Clinical Cancer Research

A Phase I Study of the CDK4/6 Inhibitor Ribociclib (LEE011) in Pediatric Patients with Malignant Rhabdoid Tumors, Neuroblastoma, and Other Solid Tumors

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Abstract

Purpose: The cyclin-dependent kinase (CDK) 4/6 inhibitor, ribociclib (LEE011), displayed preclinical activity in neuroblastoma and malignant rhabdoid tumor (MRT) models. In this phase I study, the maximum tolerated dose (MTD) and recommended phase II dose (RP2D), safety, pharmacokinetics (PK), and preliminary activity of single-agent ribociclib were investigated in pediatric patients with neuroblastoma, MRT, or other cyclin D–CDK4/6–INK4–retinoblastoma pathway-altered tumors.

Experimental Design: Patients (aged 1–21 years) received escalating once-daily oral doses of ribociclib (3-weeks-on/1-week-off). Dose escalation was guided by a Bayesian logistic regression model with overdose control and real-time PK.

Results: Thirty-two patients (median age, 5.5 years) received ribociclib 280, 350, or 470 mg/m^2. Three patients had dose-limiting toxicities of grade 3 fatigue (280 mg/m^2; $n = 1$) or grade 4 thrombocytopenia (470 mg/m^2; $n = 2$). Most common treatment-related adverse events (AE) were hematologic: neutropenia (72% all-grade/63% grade 3/4), leukopenia (63%/38%), anemia (44%/3%), thrombocytopenia (44%/28%), and lymphopenia (38%/19%), followed by vomiting (38%/0%), fatigue (25%/3%), nausea (25%/0%), and QTc prolongation (22%/0%). Ribociclib exposure was dose-dependent at 350 and 470 mg/m^2 [equivalent to 600 (RP2D)–900 mg in adults], with high interpatient variability. Best overall response was stable disease (SD) in nine patients (seven with neuroblastoma, two with primary CNS MRT); five patients achieved SD for more than 6, 6, 8, 12, and 13 cycles, respectively.

Conclusions: Ribociclib demonstrated acceptable safety and PK in pediatric patients. MTD (470 mg/m^2) and RP2D (350 mg/m^2) were equivalent to those in adults. Observations of prolonged SD support further investigation of ribociclib combined with other agents in neuroblastoma and MRT. *Clin Cancer Res; 23(10); 2433–41. ©2017 AACR.*

Introduction

High-risk neuroblastoma and malignant rhabdoid tumors (MRT) are pediatric tumors with poor survival outcomes; despite the development of intensive multimodality therapy regimens, novel effective therapies are urgently needed (1–3). Molecular abnormalities that drive disease progression by promoting cell-cycle progression might present new therapeutic targets in these cancers (4).

Numerous studies have identified genetic aberrations in neuroblastoma and MRTs that increase cyclin-dependent kinase (CDK) 4/6 activity. *CCND1*, *CDK4*, and *CDK6* have been shown to be highly expressed in neuroblastoma, and *CCND1* and *CDK6* expression were found to be uniformly high relative to other tumors (5–7). Genomic amplification of *CCND1* (cyclin D1 tumors) and *CDK4* and deletion of *CDKN2A* are correlated with

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Translational Relevance

High-risk neuroblastoma and malignant rhabdoid tumors (MRT) are pediatric tumors with poor survival outcomes; despite the use of intensive multimodality treatment regimens, novel targeted therapies are urgently required. Both diseases frequently exhibit aberrations in the cyclin D–cyclin-dependent kinase (CDK) 4/6–inhibitor of CDK4 (INK4)–retinoblastoma pathway, and preclinical evidence suggests that targeting this pathway with the CDK4/6 inhibitor ribociclib may be of therapeutic benefit.

This is the first clinical study exploring the use of a CDK4/6 inhibitor in a pediatric population. In this phase I study, we established the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of single-agent ribociclib in pediatric patients with neuroblastoma, MRTs, or other cancers with documented cyclin D–CDK4/6–INK4–retinoblastoma pathway aberrations. Ribociclib displayed an acceptable safety profile with dose-dependent pharmacokinetic characteristics, as well as preliminary signs of tumor stabilization, supporting further investigation of ribociclib in combination with other anticancer agents in pediatric cancers.

poor prognosis and, notably, approximately 30% of neuroblastomas exhibit aberrations in genes which regulate the G_1 checkpoint (6). An RNAi kinome screen in neuroblastoma cell lines identified *CDK4* as a potential therapeutic target (8). In MRTs, biallelic loss of *SMARCB1* (also known as *SNF5*, *INI1*, and *BAF47*), a gene that encodes a core subunit of the SWI/SNF chromatin remodeling complex, was reported in 12 of 13 (92%) MRT cell lines and 50 of 51 (98%) of tumors and appears to be a hallmark of this type of pediatric cancer (9, 10). SMARCB1 limits activity of cyclin D–CDK4/6 through direct transcriptional repression of *CCND1* and upregulation of genes encoding the cyclin D–CDK4/6 negative regulators, $p21^{Cip1}$ and $p16^{INK4A}$ (11, 12). Consequently, loss of *SMARCB1* results in altered expression of key cell-cycle regulators and reversal of cell-cycle arrest (13). Genetic ablation experiments have demonstrated that cyclin D1 is a key mediator in the genesis of MRTs, as *SMARCB1* heterozygous mice lacking cyclin D1 fail to develop MRTs, and siRNA-mediated knockdown of *CCND1* induces G_0–G_1 arrest and apoptosis in MRT cells (14). Therefore, targeting cyclin D1 or the cyclin D–CDK4/6–inhibitor of CDK4 (INK4)–retinoblastoma (Rb) axis is a biologically rational strategy for inhibiting neuroblastoma and MRT growth.

Ribociclib (LEE011) is an orally bioavailable, highly specific inhibitor of CDK4/6 (15). *In vitro* screens of a panel of more than 500 cell lines constituting the Novartis Cancer Cell Line Encyclopedia identified neuroblastoma and MRT cell lines to be among the most sensitive to ribociclib treatment (15). In addition, ribociclib caused cell-cycle arrest and senescence in a series of human neuroblastoma-derived cell lines (particularly those harboring *MYCN* amplification; ref. 16), and treatment of both neuroblastoma and MRT subcutaneous xenograft models resulted in tumor growth delays (15, 16). Collectively, these findings led to the hypothesis that ribociclib may have activity in neuroblastoma and MRTs with CDK4/6 activation through p16 loss or *CCND1*, *CDK4*, or *CDK6* amplification.

Here, we report results of the first clinical trial of a CDK4/6 inhibitor in pediatric patients, a phase I study of ribociclib in pediatric patients with MRT, neuroblastoma, or cyclin D–CDK4/6–INK4–Rb pathway-activated tumors (NCT01747876).

Patients and Methods

Study design and objectives

This was a phase I, multicenter, international, open-label study of single-agent ribociclib, composed of a dose-escalation portion in pediatric patients, followed by an expansion portion in pediatric patients with neuroblastoma and MRT. The primary objective was to determine the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D) of ribociclib. Secondary objectives included assessment of safety, tolerability, pharmacokinetics (PK), and preliminary clinical activity of ribociclib.

Study treatment

Patients received escalating doses of once-daily ribociclib on a 3-weeks-on/1-week-off schedule in 28-day treatment cycles. An intermittent dosing schedule was chosen on the basis of the expected bone marrow suppression associated with CDK4/6 inhibition which was confirmed in the adult phase I study with ribociclib (17). Ribociclib was administered orally in a fasted state, either as whole capsules or opened and poured onto semi-solid food or dissolved in water in case of swallowing difficulties. The starting dose was 280 $mg/m^2/d$, which was 80% of the RP2D in adults (600 mg) adjusted for body surface area.

Patient population

Patients aged 1–21 years with a confirmed diagnosis of neuroblastoma, MRT, or other tumors with documented evidence of cyclin D–CDK4/6–INK4–Rb pathway abnormalities (assessed by DNA sequencing or immunohistochemistry) that had progressed despite standard therapy were included in this study. MRT included diagnoses of atypical teratoid rhabdoid tumor [ATRT; referred to here as primary central nervous system (CNS) MRT] and rhabdoid tumor of the kidney and other soft tissues, for which the morphology and immunophenotypic panel were consistent with rhabdoid tumors. Loss of SMARCB1 was confirmed by immunohistochemistry or molecular confirmation of biallelic *SMARCB1* loss/mutation. Patients were required to have a Lansky play performance ($\leq$16 years) or Karnofsky (>16 years) score of at least 50% and measurable and/or evaluable disease. Archival tumor biopsies for molecular analysis were required from patients at diagnosis or relapse prior to study entry.

Patients who had received myeloablative therapy with autologous stem cell transplant within 3 months, or any prior allogenic stem cell transplant, were excluded. Other key exclusion criteria included uncontrolled cardiovascular conditions, prior history of QTc prolongation or QT corrected using Fridericia's formula (QTcF) > 450 ms on screening, left ventricular ejection fraction < 45%, impairment of gastrointestinal (GI) function or GI disease that may affect the absorption of ribociclib, and prior exposure to CDK4/6 inhibitors.

Safety and efficacy assessments

Dose-limiting toxicities (DLTs) were evaluated during the first treatment cycle as part of the dose-escalation procedure and were defined as adverse events (AEs) or clinically significant abnormal laboratory values assessed as unrelated to disease, disease

progression, intercurrent illness, or concomitant medications, occurring within the first 28 days of treatment with ribociclib. AEs were assessed continuously according to Common Terminology Criteria for AEs v4.03. Efficacy assessments were conducted at screening; day 22 of cycles 2, 4, and 6; day 22 of cycle 10, and every 4 cycles thereafter. Tumor response was assessed locally according to RECIST 1.1 for all patients. Where possible, patients with neuroblastoma were also assessed by modified International Neuroblastoma Response Criteria (INRC), with stable disease (SD) defined as neither sufficient tumor shrinkage to qualify for partial response nor sufficient growth to qualify for progressive disease (18), and those with primary CNS tumors were assessed by Revised Assessment in Neuro-Oncology (RANO) criteria (19).

PK assessments

Samples for PK evaluation were collected on cycle 1 day 1 (at pre-dose, and 1, 2, 4, and 8 hours post-dose), day 2 pre-dose (at 24 hours post-day 1 dose), day 8 (at pre-dose and 2 hours post-dose), day 15 (at pre-dose, and 1, 2, 4, and 8 hours post-dose), and day 22 (at 24 hours post-day 21 dose), cycle 2 day 1 (at pre-dose and 4 hours post-dose), and cycle 3 day 1 (at pre-dose). Steady-state values were calculated by combining data collected on days 15 and 22. Plasma samples were assayed using a validated liquid chromatography-tandem mass spectrometry assay with a lower limit of quantification of 1.0 ng/mL.

Biomarker assessments

Next-generation sequencing (NGS) of archival tumor samples was conducted to evaluate the relationship between antitumor activity and molecular aberrations in cancer-related genes. Tumor samples were sequenced on the Foundation Medicine T5 panel of about 300 genes known to be altered in solid tumors (20). Known and likely mutations were defined by their allelic fraction within the tumor or by mutations in genes known to be tumor suppressors or oncogenes.

Statistical analyses

Dose escalation was guided by an adaptive Bayesian logistic regression model using the Escalation With Overdose Control principle (21). The dose-determining set, which included all patients from the safety set who met the minimum exposure criterion ($\geq$16 of the 21 planned daily doses during the first cycle) and had scheduled safety evaluations or experienced a DLT, was used for DLT/MTD determination. Patients who did not experience a DLT during the first cycle were considered to have sufficient safety evaluations if observed for at least 28 days following the first dose with enough safety data to conclude that a DLT did not occur.

Initial enrollment at each dose level was in cohorts of 3 to 6 patients. The MTD was defined as the highest dose level not expected to result in DLTs in more than 33% of patients; the RP2D was subsequently selected, taking into account the overall safety profile and PK characteristics of ribociclib at each dose level. The Bayesian design allowed for enrollment of additional patients at lower dose levels that were considered safe, while higher dose levels were still being evaluated for DLTs, thereby maximizing recruitment opportunities in this rare patient population. Approximately 28 patients were required to be treated with ribociclib to ensure the model had reasonable operating characteristics to recommend an MTD.

Baseline patient characteristics, NGS, and efficacy analyses were performed on the full analysis set, comprising all patients who received at least one dose of ribociclib, whereas safety analyses were performed on the safety analysis set, consisting of all patients who received at least one dose of ribociclib and had at least one post-baseline safety assessment. PK analyses were conducted on the PK analysis set, which included all patients who had at least one blood sample providing evaluable drug concentration data. PK parameters were determined from individual concentration–time profiles in plasma by noncompartmental analysis using Phoenix software (Pharsight Corporation; Version 6.4). The parameters are summarized by dose group using descriptive statistics. SAS version 9.3 was used in all analyses, with the exception of Bayesian modeling, for which programs were compiled using R (version 2.15.1) and WinBUGS (version 1.4.3).

The cutoff date for safety and efficacy analyses was December 25, 2014, and for PK and NGS data was April 9, 2015. A further update on patient disease status was provided at the time of writing this article (February 8, 2016).

Ethics

The study was designed and conducted in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki. The study protocol and informed consent form were approved by an institutional review board or ethics committee at each site, and all patients (or their guardians) provided written informed consent prior to study entry.

Results

Patient characteristics

Between May 2013 and June 2014, 32 patients were enrolled. Median age was 5.5 years (range, 1.0–20.0 years) and 22 (69%) patients were aged $\leq$12 years (Table 1). Fifteen patients (47%) had neuroblastoma, 15 had MRT (of which 13 had primary CNS MRT), one (3%) had rhabdomyosarcoma with *CDK4* amplification, and one had anaplastic meningioma with rhabdoid differentiation and homozygous loss of *CDKN2A/B*. All patients underwent prior surgery and received prior antineoplastic therapy; the median number of prior treatment regimens was 3. Most patients (88%) also had prior radiotherapy.

Study treatment

Five patients received ribociclib 280 mg/m^2, 15 received 350 mg/m^2, and 12 received 470 mg/m^2. The median exposure to treatment was 2 (range, 0–13) cycles and 7 patients received ribociclib for $\geq$4 cycles. At data cutoff (December 25, 2014), 27 patients had discontinued treatment and 5 patients were still on treatment. The primary reasons for treatment discontinuation were disease progression (n = 23, 72%), AEs (n = 2, 6%), withdrawal of consent (n = 1, 3%), and death due to disease progression (n = 1, 3%).

DLTs

Thirty patients were evaluable for the dose-determining set. Two patients were excluded as they had not received 75% ($\geq$16 days) of the planned daily doses of ribociclib during cycle 1 and did not experience DLTs. Of the 30 evaluable patients, 3 patients

Table 1. Patient and disease characteristics

Characteristic	Ribociclib 280 mg/m^2 $n = 5$	Ribociclib 350 mg/m^2 $n = 15$	Ribociclib 470 mg/m^2 $n = 12$	All patients $N = 32$
Median age, y (range)	2.0 (1.0–17.0)	6.0 (2.0–20.0)	7.0 (1.0–20.0)	5.5 (1.0–20.0)
1–<2, *n* (%)	2 (40)	0	1 (8)	3 (9)
2–<6, *n* (%)	2 (40)	7 (47)	4 (33)	13 (41)
6–<12, *n* (%)	0	3 (20)	3 (25)	6 (19)
12–<18, *n* (%)	1 (20)	4 (27)	2 (17)	7 (22)
≥18, *n* (%)	0	1 (7)	2 (17)	3 (9)
Male, *n* (%)	4 (80)	9 (60)	8 (67)	21 (66)
Median BSA at screening, m^2 (range)	0.6 (0.4–1.7)	0.8 (0.5–1.8)	0.9 (0.6–1.7)	0.8 (0.4–1.8)
Diagnosis, *n* (%)				
Neuroblastoma	1 (20)	7 (47)	7 (58)	15 (47)
Primary CNS MRT	3 (60)	7 (47)	3 (25)	13 (41)
Extra-CNS MRT	1 (20)	0	1 (8)	2 (6)
Rhabdomyosarcoma[a]	0	1 (7)	0	1 (3)
Anaplastic meningioma with rhabdoid differentiation[b]	0	0	1 (8)	1 (3)
Performance status [Lansky scale (≤ 16 y) or Karnofsky score (> 16 y)], *n* (%)				
100	1 (20)	9 (60)	7 (58)	17 (53)
90	4 (80)	2 (13)	3 (25)	9 (28)
80	0	2 (13)	1 (8)	3 (9)
70	0	1 (7)	0	1 (3)
50	0	1 (7)	0	1 (3)
40[c]	0	0	1 (8)	1 (3)
Prior surgery, *n* (%)	5 (100)	15 (100)	12 (100)	32 (100)
Prior radiotherapy, *n* (%)	4 (80)	15 (100)	9 (75)	28 (88)
Number of prior antineoplastic regimens, *n* (%)				
0 or 1	2 (40)	3 (20)	4 (33)	9 (28)
2 or 3	2 (40)	4 (27)	3 (25)	9 (28)
≥4	1 (20)	8 (53)	5 (42)	14 (44)

NOTE: Data cutoff: December 25, 2014.
Abbreviation: BSA, body surface area.
[a]Rhabdomyosarcoma with *CDK4* amplification.
[b]Anaplastic meningioma with rhabdoid differentiation, with *CDKN2A/B* loss.
[c]Protocol waiver approved.

reported DLTs during cycle 1: 1 case of grade 3 fatigue at 280 mg/m^2 and 2 of grade 4 thrombocytopenia at 470 mg/m^2. In addition, 33% of patients at the 470 mg/m^2 dose level experienced hematologic toxicities that despite not meeting the criteria for DLT, led to dose delays and modifications in subsequent cycles; no hematologic DLTs were reported at the 350 mg/m^2 dose. The safety and tolerability data did not support further dose escalation of ribociclib and the MTD was determined as 470 mg/m^2/d on a 3-weeks-on/1-week-off dosing schedule. The 350 mg/m^2/d dose, which is equivalent to the adult RP2D (600 mg; refs. 17, 22), was selected as the RP2D based on the overall safety profile and PK characteristics (discussed below).

Safety and tolerability

All patients were evaluable for safety analysis. AEs of any grade suspected to be study drug-related occurred in 31 (97%) patients and grade 3/4 AEs occurred in 25 (78%) patients (Table 2).

The most common all-grade (≥35%) AEs suspected to be study drug-related were hematologic including neutropenia (72% of patients; 63% grade 3/4), leukopenia (63%; 38%), anemia (44%; 3%), thrombocytopenia (44%; 28%), and lymphopenia (38%; 19%). The most common all-grade (≥20%) nonhematologic AEs suspected to be study drug-related were vomiting (38%; 0% grade 3/4), fatigue (25%; 3%), nausea (25%; 0%), and QTc prolongation (22%; 0% grade 2–4). Newly occurring post-baseline values of QTcF ≥ 450 ms were observed in 3 patients (9%): 2 (13%) in the 350 mg/m^2 group at cycle 1 day 15 and 1 (8%) in the 470 mg/m^2 group at cycle 1 day 8. An increase in baseline of >30 ms was reported in 12 patients (38%): 6 (40%) in the 350 mg/m^2 group and 6 (50%) in the 470 mg/m^2 group.

Clinical activity

All 32 patients were evaluable for efficacy (Fig. 1). At data cutoff, the best overall response per RECIST 1.1 or INRC was SD in 9 of the 32 (28%) patients (7 with neuroblastoma and 2 with primary CNS MRT). Five of these patients achieved prolonged SD for more than 6, 6, 8, 12, and 13 cycles, respectively. Analysis of disease history, metaiodobenzylguanidine (MIBG) status, and prior treatment experience revealed no obvious differences between the clinical characteristics of patients with neuroblastoma who achieved SD and those who did not.

On a subsequent follow-up for clinical response in February 2016, 5 patients had SD for >6 months. Two patients with heavily pretreated neuroblastoma upon study entry progressed after achieving SD for 15 and 8 months, respectively; the patient who previously achieved prolonged SD for 13 cycles (who had MIBG-positive neuroblastoma and bone marrow metastases) remained on treatment with a best overall response of SD after 26 months; the 2 patients with primary CNS MRT remained on treatment with SD after 24 and 20 months, respectively.

PK analysis

Following oral dosing, ribociclib was rapidly absorbed with the median time to reach peak plasma concentrations (T_{max}) between 2 and 4 hours across dose levels, and exposure demonstrated dose dependency with high interpatient variability (Table 3). On the

Table 2. AEs (all grade ≥ 10%) suspected to be study drug-related

	Ribociclib 280 mg/m² *n* = 5		Ribociclib 350 mg/m² *n* = 15		Ribociclib 470 mg/m² *n* = 12		All patients *N* = 32	
AEs, *n* (%)	**All grade**	**Grade 3/4**	**All grade**	**Grade 3/4**	**All grade**	**Grade 3/4**	**All grade**	**Grade 3/4**
All AEs	4 (80)	2 (40)	15 (100)	13 (87)	12 (100)	10 (83)	31 (97)	25 (78)
Hematologic AEs								
Neutropenia	2 (40)	1 (20)	13 (87)	11 (73)	8 (67)	8 (67)	23 (72)	20 (63)
Leukopenia	1 (20)	0	11 (73)	7 (47)	8 (67)	5 (42)	20 (63)	12 (38)
Anemia	1 (20)	0	7 (47)	1 (7)	6 (50)	0	14 (44)	1 (3)
Thrombocytopenia	0	0	8 (53)	4 (27)	6 (50)	5 (42)	14 (44)	9 (28)
Lymphopenia	0	0	6 (40)	2 (13)	6 (50)	4 (33)	12 (38)	6 (19)
Nonhematologic AEs								
Vomiting	1 (20)	0	6 (40)	0	5 (42)	0	12 (38)	0
Fatigue	1 (20)	1 (20)	3 (20)	0	4 (33)	0	8 (25)	1 (3)
Nausea	1 (20)	0	4 (27)	0	3 (25)	0	8 (25)	0
QTc prolongation	0	0	4 (27)	0	3 (25)	0	7 (22)	0
Decreased appetite	1 (20)	1 (20)	3 (20)	0	2 (17)	0	6 (19)	1 (3)
AST increased	0	0	2 (13)	1 (7)	3 (25)	0	5 (16)	1 (3)
Asthenia	0	0	3 (20)	0	1 (8)	0	4 (13)	0
Increased creatinine	0	0	3 (20)	0	1 (8)	0	4 (13)	0
Hypophosphatemia	1 (20)	0	3 (20)	0	0	0	4 (13)	0

NOTE: Data cutoff: December 25, 2014.
Abbreviation: AST, aspartate aminotransferase.

basis of trough concentrations, steady state appeared to have been reached by approximately day 8 of repeat dosing. At the RP2D, the geometric mean (CV%) area under the curve from time 0 to 24 hours (AUC_{0-24}) was 25,200 h*ng/mL (46.1%), and the maximum plasma concentration (C_{max}) was 1,790 ng/mL (55.2%) at steady state. The overall accumulation of ribociclib from day 1 to steady state at day 15 was 2- to 3-fold and did not differ between dose levels. The median effective half-life at steady state ranged from 30 to 41 hours across dose levels.

Genetic alterations

Twenty-five patients had samples available for mutation analysis, of which 19 samples had mutations identified by T5 panel analysis (Fig. 2). All patients with MRT for which samples were

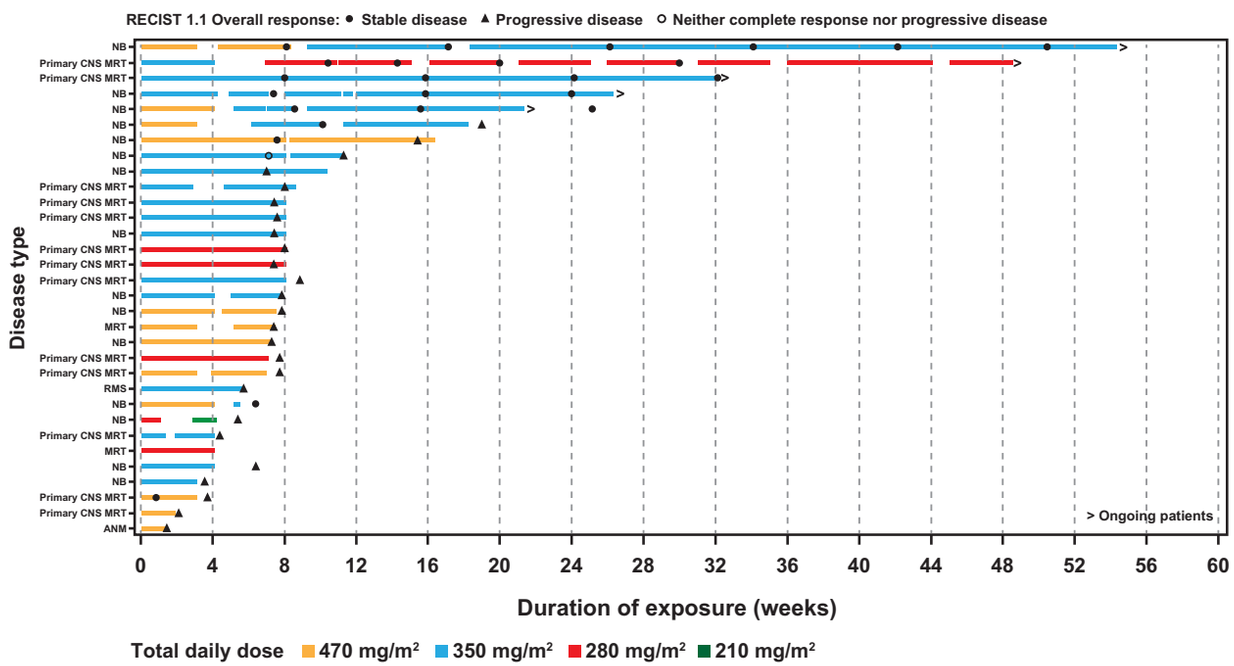

Figure 1.
Duration of exposure to ribociclib. Graph illustrates treatment responses, per RECIST 1.1, and duration of exposure following ribociclib administration in pediatric patients ($N = 32$) with primary CNS MRT, NB, ANM, MRT, and RMS. The different colors correspond to the different doses of ribociclib administered. Symbols refer to treatment responses (SD, progressive disease, neither complete nor progressive disease). Primary tumor type is indicated for each patient. At data cutoff, 4 patients had SD for more than 24 weeks; 5 patients were ongoing (>). ANM, anaplastic meningioma; NB, neuroblastoma; RMS, rhabdomyosarcoma. Data cutoff: December 25, 2014.

Table 3. PK parameters

Dose	Day	Statistics	AUC_{0-24}, h*ng/mL	C_{max}, ng/mL	T_{max}, h	CLss/*F*, L/h
Ribociclib 280 mg/m^2, *n* = 5	C1D1	*n*	5	5	5	–
		Mean (SD)	10,700 (7,000)	1,040 (542)	–	–
		Geometric mean (CV%)	9,120 (70)	944 (53)	–	–
		Median (range)	9,250 (4,580–22,000)	937 (542–1,910)	2.0 (1.1–4.1)	–
	C1D15	*n*	3	4	4	2
		Mean (SD)	27,600 (28,200)	2,070 (2,100)	–	11 (12.9)
		Geometric mean (CV%)	19,500 (131)	1,530 (99)	–	6.1 (408)
		Median (range)	13,800 (8,910–60,100)	1,110 (860–5,210)	2.1 (1.1–3.8)	11 (1.8–20.1)
Ribociclib 350 mg/m^2, *n* = 15	C1D1	*n*	12	12	12	–
		Mean (SD)	14,500 (11,900)	1,480 (1,140)	–	–
		Geometric mean (CV%)	11,500 (74)	1,210 (68)	–	–
		Median (range)	10,000 (5,320–43,600)	1,130 (514–4,140)	2.0 (1.0–4.1)	–
	C1D15	*n*	7	12	12	5
		Mean (SD)	27,700 (15,000)	2,010 (958)	–	10.1 (3.3)
		Geometric mean (CV%)	25,200 (46)	1,790 (55)	–	9.7 (31)
		Median (range)	24,500 (15,100–60,100)	2,010 (633–4,270)	2.1 (1.1–23.8)	9.4 (6.8–15.6)
Ribociclib 470 mg/m^2, *n* = 12	C1D1	*n*	7	7	7	–
		Mean (SD)	18,700 (6,730)	2,060 (1,140)	–	–
		Geometric mean (CV%)	17,500 (43)	1,830 (57)	–	–
		Median (range)	17,600 (8,010–28,500)	1,960 (796–4,360)	4.0 (2.0–4.1)	–
	C1D15	*n*	5	10	10	3
		Mean (SD)	30,300 (14,700)	2,540 (1,590)	–	9.5 (3.1)
		Geometric mean (CV%)	27,300 (57)	2,010 (92)	–	9.2 (34)
		Median (range)	29,100 (13,300–50,500)	2,500 (562–5,050)	3.9 (2.0–23.6)	9.4 (6.5–12.6)

NOTE: Data cutoff: April 9, 2015.

Abbreviations: AUC_{0-24}, area under the curve from time zero to 24 hours post-dose; C1D1, cycle 1 day 1; C1D15, cycle 1 day 15; CLss/*F*, apparent total body clearance of drug from the plasma at steady state; C_{max}, maximum plasma concentration; CV, coefficient of variation; T_{max}, time to reach maximum plasma concentration.

available ($n = 11$) were confirmed to have *SMARCB1* alterations including one of the patients with SD; no alterations related to the cyclin D–CDK4/6–INK4–Rb pathway were identified in the patients with MRT. *CDK4* amplification was identified in 3 patients with neuroblastoma; 2 of these patients had disease progression and 1 had SD and had ongoing treatment (>6 cycles) at data cutoff. Only one patient with neuroblastoma and progressive disease exhibited an amplification in *MYCN*, a gene

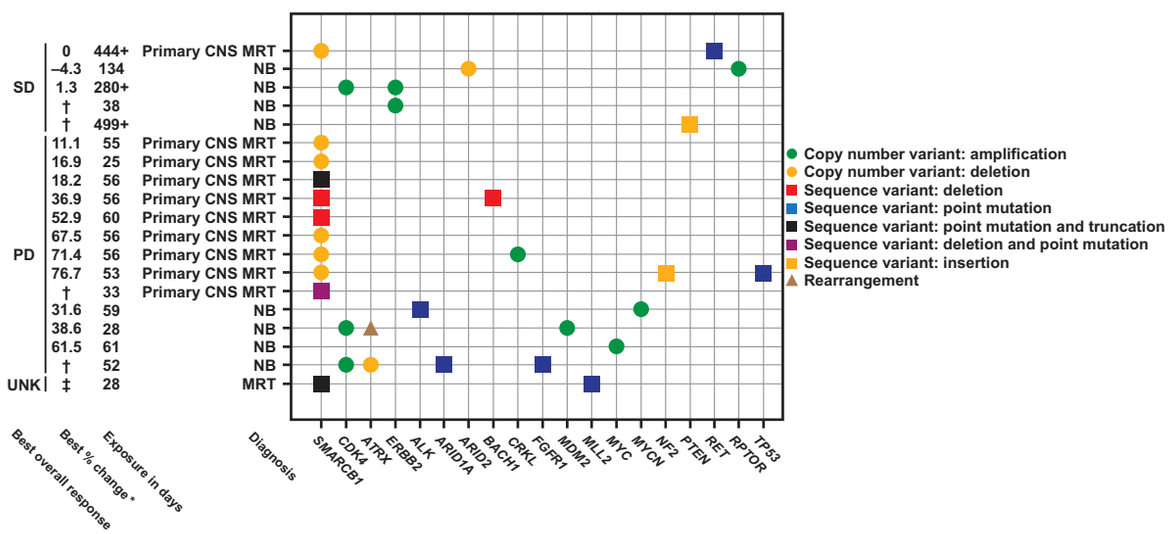

Figure 2.

Genetic alterations in tumor samples. Results of NGS analyses on 19 archival tumor samples to evaluate the relationship between antitumor activity and molecular aberrations. Tumor samples were sequenced on the Foundation Medicine T5 panel of about 300 genes known to be altered in solid tumors. Gain- or loss-of-function mutations in oncogenes and tumor suppressors and other alteration types are indicated for each patient (according to the legend). Treatment response (SD, PD, UNK), best percentage change in the sum of longest diameters (RECIST 1.1), duration of treatment exposure (days), primary tumor type, and genetic alteration are also displayed. NB, neuroblastoma; PD, progressive disease; UNK, unknown. Data cutoff: April 9, 2015. *, Best percentage change in sum of longest diameters as per RECIST 1.1; †, Best percentage change was not calculable, as patients had either non-target lesions at baseline or had different evaluation methods between baseline and post-baseline assessments; ‡, Patient did not have post-baseline efficacy evaluation.

previously linked to ribociclib sensitivity in neuroblastoma-derived cell lines (16). There were no discernible differences between the genetic profile of patients who had SD and those who had disease progression in patients who had neuroblastoma or MRT. Retrospective genetic and immunohistochemical analyses indicated that the *RB* gene was intact and expression of the protein was unaltered in all enrolled patients.

Discussion

This was the first study to evaluate the safety and show preliminary activity of the highly selective CDK4/6 inhibitor ribociclib in pediatric patients with neuroblastoma, MRT, or other cancers with documented cyclin D–CDK4/6–INK4–Rb pathway aberrations. Initiation of this first-in-class pediatric study occurred early in development due to the biological rationale (supported by preclinical data), and the urgent need for effective targeted therapies in these poor prognosis tumor types, where disease stabilization can be considered a meaningful outcome.

The first-in-human phase I study, in which adult patients with advanced solid tumors or lymphomas were treated with single-agent ribociclib, demonstrated preliminary antitumor activity. Among 132 evaluable patients, 3 had partial responses (one with head and neck acinar carcinoma and *CDK2NA* loss, one with *PIK3CA*-mutant, *CCND1*-amplified, estrogen receptor–positive breast cancer, and one with *BRAF*/*NRAS* wild-type, *CCND1*-amplified melanoma); 43 (32.6%) patients had SD (17). The most common study drug-related grade 3/4 adverse events in $\geq$10% of adult patients at the RP2D of 600 mg/d (3-weeks-on/1-week-off schedule) were neutropenia (28%), leukopenia (19%), and lymphopenia (18%; ref. 17).

In the current study, an intermittent 3-weeks-on/1-week-off schedule for ribociclib was investigated in pediatric patients. Although greater efficacy might be obtained with continuous daily dosing to prevent any potential tumor regrowth during the resting period, continuous dosing of 400 and 600 mg dose levels in adult patients was deemed infeasible due to the high level of hematologic toxicities requiring dose interruptions (17). Therefore, an intermittent schedule was selected in the current study, at doses of $\geq$280 mg/m^2 (considered to be therapeutic; equivalent to adult doses of $\geq$400 mg).

Single-agent ribociclib was well-tolerated in pediatric patients, with a similar safety profile to that observed in adult patients (17). The majority of AEs were hematologic, and there was no worsening of toxicities following cycle 1, which was also consistent with the experience in adult patients (17). Grade 3/4 hematologic AEs were more frequent at the pediatric 350 mg/m^2 dose level in this heavily pretreated patient population than the equivalent 600 mg/d intermittent dose in adult patients; neutropenia (73% vs. 28%), leukopenia (47% vs. 19%), thrombocytopenia (27% vs. 9%), and lymphopenia (13% vs. 18%; ref. 17). Hematologic AEs have also been associated with the CDK4/6 inhibitor palbociclib, suggesting an on-target effect for this class of drugs (23). At the 470 mg/m^2 dose of ribociclib, hematologic toxicities were predominant and thrombocytopenia was the DLT in pediatric patients. In addition, nausea, fatigue, and vomiting were frequently observed at this dose, preventing further escalation—the MTD was therefore established as 470 mg/m^2/d on a 3-weeks-on/1-week-off schedule.

Ribociclib exposure was dose-dependent, although PK parameters in pediatric patients exhibited high interpatient variability, as also reported in adult patients. A robust analysis of PK parameters and age or body surface area was not possible due to the limited number of patients treated; however, ribociclib exposures at 350 and 470 mg/m^2 were found to be equivalent to those observed at 600 to 900 mg fixed doses in adults in the first-in-human study (17). On the basis of all available safety and PK data, ribociclib 350 mg/m^2/d on a 3-weeks-on/1-week-off dosing schedule was selected as the RP2D in pediatric patients.

During this study, the best overall response was SD per RECIST 1.1 or INRC, achieved by 7 patients with neuroblastoma and 2 patients with primary CNS MRT. All the patients with SD received ribociclib for more than 4 cycles. There were no objective responses at data cutoff; therefore, the expansion portion of the study did not commence. Nevertheless, on a subsequent follow-up for clinical response, 1 patient with neuroblastoma and 2 patients with primary CNS MRT remained with SD on treatment for $\geq$20 months. A review of these patients' demographic profiles, prior medical history, and tumor genetics did not reveal any unique features that were predictive of clinical response. However, the observations are noteworthy and warrant further evaluation of ribociclib in these tumors in the clinic, particularly in light of recent preclinical evidence suggesting that ribociclib penetrates into the mouse CNS (24).

NGS data were limited and few mutations were identified other than those that were expected, such as *SMARCB1* mutations in patients with MRT, precluding definitive conclusions about the functions of genomic alterations (mutations, deletions, amplifications) in relation to CDK4/6 biology. None of these pediatric tumors exhibited *CCND1* gene amplification, an alteration found in 2 of 3 cancers in adult patients who experienced an objective tumor response to ribociclib. In addition, only one patient with progressive disease exhibited *MYCN* amplification, an alteration associated with ribociclib sensitivity in preclinical studies of neuroblastoma (16). It must be noted that the NGS analysis was performed on a limited number of patient samples, and the association between *CCND1* or *MYCN* amplification and treatment response could therefore not be evaluated. Further analyses in a larger patient population are required to determine the impact of genetic alterations, including *CCND1* and *MYCN* amplifications, on ribociclib sensitivity. The identification of reliable biomarkers for response to CDK4/6 inhibitors has met with significant challenges, particularly with the use of NGS. Alternative pharmacodynamic analyses using biomarkers of on-target effects, such as the impact of treatment on Rb phosphorylation, may provide further insights into the activity of ribociclib in certain patient populations.

Neuroblastoma has a complex genetic profile that can include *MYCN* amplification, somatic activating mutations in the *ALK* oncogene, and other aberrations that activate CDK4/6 activity (6, 25). It has also recently been shown that high-risk neuroblastoma may be defined by activation of telomere maintenance mechanisms caused by *MYCN* amplification, *TERT* rearrangements, or *ATRX* mutations (26), and relapsed neuroblastomas are frequently associated with RAS/mitogen-activated protein kinase (MAPK) pathway mutations that could also influence ribociclib sensitivity (27). In MRT, disruption of the *SMARCB1* transcriptional regulator can alter the expression of multiple genes upstream and downstream of CDK4/6 (28, 29). In addition, the LIN28/RAS/MAPK pathway has also recently been identified as a potential driver of MRT tumorigenesis (29). Collectively, these findings suggest that cell-cycle alterations in pediatric tumors such as

neuroblastoma and MRT may not be the sole events driving tumorigenesis. Therefore, these pediatric tumors may require targeted, combinatorial therapeutic approaches. However, a key question remains: whether these alternative approaches should select patients with cyclin D–CDK4/6–INK4–Rb pathway alterations or include patients regardless of their pathway status.

Clinical studies of ribociclib in combination with other therapies are currently ongoing in various cancer types. Combination strategies may overcome prior treatment resistance or enhance treatment efficacy where dysregulation of more than one biological pathway is responsible for driving the disease; however, the mechanism of action and cumulative toxicities of additional agents must be carefully considered when designing treatment regimens.

The results from this study demonstrate that ribociclib has an acceptable safety profile and dose-dependent PK in pediatric patients. Several heavily pretreated patients had prolonged SD. Further studies of ribociclib in combination with other active agents in patients with MRT and neuroblastoma are ongoing, such as the AcSé-ESMART multi-arm trial (NCT02813135), which includes ribociclib in combination with everolimus (a PI3K/AKT/mTOR pathway inhibitor) or chemotherapy in patients prescreened for specific molecular alterations. The combination with everolimus was based on the observation that the PI3K/AKT/mTOR pathway, for example, via MYCN, ALK, or RAS activation, may be implicated in the pathogenesis of neuroblastoma and MRT (30, 31). Other ribociclib-based combinations with other targeted therapies, such as MAPK/ERK inhibitors, may be considered in future trials.

Disclosure of Potential Conflicts of Interest

S.G. DuBois is a consultant/advisory board member for Loxo. M. Fischer is a consultant/advisory board member for Novartis. A. Marabelle reports receiving speakers bureau honoraria from Bristol-Myers Squibb, GlaxoSmithKline, Merck MSD, Merck Serono, and Roche/Genentech and is a consultant/advisory board member for Genmab, Genticel, Lytix Pharma, Merck Serono, Novartis, Pierre Fabre, and Roche/Genentech. A. Matano reports receiving commercial research grants from Novartis. No potential conflicts of interest were disclosed by the other authors.

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