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Clinical Cancer Research

A First-in-Human Phase I Study of the Oral p38 MAPK Inhibitor, Ralimetinib (LY2228820 Dimesylate), in Patients with Advanced Cancer

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Abstract

Purpose: p38 MAPK regulates the production of cytokines in the tumor microenvironment and enables cancer cells to survive despite oncogenic stress, radiotherapy, chemotherapy, and targeted therapies. Ralimetinib (LY2228820 dimesylate) is a selective small-molecule inhibitor of p38 MAPK. This phase I study aimed to evaluate the safety and tolerability of ralimetinib, as a single agent and in combination with tamoxifen, when administered orally to patients with advanced cancer.

Experimental Design: The study design consisted of a dose-escalation phase performed in a 3+3 design (Part A; $n = 54$), two dose-confirmation phases [Part B at 420 mg ($n = 18$) and Part C at 300 mg ($n = 8$)], and a tumor-specific expansion phase in combination with tamoxifen for women with hormone receptor–positive metastatic breast cancer refractory to aromatase inhibitors (Part D; $n = 9$). Ralimetinib was administered orally every 12 hours on days 1 to 14 of a 28-day cycle.

Results: Eighty-nine patients received ralimetinib at 11 dose levels (10, 20, 40, 65, 90, 120, 160, 200, 300, 420, and 560 mg). Plasma exposure of ralimetinib (C_{max} and AUC) increased in a dose-dependent manner. After a single dose, ralimetinib inhibited p38 MAPK–induced phosphorylation of MAPKAP-K2 in peripheral blood mononuclear cells. The most common adverse events, possibly drug-related, included rash, fatigue, nausea, constipation, pruritus, and vomiting. The recommended phase II dose was 300 mg every 12 hours as monotherapy or in combination with tamoxifen. Although no patients achieved a complete response or partial response,19 patients (21.3%) achieved stable disease with a median duration of 3.7 months, with 9 of these patients on study for ≥6 cycles.

Conclusions: Ralimetinib demonstrated acceptable safety, tolerability, and pharmacokinetics for patients with advanced cancer. *Clin Cancer Res; 22(5); 1095–102. ©2015 AACR.*

Introduction

Metastasis is a multistage process in which angiogenesis, extracellular matrix remodeling, and secretion of tumor growth factors contribute to tumor migration into the surrounding tissue (1, 2). The p38 MAPK protein phosphorylates a number of substrates in response to external stimuli including MAPKAP-K2. Some of the downstream effects of p38 MAPK pathway activation include regulation of TGFβ, TNFα, and interleukins (IL6, IL8, IL1β); all are known to play a role in tumor cell colonization and angiogenesis (3).

Four isoforms of p38 MAPK have been identified: p38-α, β, γ, and δ (4). These isoforms are differentially expressed and have both overlapping and unique functions. Inhibition of the most abundant isoform p38 MAPK in tumor and endothelial cells decreases prosurvival, proangiogenic, and proinflammatory soluble factors. Several p38 MAPK inhibitors have been developed for the treatment of inflammatory disease, such as chronic obstructive pulmonary disease, asthma, and rheumatoid arthritis (5–7). In addition, a selective inhibitor of the α isoform of p38 MAPK has been investigated in patients with myelodysplastic syndromes and multiple myeloma, where activation of the p38 MAPK pathway has been implicated in disease pathophysiology (8, 9).

Ralimetinib, a potent and selective inhibitor of α and β isoforms of p38 MAPK ($IC_{50} = 5.3$ and 3.2 nmol/L, respectively), competitively binds to the ATP-binding site of p38 MAPK and inhibits its kinase activity *in vitro* (10). Preclinical analyses demonstrated *in vivo* efficacy of ralimetinib in human glioblastoma, multiple myeloma, breast, ovarian, and lung cancer xenografts (10, 11). Moreover, an integrated preclinical pharmacokinetic/pharmacodynamic/TS (tumor size) modeling approach identified a daily exposure needed to achieve efficacy as an

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Translational Relevance

p38 MAPK is a signaling protein activated in cancer cells in response to environmental factors, oncogenic stress, radiotherapy, and chemotherapy. Activation of p38 MAPK within the tumor microenvironment induces the production of cytokines that promote tumor growth, invasion, and metastasis. Therefore, targeting p38 MAPK may provide a strategy for altering the tumor microenvironment and preventing cancer cell survival. Ralimetinib (LY2228820 dimesylate) is a potent and selective inhibitor of the α and β isoforms of p38 MAPK developed for patients with cancer. This first-in-human phase I study demonstrated acceptable safety, tolerability, and pharmacokinetics of ralimetinib in patients with advanced cancer both as a single agent or in combination with tamoxifen. These findings support further evaluation of ralimetinib in patients with solid tumors.

$AUC_{0—24}$ of 13,400 ng·h/mL; defined as the human targeted exposure (Data on file, Eli Lilly and Company). Given the documented antitumor activity of ralimetinib in breast cancer xenografts and evidence that activation of the p38 MAPK signaling pathway is associated with tamoxifen resistance (12), we hypothesized that ralimetinib would exhibit antitumor activity in endocrine-resistant breast cancer. Here, we report findings from the first-in-human phase I study of ralimetinib. The primary objective was to evaluate the safety and tolerability as a single agent in patients with advanced cancer or in combination with tamoxifen in metastatic breast cancer patients. Secondary objectives included analysis of pharmacokinetics of ralimetinib (including an assessment of ralimetinib on CYP3A4 activity), evaluation of pharmacodynamic biomarkers, documentation of antitumor activity, and identification of a recommended phase II dose.

Materials and Methods

Study design and patient eligibility

This multicenter, nonrandomized, open-label, phase I study had 4 parts (Supplementary Fig. S1), consisting of a dose escalation (Part A), expansions at two doses (Part B at 420 mg and Part C at 300 mg), and a tumor-specific expansion in combination with tamoxifen for hormone receptor–positive metastatic breast cancer (Part D). A drug–drug substudy was also conducted during Part B to determine whether the study drug modulated the pharmacokinetics of midazolam, a known substrate for CYP3A4. A complete description of the study design is included in the Supplementary Materials.

We enrolled adults (ages ≥18 years) with histologically confirmed solid tumors refractory to standard therapy. Other inclusion criteria included disease defined by RECIST, version 1.1 (13); discontinuance of all prior chemotherapy, radiotherapy, or immunotherapy at least 2 weeks prior to enrollment; an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤2; and adequate organ (liver, kidney, and bone marrow) function. Part D was restricted to postmenopausal women with hormone receptor–positive metastatic breast cancer with disease progression or intolerance to treatment with an aromatase inhibitor. Exclusion criteria included prior treatment with an investigational agent within 2 weeks of enrollment, major surgical resection involving the stomach or small bowel, symptomatic central nervous system malignancy or metastasis, diagnosis of inflammatory bowel disease, nonlymphoma hematologic malignancies, treatment with any drug that induces or moderately/strongly inhibits CYP3A4 or grapefruit juice within 1 week of study drug, treatment with any drug that moderately/strongly inhibits CYP2D6 within 1 week of study drug (Part D only), positive test for human immunodeficiency virus, hepatitis B surface antigen, hepatitis C antibodies, pregnancy, lactation, and concurrent administration of any immunosuppressive therapy. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, and the protocol was approved by each participating institution's ethics review board. All patients provided written informed consent.

Dose escalation was guided by safety assessments during cycle 1 using the Common Terminology Criteria for Adverse Events, version 3.0; pharmacokinetic/pharmacodynamic data were reviewed as available throughout the study. Dose-limiting toxicity (DLT) was defined as an adverse event (AE) possibly related to ralimetinib and fulfilling at least one of the following criteria: ≥ grade 3 thrombocytopenia with bleeding; grade 4 hematologic toxicity lasting >5 days; ≥ grade 3 febrile neutropenia; ≥ grade 3 nonhematologic toxicity except nausea/vomiting/diarrhea, or electrolyte disturbances responsive to medical treatment; ≥ grade 3 nausea/vomiting/diarrhea that persists ≥2 days despite medical intervention; and ≥ grade 3 electrolyte disturbances that persist despite supportive treatment. If any patient experienced DLT within the first cycle of ralimetinib, 3 additional patients were enrolled at that dose level. If a DLT was observed in 2 or more patients at any dose level, escalation ceased and the previous dose was declared the MTD.

Drug supply

Ralimetinib was provided by Eli Lilly and Company in capsules containing 5 or 20 mg of active drug or in tablets containing 20 or 100 mg of active drug. Midazolam hydrochloride 2 mg dose (2 mg/mL) was administered as syrup. Commercially available tamoxifen was supplied locally in 20 mg tablets.

Pharmacokinetic studies

Ralimetinib drug concentrations were determined for all patients using a validated liquid chromatography/tandem mass spectrometry method (see Supplementary Materials). Whole blood samples were collected on days 1 and 14 for pharmacokinetic evaluation of ralimetinib. Pharmacokinetic analyses included but were not limited to the area under the plasma concentration–time curve to the last sampling time point (AUC_{0-t}), where t is the last sampling time point, $AUC_{0-\infty}$ (0–∞), peak observed concentration (C_{max}), time to C_{max} (t_{max}), half-life ($t_{1/2}$), clearance (CL), and steady-state volume of distribution (V_d). Because *in vitro* studies using human liver microsomes demonstrated that ralimetinib inhibited the catalytic activity of cytochrome P450 3A4 (CYP3A4) by both competitive (inhibitor constant [K_i] = 1.2 μmol/L) and time-dependent mechanisms (inactivation rate constant [k_{inact}] = 0.069/min and apparent inactivation constant [K_I] = 9.5 μmol/L), we assessed the potential impact of ralimetinib on CYP3A4 activity. In Part B, plasma concentrations of midazolam and its metabolite, 1-OH midazolam, were determined to assess their pharmacokinetics pre- and post-ralimetinib treatment. Decision criteria for determining the drug–drug

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interaction (DDI) were based upon the 90% confidence intervals (CI) of the midazolam geometric mean ratios of C_{max} and $AUC_{0-\infty}$ in the presence and absence of ralimetinib.

Pharmacodynamic studies

Pharmacodynamic analyses were conducted on two plasma samples collected at the predose and on days 1 and 15 of cycle 1. Intracellular levels of pMAPKAP-K2 were measured in peripheral blood mononuclear cells (PBMC) by flow cytometry following methodology previously published (Esoterix, US Patent No. 7326577; see Supplementary Materials).

Antitumor activity

Patients were radiographically assessed according to RECIST guidelines and evaluated at baseline, cycle 2, and at every other cycle thereafter.

Results

Patient demographics, dosing, and disposition

Eighty-nine patients enrolled and received at least one dose of study drug (Parts A–D). The mean age was 61.3 years, and the majority of patients were Caucasian (Table 1). Patients with colon or rectal carcinoma (31.3%) were enrolled most frequently (Parts A–C), and Part D was restricted to breast cancer (Table 1 and Supplementary Table S1). The median number of cycles for each Part (A–D) of the study was 2 (range: Part A, 1–29; Part B, 1–6; Part C, 1–2; Part D, 1–14). Doses of ralimetinib ranged from 10 to 560 mg every 12 hours. In Parts A–D, 89 patients (100%) discontinued from the study. Reasons for discontinuation were progressive disease (70, 78.7%), AE (7, 7.9%), physician decision (5, 5.6%), patient decision (4, 4.5%), and death (3, 3.4%). The initial MTD was 420 mg, but commonly observed toxicities including grade 1 and grade 2 tremor (28.6%) and dizziness (23.8%) as well as DLT-equivalent events of rash (22.2%) led to a final MTD and recommended phase II dose of 300 mg every 12 hours for ralimetinib as a single agent. For ralimetinib, in combination with tamoxifen (Part D), the recommended phase II dose was 300 mg every 12 hours.

Table 1. Baseline patient characteristics

Characteristic	Parts A–C ($n = 80$)	Part D ($n = 9$)	All parts ($n = 89$)
Gender, *n* (%)			
Male	37 (46.3)	—	37 (41.6)
Female	43 (53.8)	9 (100.0)	52 (58.4)
Age, years			
Mean	61	61	61
Range	36–82	55–69	35–82
Ethnic origin, *n* (%)			
African American	3 (3.8)	—	3 (3.4)
Caucasian	74 (92.5)	8 (88.9)	82 (92.1)
Hispanic	3 (3.8)	1 (11.1)	4 (4.5)
ECOG PS, *n* (%)			
0	34 (42.5)	6 (66.7)	40 (44.9)
1	43 (53.8)	2 (22.2)	45 (50.6)
2	3 (3.8)	1 (11.1)	4 (4.5)
Tumor type, *n* (%)[a]			
Colorectal	25 (31.3)	—	25 (28.1)
Breast	10 (12.5)	9 (100.0)	19 (21.3)
Sarcoma	11 (13.8)	—	11 (12.4)
NSCLC	6 (7.5)	—	6 (6.7)
Renal	5 (6.3)	—	5 (5.6)
Pancreas	5 (6.3)	—	5 (5.6)
Melanoma	3 (3.8)	—	3 (3.4)
Ovary	2 (2.5)	—	2 (2.2)
Other	13 (16.3)	—	13 (14.6)

Abbreviation: PS, performance status.
[a]A detailed summary of baseline pathologic diagnosis, per Parts A–D of the study, is included in Supplementary Table S1.

Safety, MTD, and dose determination

Sixty-nine patients (77.5%) experienced at least one treatment-emergent AE (TEAE): 35 of 54 patients (64.8%) in Part A; 18 of 18 patients (100%) in Part B; 7 of 8 patients (87.5%) in Part C; and 9 of 9 patients (100%) in Part D of the study. As outlined in Table 2, the most common TEAEs (occurring in ≥10% of patients) possibly related to study drug were rash, fatigue, nausea, constipation, pruritus, vomiting, anorexia, tremor, and dizziness. There were 16 ≥ grade 3 TEAEs possibly related to study drug: rash/desquamation (7 patients), increased creatine phosphokinase, increased creatinine, lymphopenia, decreased leukocytes, confusion, ataxia, fatigue, pruritus, and spontaneous abortion in a patient who did not adhere to the recommendations for contraceptive precautions.

In dose-escalation testing (Part A), 54 patients received ≥1 dose of ralimetinib, and 3 patients (5.6%) experienced a serious AE (SAE) possibly related to ralimetinib [grade 3 increased creatine phosphokinase, 65 mg cohort; grade 4 spontaneous abortion, 200 mg cohort; and grade 3 fatigue, ataxia, and increased creatinine (reported in the same patient), 560 mg cohort]. In Part B, 18 patients received at least one dose of study drug, and 2 (11.1%) experienced the drug-related SAE of grade 3 rash. No SAEs related to study drug were reported in Part C or Part D. Overall, 7 patients (7.9%) discontinued treatment due to AEs. In Part A, 4 patients (7.4%) discontinued due to grade 3 convulsion (10 mg), grade 2 creatinine (90 mg), grade 3 erythema multiforme (200 mg), and grade 3 ataxia (560 mg). In Part B, 2 patients (11.1%) discontinued due to grade 3 hypoxia (420 mg) and grade 3 rash (420 mg), and in Part C 1 patient (12.5%) discontinued treatment due to grade 3 aspartate aminotransferase (300 mg). Of these 7 AEs, erythema multiforme, ataxia, and rash were possibly related to study drug. No patients discontinued due to AEs in Part D.

Ten AEs were considered as DLTs including rash (8), ataxia (1), and dizziness (1). For ralimetinib as a single agent, DLTs of grade 3 ataxia and grade 2 dizziness were seen at 560 mg every 12 hours, the maximum dose explored. The initial monotherapy MTD was declared at 420 mg every 12 hours; however, because a safety review of MTD level patients demonstrated a high frequency of intolerable side effects including grade 1/2 tremor (28.6%), dizziness (23.8%), and DLT-equivalent rash (22.2%), the MTD was reduced to 300 mg every 12 hours and a confirmation cohort at 300 mg every 12 hours (Part C) was completed. For ralimetinib in combination with tamoxifen, 1 patient (11.1%) experienced grade 3 rash as a DLT in the 300 mg every 12 hours cohort.

Pharmacokinetics

Over the entire study, ralimetinib was rapidly absorbed with a median t_{max} value of 1 hour both following single and multiple doses. Only predose samples collected from patients on day 1 of cycle 2 were used to assess the ralimetinib $t_{1/2}$ on day 14, and the average $t_{1/2}$ was 145 hours (range: 56.8–923 hours) across the dose range. Intracycle ralimetinib accumulation was observed between days 1 and 14 of cycle 1 across all cohorts (average accumulation ratio 2.14). Little to no intercycle ralimetinib

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Table 2. TEAEs possibly related to study drug (all grades[a] that occurred in ≥10% of patients)

	Part A (*N* = 54)		Part B (*N* = 18)		Part C (*N* = 8)		Total (Parts A–C) *N* = 80		Part D (*N* = 9)		All parts (*N* = 89)	
TEAEs	**All grades *n* (%)**	**Gr ≥3 *n* (%)**	**All grades *n* (%)**	**Gr ≥3 *n* (%)**	**All grades *n* (%)**	**Gr ≥3 *n* (%)**	**All grades *n* (%)**	**Gr ≥3 *n* (%)**	**All grades *n* (%)**	**Gr ≥3 *n* (%)**	**All grades *n* (%)**	**Gr ≥3 *n* (%)**
Rash	8 (14.8)	1 (1.9)	8 (44.4)	4 (22.2)	2 (25.0)	2 (25.0)	18 (22.5)	7 (8.8)	5 (55.6)	1 (11.1)	23 (25.8)	8 (8.9)
Fatigue	11 (20.4)	1 (1.9)	4 (22.2)	—	2 (25.0)	—	17 (21.3)	1 (1.3)	5 (55.6)	—	22 (24.7)	1 (1.1)
Nausea	10 (18.5)	—	4 (22.2)	—	—	—	14 (17.5)	—	2 (22.2)	—	16 (18.0)	0
Constipation	8 (14.8)	—	4 (22.2)	—	1 (12.5)	—	13 (16.3)	—	3 (33.3)	—	16 (18.0)	0
Pruritus	5 (9.3)	—	4 (22.2)	1 (5.6)	—	—	9 (11.3)	1 (1.3)	4 (44.4)	—	13 (14.6)	1 (1.1)
Vomiting	8 (14.8)	—	4 (22.2)	—	—	—	12 (15.0)	—	1 (11.1)	—	13 (14.6)	0
Anorexia	5 (9.3)	—	5 (27.8)	—	—	—	10 (12.5)	—	—	—	10 (11.2)	0
Tremor	4 (7.4)	—	4 (22.2)	—	1 (12.5)	—	9 (11.3)	—	1 (11.1)	—	10 (11.2)	0
Dizziness	3 (5.6)	—	4 (22.2)	—	1 (12.5)	—	8 (10.0)	—	1 (11.1)	—	9 (10.1)	0

Abbreviation: Gr, grade.

[a]Grades are according to Common Terminology Criteria for Adverse Events, version 3.0.

accumulation (R_B) occurred between day 14 of cycles 1 and 2 for the cohorts where this was explored (average R_B of 1.1). The mean concentration time profiles at the dose of interest (300 and 420 mg) are represented in Fig. 1A. In general, ralimetinib showed dose-proportional increases in exposure on both day 1 and day 14. Table 3 represents key pharmacokinetic parameters of interest at 300 and 420 mg (pharmacokinetic parameters of all dose levels are represented in Supplementary Tables S2 and S3).

In Part D, only 1 patient had quantifiable pharmacokinetic results at cycle 2, day 1 predose time point, which limited the evaluation of terminal-phase pharmacokinetics. Results from 0–12 hours postdose on day 14 allowed determination of $C_{max,ss}$

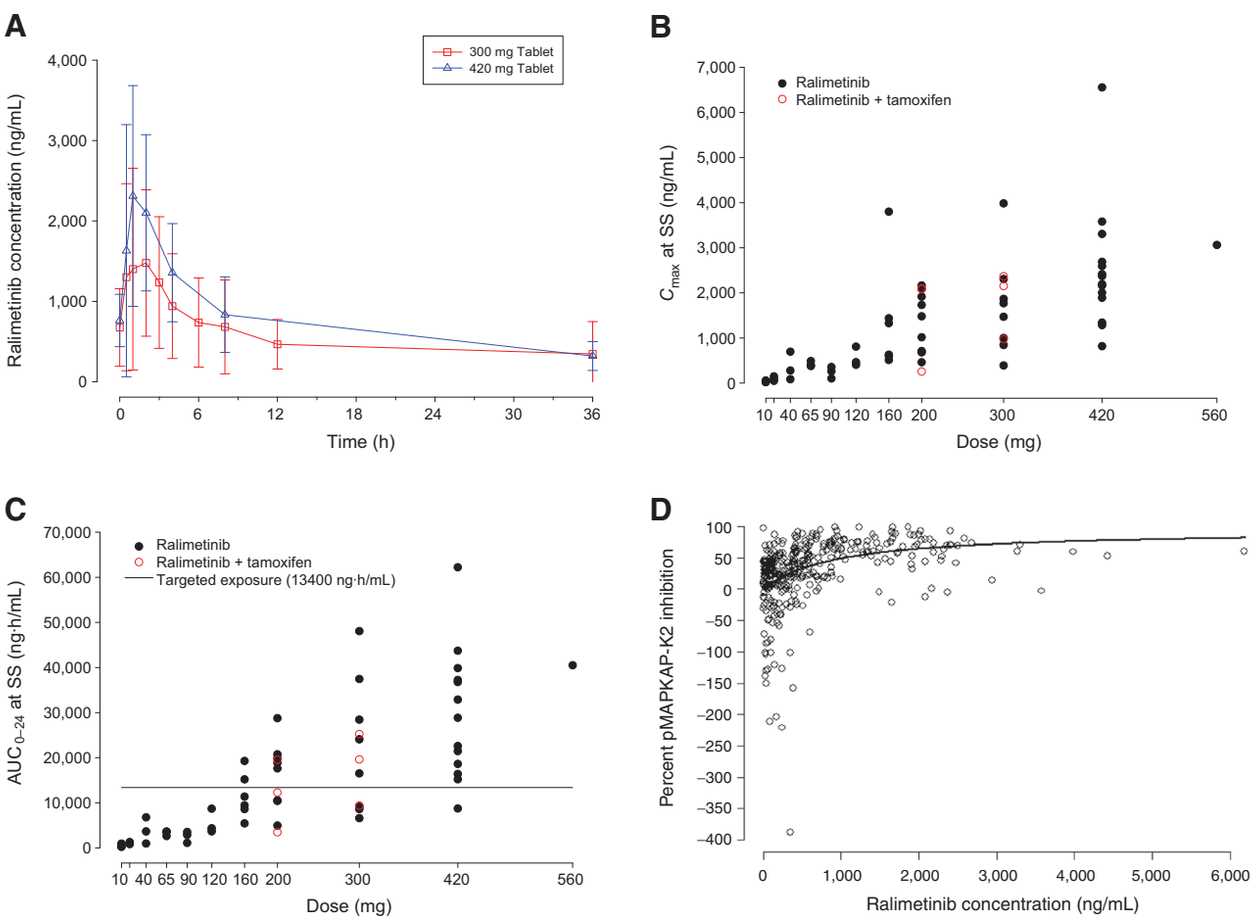

Figure 1.

Pharmacokinetic and pharmacodynamic parameters. A, mean pharmacokinetic profiles at 300 and 420 mg. Dose proportionality plots for C_{max} (B) and AUC (C) on day 14 of cycle 1. D, the relationship between pMAPKAP-K2 percent inhibition from baseline and ralimetinib plasma concentration at matching time points following the first cycle 1 day 1. Error bars represent SD.

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Table 3. Ralimetinib pharmacokinetic parameters of interest at the doses of interest

	300 mg Q12H	300 mg Q12H + tamoxifen	420 mg Q12H
Day 1, *n*	11	6	21
C_{max} (ng/mL)	1,020 (58)	1,810 (42)	1,700 (71)
t_{max}[a] (h)	1.00 (0.98–3.00)	0.74 (0.50–1.00)	1.00 (0.50–8.00)
$AUC_{(0-8)}$ ng·h/mL	3,460 (51)	4,500 (36)	5,780 (57)
Day 14, *n*	9[d]	3	14[e]
C_{max} (ng/mL)	1,400 (81)	1,700 (52)	2,230 (53)
t_{max}[a] (h)	2.02 (1.00–11.72)	0.98 (0.47–1.98)	1.53 (0.5–4.00)
$AUC_{(0-8)}$ ng·h/mL	6,620 (85)	6,910 (55)	10,200 (55)
$AUC_{(0-24,ss)}$[b] ng·h/mL	17,900 (85)	16,600 (55)	26,200 (57)
CL_{ss}/F (L/h)	33.6 (85)	NC	32.1 (57)
V_{ss}/F (L)	2,130 (100)	NC	1,620 (165)
$t_{1/2}$ (h)	92.6 (46)	NC	77.4 (150)
R_A[c]	1.89 (33)	1.58 (59)	1.79 (28)

Abbreviations: $AUC_{(0-8)}$ and $AUC_{(0-24)}$ area under the baseline corrected serum concentration versus time curve from time zero to 8 or 24 hours, respectively; CL_{ss}/F, apparent total body clearance at steady state after extravascular administration; C_{max}, maximum plasma concentration; CV, coefficient of variation; h, hours; Q12H, every 12 hours; R_A, accumulation ratio; $t_{1/2}$, terminal half life; t_{max}, time to reach C_{max}; V_{ss}/F, apparent volume of distribution at steady state after extravascular administration; NC, not calculable due to sampling time.

[a]Median (range).

[b]$AUC_{(0-24,ss)}$ represents the sum of $AUC_{(0-12,ss)}$ + $AUC_{(0-12,ss)}$.

[c]R_A: accumulation ratio between day 1 and day 14 of cycle 1 (ratio of $AUC_{[0-8]}$ [Day 14]/$AUC_{[0-8]}$ [Day 1]).

[d]$N = 8$ for all parameters except $t_{1/2}$. Excluded pharmacokinetic parameters other than $t_{1/2}$ for one patient due to missing pharmacokinetic results at early sampling time points.

[e]$N = 13$ for all parameters except C_{max} and t_{max}. Excluded pharmacokinetic parameters dependent on terminal phase estimation for one patient due to atypically high concentration results.

and $AUC_{(0-24),ss}$, which can be compared with the other study patients (Fig. 1B and C). There was no difference in pharmacokinetic parameters compared with patients in the advanced cancer population.

DDI

Prior treatment and subsequent coadministration of ralimetinib on day 8 with midazolam, a CYP3A4 probe substrate, suggested that ralimetinib is unlikely to cause a clinically relevant

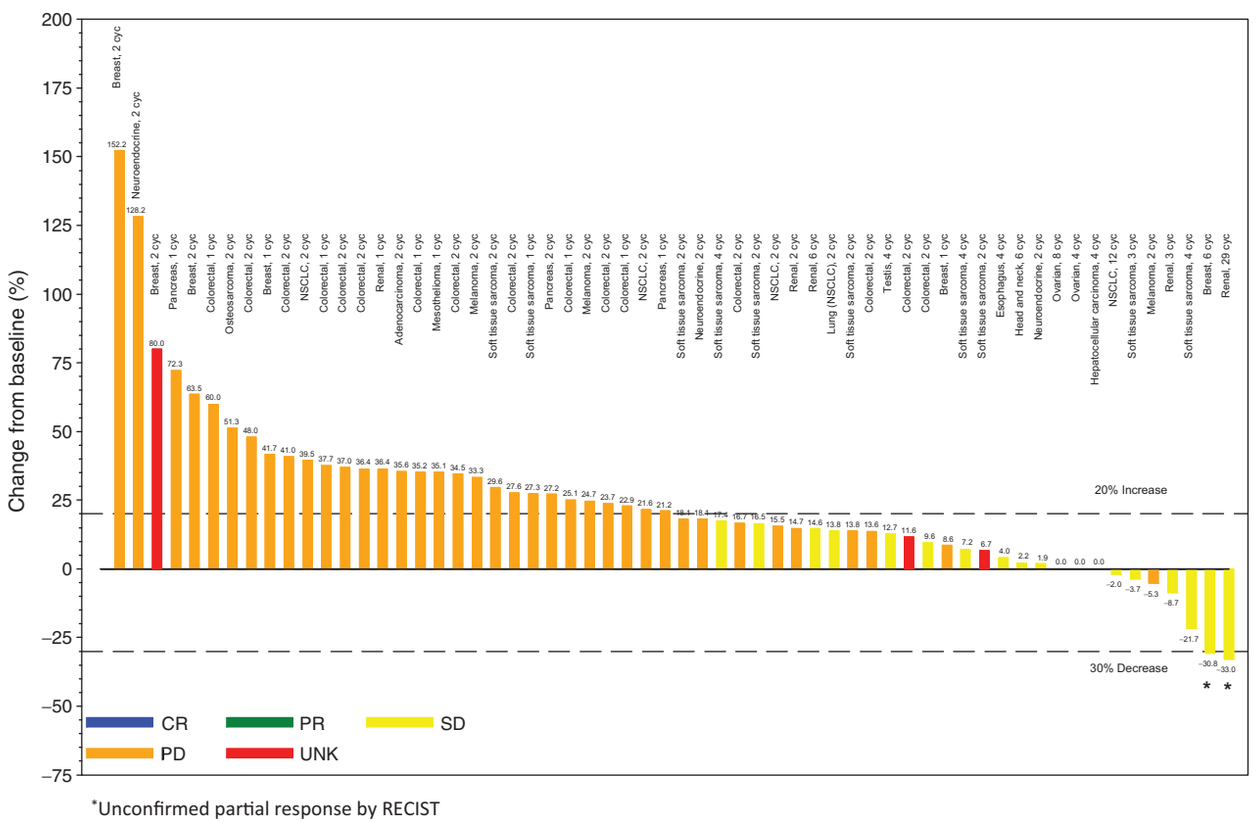

Figure 2.
Percent change in tumor size as compared with baseline for each patient.

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inhibition of CYP3A4. The geometric mean ratio $AUC_{ralimetinib}/AUC_{alone}$ of midazolam was 0.84 (90% CI, 0.67–1.06), and the geometric mean ratio $C_{max,\ ralimetinib}/C_{max\ alone}$ of midazolam was 1.01 (90% CI, 0.77–1.33). The upper bound of the 90% CI for the AUC ratio of geometric mean (1.06) is within the no effect boundary limit of 1.25 and the upper bound of the 90% CI for the C_{max} ratio of geometric mean (1.33) slightly exceeded the no effect boundary limit of 1.25, which is not considered to be clinically relevant.

Pharmacodynamics

The primary pharmacodynamic biomarker in this study was pMAPKAP-K2. Figure 1D illustrates the relationship between pMAPKAP-K2 percent inhibition from baseline and ralimetinib plasma concentration at matching time points following the first cycle 1 day 1 dose. In general, there was a reciprocal relationship between ralimetinib plasma concentration and pMAPKAPK-2 inhibition, most apparent after a single dose (Fig. 1D). At the dose of 300 mg in Part C and in Part D, the average pMAPKAPK-2 inhibition reached above 50% on day 1.

Antitumor activity

Tumor response was assessed by radiographic imaging studies in 74 of 89 patients. Fifteen patients could not be assessed due to discontinuation before radiographic assessment. Although no patients achieved a complete response or partial response, 19 patients (21.3%) exhibited stable disease: 15 (28%) in Part A, 3 (17%) in Part B, and 1 (11%) in Part D. The mean duration (±SD) of stable disease was 5.0 months (±5.3), with 9 patients [metastatic breast cancer (4), renal cell carcinoma (2), ovarian cancer, lung cancer, or adenoid cystic carcinoma] receiving ralimetinib therapy for ≥6 cycles (range 2–29). Changes in tumor size at the time of best overall response are summarized in Fig. 2. Two patients who received single-agent ralimetinib were notable. The first is a patient with ER^+, $HER2^+$ metastatic breast cancer who was on therapy (Part A 200 mg every 12 hours) for 6 cycles following progression on six previous anti-HER2–based regimens including trastuzumab-based chemotherapy (4 regimens), lapatinib (1 regimen), and trastuzumab + hormonal therapy (1 regimen). This patient had radiographic evidence of bone healing (Fig. 3), consistent with *in vivo* studies demonstrating that ralimetinib inhibits osteoclastogenesis (11). The second patient had metastatic renal cell cancer and received single-agent ralimetinib (160 mg every 12 hours) with prolonged stable disease for 29 cycles.

Discussion

Targeting p38 MAPK may provide a strategy for altering the tumor microenvironment and preventing cancer cell survival. On the basis of the nonclinical safety and efficacy data, and the potential clinical utility of disrupting the p38 MAPK pathway in cancer, ralimetinib was evaluated in patients with advanced cancer.

This first-in-human phase I study in patients with advanced cancer explored the safety, tolerability, and pharmacokinetic/pharmacodynamic properties of ralimetinib as a monotherapy or in combination with tamoxifen. Although the 420 mg dose level fulfilled the protocol MTD criterion, a high frequency of clinically significant AEs in later cycles led to further exploration of the 300 mg dose level and a phase II recommended dose of 300 mg every 12 hours for ralimetinib as a single agent. One additional justification for the recommended phase II dose was the fact that the anticipated targeted exposure of 13,400 ng·h/mL was observed in the majority of the patients at 300 mg every 12 hours (Fig. 1C).

For ralimetinib in combination with tamoxifen (Part D), the recommended phase II dose was 300 mg every 12 hours. The majority of treatment-related AEs were grade 1/2 with treatment-related safety profile consisting primarily of rash (25.8%), fatigue (24.7%), and constipation and nausea (18.0% each). At the maximum dose explored (560 mg every 12 hours), DLTs of grade 3 ataxia and grade 2 dizziness were reported; all other DLTs or DLT-equivalent events were rash.

Ralimetinib demonstrated a pharmacodynamic response as observed by inhibition of pMAPKAP-K2 in PBMCs at the phase II recommended dose of 300 mg. Further studies are needed to determine the pharmacodynamic response of ralimetinib within the tumor and tumor microenvironment at this dose and

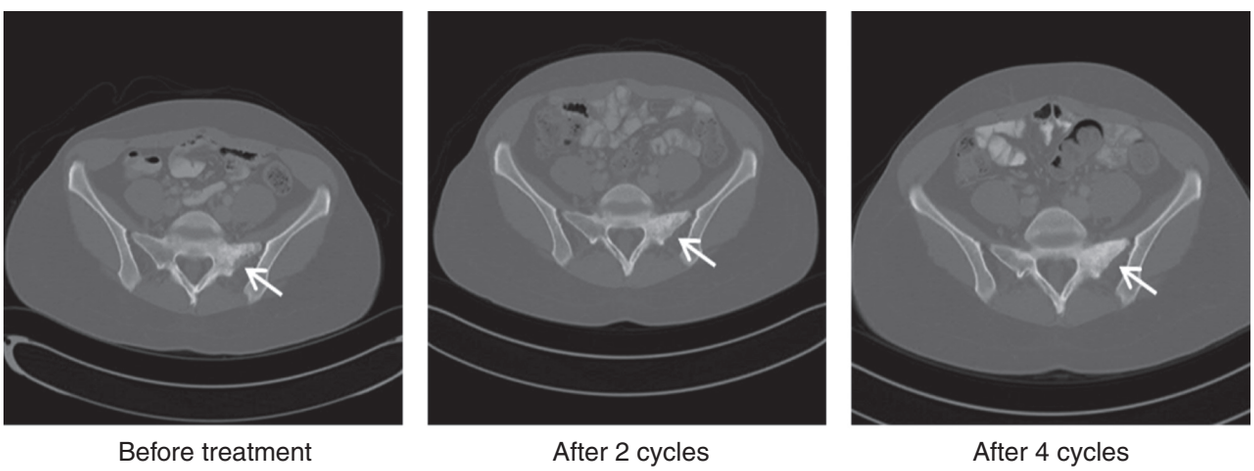

Figure 3.
Bone healing in a patient with metastatic ER^+, $HER2^+$ breast cancer who received single-agent ralimetinib (200 mg every 12 hours). Arrows indicate a lesion metastatic to bone both before and after ralimetinib therapy.

schedule. Pharmacokinetic analysis revealed that ralimetinib exposure was dose proportional on days 1 and 14 and was characterized by low apparent clearance and large apparent peripheral volume of distribution with a long terminal elimination phase. A DDI evaluation using midazolam as a CYP3A4 substrate suggested that ralimetinib is unlikely to cause a clinically significant inhibition of CYP3A4. However, the lower bound of the 90% CI for both AUC and C_{max} ratios of geometric mean, 0.67 and 0.77, respectively, are lower than the no effect boundary limit of 0.8, suggesting potential induction of the CYP3A4 activity following ralimetinib treatment. The reason for the observed increase in CYP3A4 activity is not believed to be due to direct activation of the pregnane X receptor, as ralimetinib is not an *in vitro* inducer of CYP3A4. A reasonable explanation for the observed decrease in midazolam plasma exposure post-ralimetinib treatment compared with the baseline could be due to reversal of disease state as a result of pharmacologic inhibition of p38 MAPK. Such inhibition of p38 MAPK has been shown to attenuate the proinflammatory response to CRP in human PBMCs (14, 15). Although no significant alterations in the pharmacokinetics of either tamoxifen or ralimetinib were observed in Part D, the study design used in Part D was suboptimal to explore the potential interaction between tamoxifen and ralimetinib. Continuous daily dosing of tamoxifen for at least 4 weeks is necessary to achieve steady-state exposures of tamoxifen and even longer for its metabolites.

Although there were no RECIST-type responses observed in this study, 19 patients (21.3%) achieved stable disease with 9 of these patients continuing ralimetinib without progression for $\geq$6 cycles (range 2–29). Two patients on study for $\geq$6 cycles were notable. The patient with renal cell carcinoma had received extensive prior therapy and remained on single-agent ralimetinib for 29 cycles. The patient with ER^+, $HER2^+$ metastatic breast cancer was heavily pretreated with multiple HER2-targeted therapies. She received single-agent ralimetinib for 6 cycles and had radiographic evidence of bone healing (Fig. 3) consistent with preclinical studies suggesting that ralimetinib inhibits development of osteoclasts, which play a key role in bone resorption and are aberrantly stimulated by a variety of different tumors (11).

Previous studies have implicated the p38 MAPK pathway in development of resistance to tamoxifen (16). In this study, tamoxifen was combined with ralimetinib in a cohort of women with tumor progression after prior endocrine therapy for metastatic breast cancer (Part D). In this cohort, no significant increase in toxicities or other drug interactions were observed.

In summary, ralimetinib interacted with the desired p38 MAPK target, as demonstrated by a pharmacodynamic inhibition of the p38 MAPK pathway at 300 mg. Ralimetinib was generally well tolerated at the recommended phase II dose of 300 mg alone or in combination with tamoxifen. Further studies are needed to identify biomarkers that predict clinical efficacy of ralimetinib for patients with advanced cancer. Ralimetinib is currently being investigated in combination with gemcitabine and carboplatin in a randomized, double-blind, placebo-controlled phase II study for women with platinum-sensitive ovarian cancer (NCT01663857).

Disclosure of Potential Conflicts of Interest

A.W. Tolcher is a consultant/advisory board member for AbbVie, Akebia, AP Pharma, ArQule, Astex, Avid, Bayer, Bind, BioMed Valley Discoveries, Blend, Bristol-Myers Squibb Japan, Celator, Clovis, Curis, Dicerna, Eisai, Eli Lilly, Endo, Genentech, Heron, Janssen, MedImmune, Mersana, Merus, Nanobiotix, Nektar, Neumedicines, Novartis, Pfizer, Pharmacyclics, Pierre Fabre, Sanolfi-Aventis, Symphogen, Vaccinex, Valent, and Zyngenia. C. Erlichman is a consultant/advisory board member for Eli Lilly. D.L. Farrington has ownership interests (including patents) at Eli Lilly. E.M. Chan is listed as a coinventor on a patent, which is owned by Eli Lilly, on combination therapy. M.P. Goetz is a consultant/advisory board member for and reports receiving commercial research support from Eli Lilly. No potential conflicts of interest were disclosed by the other authors.

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Clinical Cancer Research

Correction: A First-in-Human Phase I Study of the Oral p38 MAPK Inhibitor, Ralimetinib (LY2228820 Dimesylate), in Patients with Advanced Cancer

In this article (Clin Cancer Res 2016;22:1095–102), which was published in the March 1, 2016, issue of *Clinical Cancer Research* (1), the corresponding author informed us of a labeling error in Fig. 1D in the published article. This figure depicts the relationship between pMAPKAP-K2 percent inhibition from baseline and ralimetinib plasma concentration at matching time points. The figure legend and associated text refer to the data as being from "cycle 1 day 1." However, the current plot is actually pharmacokinetic/pharmacodynamic data from "cycle 1 day 14."

On page 1098, the legend for Fig. 1D should read as follows:

> D, the relationship between pMAPKAP-K2 percent inhibition from baseline and ralimetinib plasma concentration at matching time points following the cycle 1 day 14. Error bars represent SD.

On page 1100, the paragraph under the "Pharmacodynamics" heading in the Results section should read as follows:

> The primary pharmacodynamic biomarker in this study was p-MAPKAP-K2. Figure 1D illustrates the relationship between p-MAPKAP-K2 percent inhibition from baseline and ralimetinib plasma concentration at matching time points following the cycle 1 day 14 dose. In general, there was a reciprocal relationship between ralimetinib plasma concentration and pMAPKAPK-2 inhibition. At the dose of 300 mg in Part C and in Part D, the average pMAPKAPK-2 inhibition reached above 50% on day 1.

The conclusions put forth in this article remain unchanged. The authors regret this error.

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1. Patnaik A, Haluska P, Tolcher AW, Erlichman C, Papadopoulos KP, Lensing JL, et al. A first-in-human phase I study of the oral p38 MAPK inhibitor, ralimetinib (LY2228820 Dimesylate), in patients with advanced cancer. Clin Cancer Res 2016;22:1095–102.

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A First-in-Human Phase I Study of the Oral p38 MAPK Inhibitor, Ralimetinib (LY2228820 Dimesylate), in Patients with Advanced Cancer

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