a sponsor-designated central laboratory. The primary objective of the study was to establish the MTD and/or the RDE for this patient cohort. Secondary objectives included the evaluation of safety and tolerability, antitumor efficacy, and PK properties for ribociclib.

In the dose-escalation portion of the study, groups of 3-6 patients received oral ribociclib on a 3-weeks-on/1-week-off schedule. The starting dose was based on MTD results (900 mg) from a phase I dose-escalation study in patients from the USA and Europe (NCT01237236). As this was the first clinical study of ribociclib in Asia, the starting dose was selected at 400 mg. After every evaluable patient in each group completed a minimum of one cycle of

treatment or experienced a DLT, dose-escalation decisions were made by investigators and study personnel at dose-escalation meetings. In this study, a DLT was defined as a \geq grade 3 AE or abnormal laboratory value per the CTCAE version 4.03¹⁰ that occurred during the DLT evaluation period and was determined by the investigator to be unrelated to disease, disease progression, or concomitant medication and to warrant classification as a DLT prior to the dose-escalation meeting. The recommended dose for the next group was guided by the adaptive BLRM with the EWOC principle.^{11,12} Dose escalation was planned to continue until identification of the MTD/RDE, which was defined using the following criteria: when (i) at least 6 patients had been treated at this dose, and (ii.a) the dose had a more than 50% probability to have a true DLT rate between 16% and 33% (targeted toxicity) and was the highest among potential doses, or (ii.b) a minimum of 12 patients had already received treatment on the study, and (iii) the dose was recommended for patients per the BLRM or review of all clinical data by investigators and sponsor.

In the dose-expansion portion of the study, a minimum of 12 Japanese patients with ESCC and at least one measurable lesion per RECIST version 1.1 were planned to be evaluated to determine the safety, preliminary antitumor activity, and PK profile for ribociclib. The sample size for the dose-expansion portion of the study was chosen to assess safety: at least 18 patients (comprising at least 6 patients from the dose-escalation portion and at least 12 patients from the dose-expansion portion) were required to be treated at the MTD/RDE for AEs occurring with a true incidence rate of \geq 10% to have a probability of \geq 85% for detection under the assumption that the true incidence rate was the same across the population enrolled.

2.2 | Patients

Adult Japanese patients with histologically confirmed advanced solid tumors that had progressed on conventional therapy, or for which no therapy was currently available, were eligible for the dose-escalation portion of the study. Tumors must have had centrally documented Rb+ status. Confirmed Rb+ status was not required for patients with breast cancer, ESCC, liposarcoma, or human papillomavirus-negative head and neck squamous cell carcinoma because pRb expression is frequently reported in these tumor types. Samples from patients with these tumor types were tested retrospectively for Rb expression. The dose-expansion portion was planned to include only patients with ESCC. Patients with primary central nervous system tumors or brain metastases were only permitted if treated and stable for \geq 3 months with no need for concomitant steroids or antiepileptic medication. Any number of prior therapies was permitted (including chemotherapy or radiation); a sufficient washout interval must have elapsed from the completion of prior anticancer therapy until study enrollment (\geq 2 weeks for cytotoxic chemotherapy or radiation, \geq 4 weeks for biologic therapy, and \geq 5 half-lives or \geq 4 weeks for other investigational agents, whichever is shorter). Other inclusion criteria were ECOG performance status of 0 or 1 and adequate bone marrow (absolute neutrophil count \geq 1.5 \times 10⁹/

L; hemoglobin ≥ 9 g/dL; platelet count $\geq 100 \times 10^9/L$, liver (total bilirubin $\leq 1.5 \times$ ULN; ALT/AST $\leq 3 \times$ ULN; for patients with liver lesions, ALT/AST $\leq 5 \times$ ULN), and renal (serum creatinine $\leq 1.5 \times$ ULN or 24-hour clearance ≥ 40 mL/min) function. Patients were excluded if they showed impaired gastrointestinal function that could disrupt ribociclib absorption or impaired cardiac function/clinically significant cardiac disease (including baseline QTcF > 450 ms). Pregnant or nursing women were excluded from the study. All patients provided written informed consent before enrollment. This study followed the ethical principles of the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use for Good Clinical Practice and was approved by the institutional review board.

2.3 | Study assessments

In the dose-escalation phase, the MTD/RDE for the 3-weeks-on/1-week-off dosing schedule was assessed by examination of the incidence and grade of DLTs during cycle 1. Efficacy was assessed by RECIST version 1.1 criteria using appropriate radiologic methods (computed tomography and MRI) or physical examination, depending on tumor type. All CRs and PRs had to be confirmed by a second assessment occurring at least 4 weeks after the initial antitumor response was observed. Incidence, duration, and severity of all AEs and their relationship to the study drug were assessed. Ribociclib plasma PK was assessed using sequential blood samples collected after study drug administration on cycle 1 day 1 and cycle 1 day 21 from all patients. Study data were analyzed when all patients in the dose-escalation portion had discontinued treatment.

3 | RESULTS

3.1 | Patient characteristics

From June 2013 to January 2015, a total of 17 patients were enrolled at 2 centers in Japan. The median patient age was 57.0 years, with 70.6% of patients < 65 years old. Approximately half of the patients (52.9%) were women. The most common primary cancer was esophageal ($n = 9$, 52.9%), followed by breast ($n = 4$, 23.5%). All patients received prior antineoplastic therapy, with the majority ($n = 12$, 70.6%) having received 3 or more lines of prior antineoplastic medication and/or prior radiotherapy ($n = 12$, 70.6%) (Table 1).

3.2 | Dose escalation

Patients were enrolled in 2 dose levels, 400 mg ribociclib ($n = 4$) and 600 mg ribociclib ($n = 13$), both on 3-weeks-on/1-week-off dosing schedules. Four patients experienced DLTs. In the 400 mg group, 1 patient experienced grade 3 febrile neutropenia. In the 600 mg group, 1 patient experienced grade 3 febrile neutropenia, 1 patient experienced grade 3 QT prolongation plus grade 4 neutropenia, and 1 patient experienced grade 3 QT prolongation plus grade 4

TABLE 1 Patient data and disease characteristics at baseline

	All (n = 17)
Median age, years (range)	57.0 (33–73)
Male gender, n (%)	8 (47)
ECOG performance status, n (%)	
0	11 (65)
1	6 (35)
Primary cancer, n (%)	
Breast	4 (24)
Esophagus	9 (53)
Peritoneum	3 (18)
Soft tissue	1 (6)
Prior systemic antineoplastic medications, n (%)	
1	2 (12)
2	3 (18)
≥ 3	12 (71)
Patients who received prior surgery, n (%)	9 (53)
Patients who received prior radiotherapy, n (%)	12 (71)

thrombocytopenia. Although the 750 mg dose could have been tested per BLRM along with the EWOC principle, the investigators and sponsor agreed that the 600 mg dose satisfied the criteria specified (see section above) to be declared the RDE, with an observed DLT rate of 23%. Therefore, the RDE for single-agent ribociclib was declared as 600 mg/d on the 3-weeks-on/1-week off schedule, and the escalation was stopped.

3.3 | Safety and tolerability

The median duration of exposure for all patients was 58.0 days. In the 400 mg dose group, the median duration of exposure was 54.5 days (range, 28–62 days), and at the RDE, the median duration of exposure was 59.0 days (range, 21–165 days). Median relative dose intensity was 1.0 for all patients (range, 1.00–1.00 in the 400 mg dose group and 0.73–1.00 at the RDE). A total of 11 patients (2 patients in the 400 mg dose group and 9 patients at the RDE) had dose interruptions due to the occurrence of at least one AE. Adverse events requiring dose interruption included grade 3/4 neutropenia (7 patients), grade 2/3 thrombocytopenia (2 patients), grade 1/2 vomiting (2 patients), grade 2 decreased appetite (1 patient), grade 1 pyrexia (1 patient), and grade 1 nausea (1 patient). Of the 11 patients with dose interruptions, 8 resumed treatment with no dose reduction, and 2 patients in the 600 mg dose group permanently discontinued treatment due to disease progression during the interruption. Dose reduction for management of DLTs was required for only 1 patient at the RDE. This patient was dose reduced to 400 mg ribociclib because of grade 4 thrombocytopenia. Prior to this, the same patient had grade 3 QT prolongation (also a DLT), which was managed with dose interruption.

All patients enrolled in the study experienced at least one AE, and all but 1 patient in the 400 mg dose group experienced at

least one AE of ≥ 3 grade. The most frequent AEs were hematologic, followed by nausea and increased laboratory values. At the RDE, the most frequent treatment-related ≥ 3 grade AEs were leukopenia (85%), neutropenia (77%), lymphopenia (69%), thrombocytopenia (31%), and prolonged QT (15%) (Table 2). The most frequent AEs of any grade were hematologic, a finding consistent with other studies of ribociclib.^{4,13} Hepatic AEs recorded during the study included increases in ALT, AST, and bilirubin. These AEs were generally mild, and none of them individually occurred in more than 2 patients. One patient experienced concurrent liver enzyme level elevations due to temporary blockage of bile flow from a metastatic retroperitoneal tumor, and as such did not meet the criteria for Hy's law. A total of 7 patients (1 patient in the 400 mg dose group and 6 patients at the RDE) experienced an electrocardiogram QT prolongation event, all of which were considered to be study drug-related (Table 2). All events resolved without action, with the exception of a grade 3 QT prolongation event that resolved with dose interruption followed by restarting ribociclib at a lower dose.

No patient discontinued treatment due to an AE. A total of 3 patients in the study, all at the RDE, experienced a single serious AE (one each of grade 3 upper abdominal pain, grade 3 small intestinal obstruction, and grade 2 vomiting). Only a single serious AE (grade 2 vomiting) was suspected to be study drug-related. There were no patient deaths during the treatment or safety follow-up period.

3.4 | Pharmacokinetic analysis

Ribociclib was rapidly absorbed, reaching maximal concentration at 3.0–5.0 hours; the effective half-life at cycle 1 day 21 was 63.6 hours for the 400 mg group and 53.6 hours at the RDE. Exposure increased as the dose increased in a slightly overproportional manner, with the oral clearance of the 600 mg dose (11.6 L/h) smaller than that for the 400 mg dose (14.4 L/h). The accumulation ratios for $AUC_{0-24\text{ h}}$ for cycle 1 day 21/cycle 1 day 1 were 4.36 at 400 mg and 4.01 at the RDE (Figure 1, Table 3). Elimination of ribociclib is dominated by oxidative metabolism, mainly through CYP3A4. For the oxidative metabolite LEQ803, time to maximal concentration was similar to that of ribociclib, where the metabolite-to-parent ratio $AUC_{0-24\text{ h}}$ was 0.15 at the 400 mg dose and was a smaller ratio (0.08) at the higher 600 mg dose (the RDE).

3.5 | Efficacy

All patients in the study were heavily pretreated (Table 1). At the time of analysis (July 2015), 15 (88%) patients had discontinued treatment due to progressive disease (3 patients in the 400 mg group and 12 patients at the RDE). No patients in the study achieved CR or PR; 4 patients at the RDE experienced SD, including SD for 4 cycles in 1 patient with peritoneal cancer and SD for ≥ 5 cycles in 3 patients (1 patient each with esophageal cancer, peritoneal cancer, and breast cancer) (Figure 2). The remaining 2 patients

TABLE 2 Adverse events (all grades) suspected to be study drug-related in $>10\%$ of Japanese patients with advanced solid tumors treated with ribociclib ($n = 17$)

Adverse event, n (%)	Ribociclib 400 mg ($n = 4$)		Ribociclib 600 mg ($n = 13$)		All ($n = 17$)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Total	4 (100)	3 (75)	13 (100)	13 (100)	17 (100)	16 (94)
Leukopenia	4 (100)	3 (75)	13 (100)	11 (85)	17 (100)	14 (82)
Neutropenia	3 (75)	3 (75)	13 (100)	10 (77)	16 (94)	13 (76)
Lymphopenia	2 (50)	0 (0)	12 (92)	9 (69)	14 (82)	9 (53)
Thrombocytopenia	3 (75)	0 (0)	9 (69)	4 (31)	12 (71)	4 (24)
ECG QT prolonged	1 (25)	0 (0)	6 (46)	2 (15)	7 (41)	2 (12)
Blood creatinine increased	2 (50)	0 (0)	5 (38)	0 (0)	7 (41)	0 (0)
Nausea	2 (50)	0 (0)	5 (38)	0 (0)	7 (41)	0 (0)
Vomiting	1 (25)	0 (0)	6 (46)	0 (0)	7 (41)	0 (0)
Anemia	1 (25)	0 (0)	5 (38)	1 (8)	6 (35)	1 (6)
Decreased appetite	0 (0)	0 (0)	3 (23)	0 (0)	3 (18)	0 (0)
Pyrexia	0 (0)	0 (0)	3 (23)	0 (0)	3 (18)	0 (0)
Febrile neutropenia	1 (25)	1 (25)	1 (8)	1 (8)	2 (12)	2 (12)
Hypophosphatemia	2 (50)	1 (25)	0 (0)	0 (0)	2 (12)	1 (6)
Constipation	1 (25)	0 (0)	1 (8)	0 (0)	2 (12)	0 (0)
Diarrhea	1 (25)	0 (0)	1 (8)	0 (0)	2 (12)	0 (0)
Fatigue	1 (25)	0 (0)	1 (8)	0 (0)	2 (12)	0 (0)
PPE	1 (25)	0 (0)	1 (8)	0 (0)	2 (12)	0 (0)
Dermatitis acneiform	0 (0)	0 (0)	2 (15)	0 (0)	2 (12)	0 (0)

ECG, electrocardiogram; PPE, palmar–plantar erythrodysesthesia.

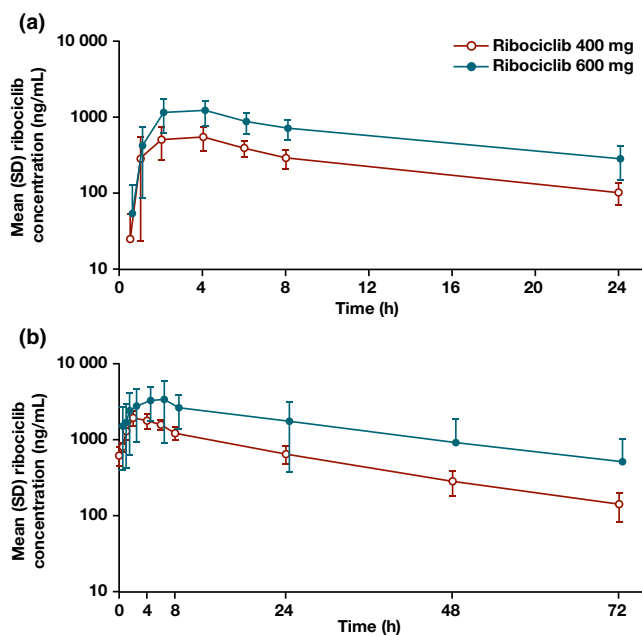


FIGURE 1 Ribociclib pharmacokinetic profile in Japanese patients with advanced solid tumors ($n = 17$). Mean plasma concentration–time profiles at cycle 1 day 1 (A) and cycle 1 day 21 (B)

(12%) discontinued treatment per physician decision. As no signs of clinical activity were observed for the 9 ESCC patients treated in the dose-escalation portion of the study, the planned dose expansion did not proceed.

4 | DISCUSSION

In this phase I study in adult Japanese patients with Rb+ advanced solid tumors whose disease had progressed on prior therapy, the RDE of single-agent ribociclib was determined to be 600 mg on a 3-weeks-on/1-week-off schedule. At the doses investigated in this study, single-agent ribociclib showed an acceptable safety and tolerability profile, with limited preliminary clinical activity. The results of the study were consistent with a phase I study of adult patients with solid tumors carried out in the USA and Europe.⁴

A total of 17 patients were enrolled (4 patients in the 400 mg dose group and 13 patients in the 600 mg dose group). A total of 4 patients in the study experienced DLTs (1 patient in the 400 mg

dose group and 3 patients in the 600 mg dose group). All toxicities were well managed by dose adjustment or interruption. The 2 DLTs of grade 3 QT prolongation at the RDE were resolved (one without action and one with dose interruption followed by dose reduction). The most frequently reported AEs were hematologic (leukopenia, neutropenia, lymphopenia, thrombocytopenia, and anemia). Hepatic AEs were generally grade 1/2, and occurred at rates similar to those observed in a phase I clinical trial of single-agent ribociclib in patients from the USA and Europe.⁵ Hematologic AEs were also the most frequent grade ≥ 3 AEs, and occurred more frequently than in previous studies in non-Japanese patients. Single-agent ribociclib at the RDE showed acceptable tolerability for Japanese patients with advanced solid tumors, with no major differences in the safety profile observed from previous studies in other patient populations.¹³

Ribociclib exposure increased with increasing dose, and exposure accumulation occurred after repeat dosing. The clearance of parent drug and the metabolite-to-parent AUC ratio were reduced for the 600 mg dose vs the 400 mg dose, suggesting a change in metabolism with increasing doses, which could be due to saturation in metabolism and/or auto-inhibition of CYP3A4, as reversible and time-dependent inhibition of CYP3A4/5 has been observed in vitro.¹⁴ Although the exposures at both dose levels (400 and 600 mg) were higher on average than those observed in a phase I clinical trial of single-agent ribociclib in patients from the USA and Europe,⁴ interindividual variability also was observed (Table 3), and the range of individual values overlapped between studies. Therefore, no conclusions could be made for PK ethnic sensitivity in this study.

As a single agent, ribociclib showed limited clinical activity. No patients in the study achieved a CR or PR. However, 4 patients at the RDE achieved a best overall response of SD. This lack of observed antitumor activity could be due in part to the extensive level of pretreatment observed for patients in the study. Because of the absence of activity observed for patients with ESCC, the planned dose-expansion portion of the study was not pursued.

Several ongoing studies are examining ribociclib at the RDE in combination with other agents as treatment for a variety of advanced cancers. MONALEESA-2, an ongoing phase III clinical trial of ribociclib in combination with endocrine therapy for hormone receptor-positive advanced breast cancer in the first-line setting, indicated significant increase in progression-free survival with ribociclib plus letrozole compared with placebo plus letrozole.¹³ This led

TABLE 3 Pharmacokinetic parameters of ribociclib in Japanese patients with advanced solid tumors ($n = 17$)

Dose	Day	Median T_{max} , h (range) [n]	Geometric mean C_{max} , ng/mL (CV%) [n]	Geometric mean AUC_{0-24h} , h·ng/mL (CV%) [n]	Geometric mean $T_{1/2,acc}$, h (CV%) [n]	Geometric mean CL/F, L/h (CV%) [n]
Ribociclib 400 mg ($n = 4$)	C1D1	3.12 (1.97-6.00) [4]	591 (26.4) [4]	6170 (25.9) [3]	–	–
	C1D21	3.00 (1.98-4.00) [4]	2180 (15.8) [4]	27 700 (15.8) [4]	63.6 (9.2) [3]	14.4 (15.8) [4]
Ribociclib 600 mg ($n = 13$)	C1D1	2.97 (1.92-5.87) [12]	1260 (38.3) [12]	14 200 (35.1) [11]	–	–
	C1D21	5.00 (4.00-7.55) [8]	3280 (59.9) [8]	51 600 (59.2) [8]	53.6 (44.8) [7]	11.6 (59.2) [8]

–, not applicable; AUC_{0-24h} , area under concentration–time curve between 0 and 24 h; C, cycle; CL/F, apparent total body clearance of drug from the plasma; C_{max} , maximum plasma concentration; CV, coefficient of variation; D, day; $T_{1/2,acc}$, effective elimination half-life; T_{max} , time to reach maximum plasma concentration.

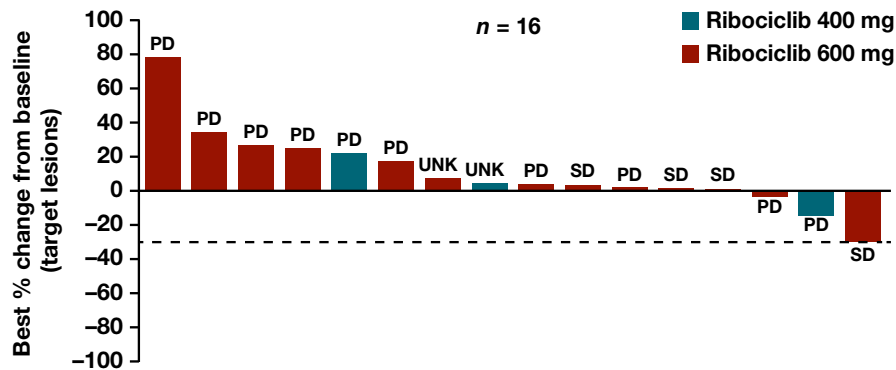


FIGURE 2 Best percentage change from baseline in sum of longest diameters and best overall response by investigator assessment among Japanese patients with advanced solid tumors treated with single-agent ribociclib ($n = 17$). Responses (per RECIST version 1.1) were assessed at baseline, at cycle 3 day 1, and on the first day of each cycle thereafter. Unknown patients (UNK) are those not qualifying for confirmed complete response or partial response and without stable disease (SD) after >6 weeks or early progression within the first 12 weeks. One patient with missing best percentage change from baseline and unknown overall response is not included. PD, progressive disease

to the recent approvals in the USA and Europe of ribociclib in combination with an aromatase inhibitor for the first-line treatment of hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer.^{14,15} A recent subgroup analysis of this trial reported no significant differences in efficacy or safety with the use of ribociclib plus letrozole in Asian (non-Japanese) patients compared with non-Asian patients.¹³ These results are consistent with those observed in the current study, with no new AEs reported for Japanese patients with Rb+ advanced solid tumors.

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CONFLICT OF INTEREST

Becker Hewes was a Novartis employee during the study. Tomoyuki Kakizume, Takeshi Tajima, and Norifumi Ishikawa are Novartis employees. Toshihiko Doi and Yasuhide Yamada have no conflict of interest.

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