Phase I Study of RGB-286638, A Novel, Multitargeted Cyclin-Dependent Kinase Inhibitor in Patients with Solid Tumors

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Abstract

**Purpose:** RGB-286638 is a multitargeted inhibitor with targets comprising the family of cyclin-dependent kinases (CDK) and a range of other cancer-relevant tyrosine and serine/threonine kinases. The objectives of this first in human trial of RGB-286638, given i.v. on days 1 to 5 every 28 days, were to determine the maximum tolerated dose (MTD) and to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of this new drug.

**Experimental Design:** Sequential cohorts of 3 to 6 patients were treated per dose level. Blood, urine samples, and skin biopsies for full PK and/or PD analyses were collected.

**Results:** Twenty-six patients were enrolled in 6-dose levels from 10 to 160 mg/d. Four dose-limiting toxicities were observed in 2 of the 6 patients enrolled at the highest dose level. These toxicities were AST/ALT elevations in 1 patient, paroxysmal supraventricular tachycardias (SVTs), hypotension, and an increase in troponin T in another patient. The plasma PK of RGB-286638 was shown to be linear over the studied doses. The interpatient variability in clearance was moderate (variation coefficient 7%–36%). The PD analyses in peripheral blood mononuclear cells, serum (apoptosis induction) and skin biopsies (Rb, p-Rb, Ki-67, and p27KIP1 expression) did not demonstrate a consistent modulation of mechanism-related biomarkers with the exception of lowered Ki-67 levels at the MTD level. The recommended MTD for phase II studies is 120 mg/d.

**Conclusions:** RGB-286638 is tolerated when administered at 120 mg/d for 5 days every 28 days. Prolonged disease stabilization (range, 2–14 months) was seen across different dose levels. Clin Cancer Res; 20(18); 4776–83. ©2014 AACR.
Phase I Study of RGB-286638

Translational Relevance

RGB-286638 is a multitargeted protein kinase inhibitor directed at a selected spectrum of target protein kinases, including the cyclin-dependent kinase (CDK) family, several serine/threonine kinases, and non-receptor as well as receptor tyrosine kinases. In preclinical studies, antitumor activity was seen against a broad range of human tumor cell lines both in vitro as well as in vivo. In mouse xenograft models for solid and hematologic tumors, inhibition of tumor growth was observed, including complete responses. This first in human study was set up to determine the maximum tolerable dose of RGB-286638 for further development and to evaluate pharmacokinetic and pharmacodynamic profiles in patients with solid tumors. A prolonged disease stabilization was accomplished in several patients and the data suggest that there is a rationale to study RGB-286638 efficacy in tumors that depend on specific CDKs.

Patients and Methods

Eligibility criteria

Patients with a cytologic or histologic confirmed diagnosis of an advanced and evaluable solid tumor according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1), were eligible. Additional criteria at baseline included: age ≥ 18 years; ECOG (Eastern Cooperative Oncology group) performance status 0 or 1; an adequate bone marrow function (hemoglobin ≥ 6.2 mmol/L, platelet count ≥ 75 × 10⁹/L, absolute neutrophil count ≥ 1.5 × 10⁹/L), liver function (bilirubin ≤ 1.5 the upper limit of normal (ULN), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 2.5 × ULN [and 5 × ULN in case of liver metastasis]), and renal function (calculated creatinine clearance ≥ 50 ml/min), left ventricular ejection fraction (LVEF) ≥ 50%, QTc interval ≤ 450 ms, systolic blood pressure ≥ 100 mm Hg and ≤ 150 mm Hg and diastolic blood pressure ≤ 100 mm Hg.

Specific exclusion criteria included (but were not limited to) prior treatment with a CDK inhibitor; prior irradiation to >30% of the bone marrow reserve; concurrent therapies known to prolong QT interval or potent cytochrome P450 (CYP) 3A4 inducers or inhibitors. This study was performed according to the principles defined by the Declaration of Helsinki, in Rotterdam, the Netherlands, and approved by the Institutional Ethics Committee MEC 08–295. All patients gave written informed consent before study entry.

Treatment and dose escalation

RGB-286638 was supplied by GPC Biotech AG as an aqueous solution for infusion in glass vials, containing 20 mg/mL of active drug. The vials were stored at room temperature (15°C–25°C) and were protected from light. RGB-286638 concentrate for solution for infusion were found stable for up to 72 hours when exposed to light. Solutions of 0.1 and 10 mg/mL of RGB-286638 were preserved for 30 hours at ambient temperature. The content of the vials was added to a polyvinylchioride bag with 5% aqueous dextrose to a total volume of 100 mL before infusion. The solution was kept at room temperature protected from light until administration. RGB-286638 was administered i.v. more than 60 minutes on days 1 to 5 of a 4-weekly cycle. With the exception of the first course, during which patients were hospitalized for PK and PD sampling, patients were treated on an outpatient basis.

Patients received RGB-286638 until disease progression and during the absence of unacceptable toxicity. Initially, 3 patients were treated in each cohort with RGB-286638 with 10 mg/d for 5 days. Dose escalations were based on toxicities during the prior dose level allowing a dose escalation of 20% to 100% (which was determined by the worst significant toxicity). The dose was escalated by 100% increments at each subsequent level until grade 2.

Drug-related toxicity occurred. Thereafter, the dose of RGB-286638 would be increased by increments of 20% to 67%. The stopping dose was defined as the dose level that induced DLT during course 1 in 1 or more of 3, or 2 or more of 6 patients. Three more patients were to be treated at the
dose level below the MTD, if only 3 patients were previously treated at that prior dose. DLTs were defined as grade 4 granulocytopenia for more than 7 days, ≥ grade 3 neutropenia complicated by fever ≥38.5°C, platelets <25.0 × 10^9/L or <50.0 × 10^9/L complicated with bleeding, and/or non-hematologic toxicities ≥ grade 3, including prolonged QTc interval >500 ms or an increase >60 ms from baseline, and ocular toxicity. Ocular toxicities were defined as any significant worsening in fundus auto fluorescence (FAF) patterns and worsening of grade ≥ 1 retinopathy by ophthalmologic examination versus baseline. Nausea, vomiting, and diarrhea, subsequently responding to supportive therapy, were not considered as a DLT. Inability to administer ≥4 of 5 scheduled treatment days or to start a second course after a 2-week delay, due to ongoing toxicity was also considered as a DLT.

At re-treatment the patient had to fulfill the baseline criteria. Dose modifications to the next lower dose level were permitted once a patient had experienced a DLT. No intra-patient dose escalation was allowed. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTCAE) Version 3.0.

Pretreatment and follow-up studies

Before therapy, a complete medical history was taken and a physical examination was done, including ECOG performance status, body weight, height, and vital signs. A complete blood cell count, including WBC differential, coagulation parameters and serum biochemistry, which included total and direct bilirubin, serum transaminases, alkaline phosphatase, lactic dehydrogenase, amylase, lipase, creatinine, albumin, sodium, potassium, calcium, creatinine and glucose, were done as well as urinalysis, 12-lead electrocardiograms (ECC) and a pregnancy test (if applicable). The 12-lead ECG was repeated on days 1 to 5 of the first-cycle predose and within 4 hours of end of infusion. In subsequent cycles, an ECG was performed on day 1 pre-infusion and if clinically indicated. The left ventricular ejection fraction was evaluated by a MUGA scan before study start and repeated within 24 hours after day 5 administration during the first cycle and at off-treatment. In addition, an ophthalmologic assessment, including visual acuity, intraocular pressure, ophthalmoscopy, and FAF imaging, was performed and repeated after the first cycle and at off-treatment. During the first cycle, heart rate and blood pressure were intensively monitored (predosing, every 20 minutes during infusion, at the end of infusion, after 30 minutes and every hour up to 6, 8, and 12 hours after the end of the infusion) with an adjusted schedule from the second cycle onwards. Hematology and biochemistry assessments were performed weekly (or more frequently if clinically indicated) of every cycle and in addition on day 5 of the first cycle. Furthermore, weekly evaluations of each cycle included physical examination and toxicity assessments.

Prophylactic premedication with antiemetics was only to be introduced in case more than 2 patients experienced ≥ grade 2 nausea or vomiting. Tumor imaging was performed within 28 days before study treatment and after every second cycle. Tumor evaluation was performed after every two courses, according to RECIST, version 1.1.

PK and PD sampling

For RGB-286638 PK analyses, blood samples (4 ml) were collected using an indwelling i.v. canula in the opposite arm of infusion before dosing, during the infusion (after 30 minutes and 5 minutes before the end of the infusion), 5 and 15 minutes after the end of the infusion and 0.5, 1, 2, 4, 6, 8, 10, and 24 hours after end of RGB-286638 infusion on days 1 and 5 of cycle 1. In addition, blood samples were taken on days 8 and 10. Blood samples for PK analyses were collected in potassium EDTA tubes and were kept at 4°C until centrifugation within 10 minutes of collection at 2,800 × g for 10 minutes. The plasma samples were stored at T < −70°C until analysis using a validated LC/MS-MS method (9). In addition, two urine samples were collected over a 24-hour period; 0 to 8 hours and 8 to 24 hours. After estimation of the total urine volumes, exactly 10 ml samples were frozen and stored at T < −78°C until analysis.

For PD analyses paired skin biopsies were collected as previously described (10). Skin biopsies were taken before study start (pretreatment sample) and during therapy (on-therapy sample) within 24 hours after the end of infusion on day 5 of the first cycle. RGB-286638 activity was assessed in skin biopsies from all dose cohorts by immunohistochemical analyses of the levels of retinoblastoma protein (Rb), phosphorylated Rb (p-Rb), the proliferation marker Ki-67, and the differentiation marker p27kip1. In addition, the expression levels of the proliferation marker (Ki-67) and differentiation marker (p27kip1) were determined in the skin biopsies for all dose cohorts. Antibodies used for IHC were: monoclonal mouse anti-human Ki-67 antigen (clone MIB-1; Dako, code M7240); monoclonal mouse anti-human p27 protein (clone 1B4; Novoceastra, NCL-p27); Rb antibody (Anaspec; code 53823); phospho-Rb (Ser780) (p-Rb) antibody (Cell Signaling Technology; #9307). Appropriate isotype-matched negative control monoclonal antibodies (negative control mouse IgG1, kappa [clone DAK-G01, Dako, code X0931] and negative control mouse IgG2a, kappa [clone DAK-G05, Dako, code X0953]) were used to validate the specificity of the Ki-67 and p27kip1 staining. Furthermore, p-Rb (Ser780) blocking peptide (Cell Signaling Technology; #21200B) was included to validate the specificity of the p-Rb staining. All antibodies were appropriately diluted in antibody diluent (Dako; code S0809). Furthermore, all antibodies required antigen retrieval in a water bath.

The apoptotic status of blood leukocyte subsets was assessed using Annexin V/7-AAD staining using flow cytometry in blood samples collected on days 1 and 5 before dosing, 2 and 24 hours after the end of the infusion. Leukocyte subsets were defined by surface marker antibody conjugates, i.e., lymphocytes by CD45/APC and CD3/PE; monocytes by CD45/APC and CD64/PE and granulocytes by CD45/APC and side scatter pattern. All antibodies and Annexin V/FITC were from BD Biosciences, 7-AAD from...
Sigma-Aldrich, and data were acquired on a Canto flow cytometer (BD Biosciences). The amount of caspase-cleaved M30 fragments of cytokeratin-18 was quantitated by ELISA (M30-Apoptosense ELISA, Peviva AB) in serum as a marker for tumor apoptosis as well on days 1 and 5 before the dosing, 2 and 24 hours after the end of the infusion and once every week for 3 weeks.

Patient evaluation and PK and PD analyses

All patients who received at least one dose of RGB-286638 were evaluable for all analyses. Descriptive statistics were used to analyze safety. PK analysis for RGB-286638 in plasma was performed using the WinNonlin software (version 4.1; Pharsight Corp.) and included the determination of maximum plasma concentration (C\text{max}), area under the plasma curve from time zero to infinity (AUC\text{0-inf}), area under the curve from time zero to 24 hours (AUC\text{0–24}), and elimination half-life (T1/2). Total body clearance (CL) was calculated as the ratio between the administered dose and the AUC\text{0-inf} or administered dose and the AUC\text{0–24}. PK analysis for RGB-286638 in urine included the determination of the amount of excreted parent drug over a 24-hour period.

Previous treatment

The staining of Ki-67 and p27\textsuperscript{KIP1} was scored by counting at least 1,000 epidermal keratinocytes; the number of positive epidermal keratinocytes were scored and expressed as the percentage. To investigate RGB-286638–induced changes on the expression of Rb and p-Rb, the total number of positive epidermal keratinocytes and the intensity of the staining were estimated according to the frequently used Allred scoring system (11). The percentage of apoptotic cells staining were estimated according to the frequently used epidermal keratinocytes and the intensity of the staining.

Statistical analysis

All PK data are presented as mean values and coefficient variations (%). A paired Student t test was used to examine statistically significant changes in biomarker levels.

Results

Patients

Between December 2008 and January 2011, a total of 26 patients (16 female and 10 male) were enrolled into 6-dose cohorts. Patient characteristics are listed in Table 1. One patient at the dose level of 120 mg developed a therapy unrelated sepsis during the first cycle. Therefore, only the first day of treatment could be completed. As a result, this patient was only evaluable for PK and PD analyses of the first day, but not for toxicities, and was, therefore, replaced. The 26 evaluable patients were either asymptomatic or had only mild symptoms at study entry. Their median age was 64 years.

The number of cycles administered had a median of 2 cycles per patient, range 1 to 14. The dose levels studied were 10, 20, 40, 80, 120, and 160 mg administered i.v. on days 1 to 5 within 1 hour, with cycles repeated once every 28 days.

Safety

DLTs. In the absence of grade 2 or more toxicity in the first cycle, patients were treated in following sequence at 10 mg (n = 3), 20 mg (n = 3), 40 mg (n = 3), and 80 mg (n = 3). At the first cycle of 160 mg, two patients developed a DLT. One of the DLTs consisted of AST grade 3, the other DLT consisted of grade 2 cardiac arrhythmia, grade 2 hypotension, and grade 2 troponin T in the same patient. As a result, another 3 patients were treated at the next lower dose level (80 mg), of which one developed a DLT consisted of a grade 3 AST and grade 3 ALT at the third day of infusion. Because of the fact, there was only 1 DLT of 6 patients at 80 mg, and an intermedian level of 120 mg i.v. was explored. At this dose level there were no DLT at the first cycle. Overall the dose-limiting cardiovascular toxicities were hypertension grade 3 and QTc prolongation grade 3 (Table 3).

Other toxicities. The mild cardiovascular toxicities were grade 1 and 2 hypotension and asymptomatic paroxysmal atrial fibrillation grade (Table 3).

The most frequent hematologic side effects were mild grade 1 and 2 leucopenia, grade 1 neutropenia, and grade 1 thrombopenia. The most common non-hematologic toxicities were nausea, vomiting, diarrhea and fatigue, all grade 1–2 (Table 2).

Because of high incidence of phlebitis at doses 10, 40, and 80 mg, RGB-286638 was administered i.v. through a central venous line from dose level 80 mg/d onward (Table 2).

No changes in retina pigmentation were observed, neither any other ocular changes.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>26</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients entered</td>
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<td></td>
</tr>
<tr>
<td>Number of patients assessable for toxicities</td>
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<td>Age, y</td>
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<tr>
<td>Sex</td>
<td>Female 16</td>
<td>Male 10</td>
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Clin Cancer Res; 20(18) September 15, 2014

Published OnlineFirst July 14, 2014; DOI: 10.1158/1078-0432.CCR-14-0325
At the recommended dose level of 120 mg, at the third-cycle AST/ALT grade 3, and electrolyte disturbances grade 3 were seen in the same patient (Table 3). Prophylactic antiemetics was introduced at this dose level.

Tumor responses
There were no partial responses observed. According to RECIST 1.1 stabilization of disease (SD) occurred in 6 patients, of which three were dosed at the recommended dose level of 120 mg. Two patients with prostate cancer, one with renal cancer, one with colon carcinoma, one with leiomyosarcoma, and one patient with cholangiocarcinoma, which lasted 14 months. This last patient was dosed at 160 mg.

Description PK results
Plasma samples for the PK study were obtained from all 26 patients (25 eligible patients for toxicity). A total of 26 plasma PK profiles were analyzed on day 1, and 22 plasma PK profiles on day 5. The mean PK parameters derived from the plasma concentration–time curves are summarized in Table 4. The relationship between dose and plasma exposure was investigated on day 1 over the dose range of 20 to 160 mg/d. The increase in AUC0–inf was proportional to the administered dose, with an average clearance of 55.1 ± 5.21 L/h (Supplementary Fig. S2). The comparison of AUC0–24 between days 5 and 1 reveals a 1.5-fold drug accumulation after once daily dosing. The mean terminal T1/2 values did not markedly vary with the dose. Figure 1 shows a representative concentration–time profile on days 1 and 5 of RGB-286638 from a patient who received a single dose of RGB-286638 at 80 mg/m² during the 24-hour period after dose administration. The cumulative urinary excretion of the parent drug was consistently low and averaged 1.71 ± 0.215% (±SD) of the dose.

### Table 2. Worst toxicity in the first cycle according to NCI-CTC version 3.0

<table>
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<tr>
<th>Dose (mg/d)</th>
<th>Number of patients</th>
<th>WBC 1-2 3-4</th>
<th>ANC 1-2 3-4</th>
<th>Platelets 1-2 3-4</th>
<th>Nausea 1 2 3</th>
<th>Vomiting 1-2 3-4</th>
<th>Diarrhea 1 2 3-4</th>
<th>Phlebitis 1 2 3-4</th>
<th>Fatigue 1-2 3-4</th>
<th>AST/ALT 1-2 3-4</th>
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<tr>
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<td>-</td>
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<td>1</td>
<td>-</td>
<td>1</td>
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<tr>
<td>120</td>
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<td>1</td>
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</table>

Abbreviation: ANC, absolute neutrophil count.

### Table 3. Toxicities

<table>
<thead>
<tr>
<th>Dose (mg/d)</th>
<th>Summary DLT in first cycle according to NCI-CTC version 3.0. Cycle</th>
<th>Summary DLT in all subsequent cycles according to NCI-CTC version 3.0. Cycle</th>
<th>Cardiovascular toxicity in all cycles according to NCI-CTC version 3.0.</th>
</tr>
</thead>
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<td>160 mg/d</td>
<td>AST grade 3 (1 pt)</td>
<td>Hypertension grade 3 (1 pt)</td>
<td>Hypertension grade 3, cardiac arrhythmia grade 2, troponin T elevation grade 2 (1 pt)</td>
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<tr>
<td>160 mg/d</td>
<td>Hypotension grade 2, cardiac arrhythmia grade 2, troponin T elevation grade 2 (1 pt)</td>
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<td>1</td>
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<tr>
<td>80 mg/d</td>
<td>AST grade 3 (1 pt)</td>
<td>Hypertension grade 3 (1 pt)</td>
<td>1</td>
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<tr>
<td>10 mg/d</td>
<td>Hypertension grade 3 (1 pt)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>120 mg/d</td>
<td>QTc prolongation grade 3 (1 pt) a Cycle 2</td>
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<td>2</td>
</tr>
<tr>
<td>80 mg/d</td>
<td>QTc prolongation grade 3 (1 pt) a Cycle 3</td>
<td>3</td>
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<td>120 mg/d</td>
<td>AST/ALT grade 3, electrolyte disturbances grade 3 (1 pt) Cycle 3</td>
<td>3</td>
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<tr>
<td>160 mg/d</td>
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<tr>
<td>120 mg/d</td>
<td>Asymptomatic paroxysmal atrial fibrillation grade 2</td>
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<td>QTc prolongation grade 3 (1 pt) a Cycle 3</td>
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<tr>
<td>160 mg/d</td>
<td>Asymptomatic paroxysmal atrial fibrillation grade 1</td>
<td>1</td>
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</table>

aSame patient.
PD results
The p-Rb (Ser780) site is phosphorylated by various kinases, including cyclin D-dependent kinases (i.e., CDK4 and CDK6), if these CDKs are inhibited by RGB-286638 one would expect to detect reduced or absence of p-Rb compared with Rb as has been observed in in vitro experiments involving cell lines (4). More general inhibitory effects of RGB-286638 on cell proliferation and differentiation in the skin can be detected by measuring Ki-67 and p27KIP1. Immunohistochemical analyses failed to demonstrate significant modulation of both total and activated Rb (p-Rb) in paired skin biopsies (Fig. 2A and B) taken before and during RGB-286638 treatment. However, at the MTD (120 mg/d) 3 of 4 patients showed a significant decrease in Ki-67-positive epidermal keratinocytes (Fig. 2C–F). No changes were observed in p27KIP1 levels in the skin during treatment. As it is reported that RGB-286638 displays in vitro toxicity in cancer cell lines and against multiple myeloma xenografts through the induction of apoptosis (3, 7), we attempted to measure apoptosis in healthy peripheral blood mononuclear cells (PMBC) as a marker of RGB-286638 efficacy. We also carried out experiments to obtain evidence for apoptosis occurring in tumors of epithelial origin by determining the levels of a caspase-cleaved fragment of cytokeratin-18. However, RGB-286638 treatment did not induce significant levels of apoptosis in blood leukocyte subsets, nor significant changes in the serum level of the M30 apoptosis-associated biomarker were detected.

Conclusions
In this first in human phase I study in patients with solid tumors the recommended dose of RGB-286638 for phase II studies was identified at 120 mg/d i.v. at 1 to 5 days every 4 weeks, given through a central venous line preceded by antiemetics. RGB-286638, a novel CDK inhibitor of the indenopyrazole family, is active at low nanomolar concentrations against CDK1, 2, 3, 4, and 6, key regulators of cell-cycle progression and against the non–cell-cycle–dependent kinases CDK 5, 7, and 9. In addition, RGB-286638 was active in preclinical models against several non-receptor and receptor tyrosine kinases and inhibited several of the serine/threonine kinases (5).

In in vitro studies RGB-286638 had the potential to block ion channels in both the hERG and Purkinje fiber assays, suggesting a potential to elongate QTc. Preclinical studies in the dog had not revealed any change in cardiac action potential but revealed a marked increase in heart rate and decline in blood pressure several hours after drug administration. Systematic ECG reviews in our phase I study did not show a (dose-dependent) QTc prolongation over the dose range studied. Neither was a decline in LVEF established. Also other CDK inhibitors are associated with cardiovascular side effects (see Supplementary Table S1). In contrast with RGB-286638, the administration of AT7519 resulted in QTc prolongation. However, dinaciclib (SCH727965) was associated with hypotension, cardiac troponin T elevation—like RGB-286638, but also with syncope and cardiac ischemia. It is, therefore, recommended to continue the evaluation of adverse cardiovascular side effects in this class of agents, for the safety of the patients and to get a better understanding of this adverse effect. Transient rises in hepatic enzymes have been reported with other CDK inhibitors as well.
Other hematologic and non-hematologic side effects were mild and consisted predominantly of gastrointestinal toxicity and fatigue, comparable with the side effects generally observed with CDK inhibition (see Supplementary Table S1).

The PK data obtained in this study revealed that plasma PK of RGB-286638 was linear over the dose range studied, with a slight accumulation of the plasma exposure on day 5. Urinary excretion was low. The fact that we did not observe apoptosis of PMBCs (different leukocyte subsets) was disappointing but not without a precedent as Cirstea and colleagues clearly showed activity of RGB-286638 in freshly isolated tumor cells from patients with multiple myeloma but also noted that RGB-286638 was clearly less cytotoxic in healthy PMBCs (3). Modulation of p-Rb has not been consistently reported on exposure to CDK inhibitors. In the present study, immunohistochemical analyses failed to show significant modulation of p-Rb levels in paired skin biopsies. In agreement with our results, Cirstea and colleagues were also unable to show that Rb phosphorylation at the S780 site was affected by RGB-286638 (3). We did, however, observe toxicities and at the MTD (120 mg/d) a significant reduction of Ki-67 expression (a proliferation marker) in the skin, suggesting a molecular interaction of the drug with, at least some, of its molecular targets. As RGB-286638 inhibits multiple kinases, not only CDKs, with IC<sub>50</sub> values < 50 nmol/L, it may be difficult to determine which kinase or kinases caused the observed disease stabilization and, hence, what will be the best efficacy biomarker for RGB-286638 in the patient setting.

In our study no objective tumor responses were observed, although several patients had a prolonged period of disease stabilization while on treatment. It may well be the case that at the dose levels that can be safely reached in patients, tumors mainly respond with proliferation inhibition due to an impaired cell-cycle progression. Evidence is accumulating that specific tumor cells might be dependent for their growth on specific CDKs depending on their developmental origin (2). Selecting patients based on these insights will be essential for further development of CDK inhibitors especially in solid tumors. Data in multiple myeloma indicate that treatment with RGB-286638 results in nuclear stress and depletion of MDM2 mediated through transcriptional arrest (4). The strong <i>in vitro</i> inhibition of CDK9 could be a rationale for...
further combination studies in solid tumors in addition to exploration of the drug in hematologic malignancies.

Disclosure of Potential Conflicts of Interest
H. Loferer is an employee of Agennix AG. No potential conflicts of interest were disclosed by the other authors.

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Grant Support
This study was supported by Agennix AG, Germany.

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Received February 7, 2014; revised June 20, 2014; accepted June 30, 2014; published OnlineFirst July 14, 2014.

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Phase I Study of RGB-286638, A Novel, Multitargeted Cyclin-Dependent Kinase Inhibitor in Patients with Solid Tumors

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