The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 29, 2012 VOL. 367 NO. 22

Ponatinib in Refractory Philadelphia Chromosome–Positive Leukemias

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ABSTRACT

BACKGROUND

Resistance to tyrosine kinase inhibitors in patients with chronic myeloid leukemia (CML) and Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph-positive ALL) is frequently caused by mutations in the BCR-ABL kinase domain. Ponatinib (AP24534) is a potent oral tyrosine kinase inhibitor that blocks native and mutated BCR-ABL, including the gatekeeper mutant T315I, which is uniformly resistant to tyrosine kinase inhibitors.

METHODS

In this phase 1 dose-escalation study, we enrolled 81 patients with resistant hematologic cancers, including 60 with CML and 5 with Ph-positive ALL. Ponatinib was administered once daily at doses ranging from 2 to 60 mg. Median follow-up was 56 weeks (range, 2 to 140).

RESULTS

Dose-limiting toxic effects included elevated lipase or amylase levels and pancreatitis. Common adverse events were rash, myelosuppression, and constitutional symptoms. Among Ph-positive patients, 91% had received two or more approved tyrosine kinase inhibitors, and 51% had received all three approved tyrosine kinase inhibitors. Of 43 patients with chronic-phase CML, 98% had a complete hematologic response, 72% had a major cytogenetic response, and 44% had a major molecular response. Of 12 patients who had chronic-phase CML with the T315I mutation, 100% had a complete hematologic response and 92% had a major cytogenetic response. Of 13 patients with chronic-phase CML without detectable mutations, 100% had a complete hematologic response and 62% had a major cytogenetic response. Responses among patients with chronic-phase CML were durable. Of 22 patients with accelerated-phase or blast-phase CML or Ph-positive ALL, 36% had a major hematologic response and 32% had a major cytogenetic response.

CONCLUSIONS

Ponatinib was highly active in heavily pretreated patients with Ph-positive leukemias with resistance to tyrosine kinase inhibitors, including patients with the BCR-ABL T315I mutation, other mutations, or no mutations. (Funded by Ariad Pharmaceuticals and others; ClinicalTrials.gov number, NCT00660920.)

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N Engl J Med 2012;367:2075-88.
DOI: 10.1056/NEJMoa1205127

The fusion protein product of the Philadelphia chromosome (Ph), BCR-ABL, is a constitutively active tyrosine kinase that gives rise to chronic myeloid leukemia (CML) and a subset of acute lymphoblastic leukemia (Ph-positive ALL).[1,2] Three tyrosine kinase inhibitors targeting the BCR-ABL protein (imatinib, nilotinib, and dasatinib) have been approved for the treatment of patients with newly diagnosed chronic-phase CML.[3-5]

Resistance to tyrosine kinase inhibitors is the major reason for the failure of therapy in patients with Ph-positive disease. Primary or secondary resistance to imatinib occurs in approximately 20 to 30% of patients with newly diagnosed chronic-phase CML.[3,6] Second-generation tyrosine kinase inhibitors, dasatinib and nilotinib, are available for the treatment of patients in whom resistance or intolerance to imatinib develops; these two drugs can induce a major cytogenetic response in 35 to 63% of such patients.[7-10] However, for patients with primary or secondary resistance to dasatinib or nilotinib, whether their disease is newly diagnosed or imatinib-resistant, no approved treatment is currently available. A major mechanism of resistance is mutation of the BCR-ABL kinase domain.[11,12] One of the most common mutations, which is present in up to 20% of patients with resistance to tyrosine kinase inhibitors,[12-17] is the so-called gatekeeper T315I substitution,[18] which blocks access of the drug to the enzyme's ATP-binding site and confers a high degree of resistance to all currently approved tyrosine kinase inhibitors.[19]

Ponatinib (AP24534) is the product of a computational and structure-based approach to the design of a small-molecule tyrosine kinase inhibitor. It contains a novel triple-bond linkage that avoids the steric hindrance caused by the bulky isoleucine residue at position 315 in the T315I mutant (Fig. 1A and 1B).[22] In vitro experiments have shown that ponatinib has potent activity against native BCR-ABL and against all tested mutant forms of BCR-ABL (including T315I). Moreover, in these preclinical experiments, ponatinib suppressed the emergence of any mutation at a concentration of 40 nM.[20] These data support the characterization of ponatinib as a pan–BCR-ABL inhibitor and suggest that ponatinib may have substantial clinical utility in the treatment of patients with Ph-positive disease who have received previous therapy with currently approved tyrosine kinase inhibitors.

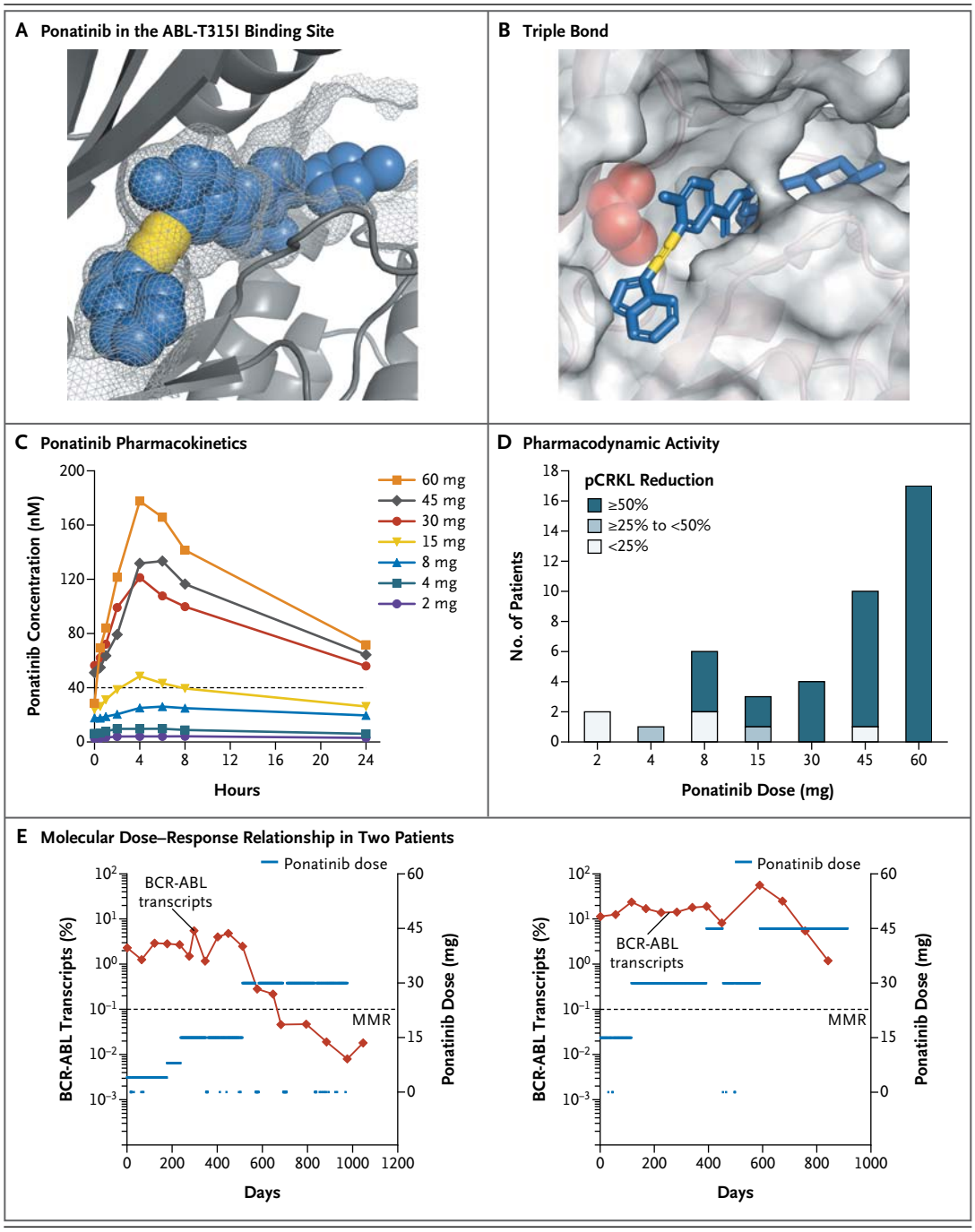
Figure 1 (facing page). Structure and Activity of Ponatinib.

In Panel A, ponatinib (shown as blue and yellow space-filling spheres) displays an optimal fit to the binding cavity of ABL-T315I (indicated by a mesh pattern). In Panel B, the triple bond (yellow) is a unique structural feature of ponatinib (blue) that allows it to evade the mutant gatekeeper residue I315 (red space-filling spheres). In Panel C, the concentration of ponatinib (as the geometric mean) is shown during a 24-hour period in patients on day 29 after administration at 0 hours. Dose groups and the number of patients who could be evaluated in each group were as follows: 2 mg, 2 patients; 4 mg, 6 patients; 8 mg, 6 patients; 15 mg, 8 patients; 30 mg, 9 patients; 45 mg, 21 patients; and 60 mg, 9 patients. The dashed line indicates the concentration that was found to completely suppress the emergence of BCR-ABL mutations in preclinical analyses.[20] In Panel D, the pharmacodynamic activity of ponatinib, on the basis of CRKL phosphorylation (pCRKL), a surrogate marker for BCR-ABL inhibition, is shown according to dose for 43 Ph-positive patients who could be evaluated. Shown are reductions from baseline of at least 50%, 25% to less than 50%, or less than 25% at trough time points (before the administration of ponatinib). (Details are provided in Appendix E in the Supplementary Appendix, available with the full text of this article at NEJM.org.) In Panel E, the dose-related molecular response is shown for two representative patients with chronic-phase CML with the T315I mutation who were undergoing dose escalation, with changes in BCR-ABL transcripts, shown as the ratio of BCR-ABL to ABL (as expressed as a percentage on the International Scale[21]) over time. The dashed line indicates the threshold for achieving a major molecular response (MMR). The blue line indicates the ponatinib dose at each time point. In the left panel, the first patient had a molecular response 4 (≤0.01% transcript ratio [International Scale] in peripheral blood) during the study. In the right panel, the second patient had a partial cytogenetic response.

METHODS

STUDY OVERSIGHT

The study was developed jointly by the sponsor, Ariad Pharmaceuticals, and the investigators. The study protocol, available with the full text of this article at NEJM.org, was approved by the institutional review board at each center. Data were collected with the use of the sponsor's data-management system and were analyzed and interpreted by representatives of the sponsor in close collaboration with the investigators. All authors reviewed the data reported and vouch for the completeness of the data set and the integrity of the analysis. The authors also verify that the study was conducted in fidelity to the study protocol. All authors reviewed, edited, and approved the manuscript.



Professional medical-writing assistance was provided by the sponsor.

PATIENTS

Patients were eligible if they had a hematologic cancer (excluding lymphoma) that had relapsed or was resistant to standard care or for which no standard care was available or acceptable. Ph-positive disease was classified and characterized as relapsed or refractory disease on the basis of standard criteria (for details, see Appendix B in the Supplementary Appendix, available at NEJM.org).[8,23] In addition, patients were required to be at least 18 years old and to have an Eastern Cooperative Oncology Group performance status of 2 or lower (on a scale ranging from 0 to 5, where 0 indicates that the patient is fully active and higher numbers indicate increasing disability)[24] and adequate re-

nal, hepatic, and cardiac function (left ventricular ejection fraction, ≥40%). All patients provided written informed consent.

STUDY DESIGN AND TREATMENT

The primary objective of this phase 1 trial was to determine the maximum tolerated dose or a recommended dose of oral ponatinib administered once daily. Secondary objectives included safety, antileukemia activity, pharmacokinetics, pharmacodynamics, and potential pharmacogenomic markers. For the dose-escalation portion of the study, patients were assigned to cohorts of at least three patients. Dose escalations in the same patient were allowed up to the dose immediately preceding the highest studied dose, without exceeding the maximum tolerated dose, which was defined as the dose at which a dose-limiting toxic effect occurred in no more than one in six patients.[25] Treatment was continued until disease progression, an adverse event leading to cessation, withdrawal of consent, or investigator discretion (Appendix B in the Supplementary Appendix).

SAFETY

We evaluated safety in all 81 patients who were enrolled in the trial. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). Dose-limiting toxic effects, which were assessed during cycle 1, were defined as follows: grade 3 or higher nonhematologic toxic effects that lasted more than 3 days despite adequate supportive care, with the exception of self-limited or medically controllable toxic effects; missed doses owing to toxicity for more than 25% of the first cycle; or febrile neutropenia not related to leukemia. Hematologic dose-limiting toxic effects were grade 4 cytopenia (>28 days) unrelated to underlying disease, with bone marrow examination showing less than 5% cellularity. We also evaluated the effect of ponatinib on the QT interval during cycle 1 in patients receiving 30 mg or more of the drug (Appendix C in the Supplementary Appendix).

PHARMACOKINETICS AND PHARMACODYNAMICS

We obtained peripheral-blood samples for the evaluation of pharmacokinetics and pharmacodynamics. Details regarding the collection schedules and methods are provided in Appendixes D and E in the Supplementary Appendix. Pharmacokinetics data are presented for all 61 patients with samples that could be evaluated from day 29 (day 1 of cycle 2). Pharmacodynamics data are presented for 43 Ph-positive patients who had data that could be evaluated.

ANTILEUKEMIA ACTIVITY

We performed complete blood counts and white-cell differential counts three times per week for the first 3 weeks, weekly through cycle 3, and then every 2 weeks. We recorded assessments of hematologic responses on day 1 of each cycle. Bone marrow aspirations for morphologic and cytogenetic assessments were performed within 28 days before study entry and at least every 3 months while patients were receiving treatment. Quantitative reverse-transcriptase–polymerase-chain-reaction assays for molecular response were performed on day 1 of cycles 3, 5, 7, and 9 and every 3 cycles thereafter.

Responses were defined according to standard criteria (Appendixes F and G in the Supplementary Appendix).[8,21,26-31] Hematologic and cytogenetic responses were assessed at the investigators' institutional laboratories. Molecular response and mutations (Sanger sequencing) were assessed by a central laboratory (MolecularMD). We performed post hoc analyses of responses according to the patient's therapy history and baseline mutation status. Differences in response rates among these subgroups were evaluated with the use of Fisher's exact test.

RESULTS

PATIENTS

From June 5, 2008, to October 14, 2010, we enrolled 81 patients at five centers. The treatment status for the patients is presented in Table 1. As of October 13, 2011, a total of 35 patients (43%) were continuing to receive therapy, and 17 had died. Median follow-up at analysis was 56 weeks (range, 2 to 140). In the first two cohorts, 1 patient with a myelodysplastic syndrome, 1 with multiple myeloma, and 2 with myelofibrosis were enrolled. Twelve patients with acute myeloid leukemia (AML) were enrolled after the maximum tolerated dose was established to explore the inhibitory activity of ponatinib on FMS-like tyrosine

Table 1. Treatment Status of the 81 Study Patients.*

Treatment Status	Philadelphia Chromosome–Positive Leukemia (N=65)					AML (N=12)	Other Diagnoses† (N=4)
	Total Ph-Positive (N=65)	Chronic-Phase CML (N=43)	Accelerated-Phase CML (N=9)	Blast-Phase CML (N=8)	Ph-Positive ALL (N=5)		
	number (percent)						
Received treatment	65 (100)	43 (100)	9 (100)	8 (100)	5 (100)	12 (100)	4 (100)
Continued to receive treatment at time of analysis	35 (54)	33 (77)	2 (22)	0	0	0	0
Discontinued treatment‡	30 (46)	10 (23)	7 (78)	8 (100)	5 (100)	12 (100)	4 (100)
Documented progressive disease	10 (15)	3 (7)	1 (11)	5 (62)	1 (20)	2 (17)	2 (50)
Adverse event	9 (14)	5 (12)	3 (33)	0	1 (20)	3 (25)	1 (25)
Death§	3 (5)	0	1 (11)	1 (12)	1 (20)	5 (42)	0
Withdrawal of consent	2 (3)	1 (2)	1 (11)	0	0	0	0
Administrative decision	6 (9)	1 (2)	1 (11)	2 (25)	2 (40)	2 (17)	1 (25)

* ALL denotes acute lymphoblastic leukemia, AML acute myeloid leukemia, CML chronic myeloid leukemia, and Ph Philadelphia chromosome.
† Other diagnoses included one patient with the myelodysplastic syndrome, one with multiple myeloma, and two with myelofibrosis.
‡ The primary reasons for discontinuation are listed for patients who received at least one dose of ponatinib.
§ Of the 81 patients, 17 (21%) died within 30 days after the last ponatinib dose. Of these patients, 8 were categorized as having had treatment discontinued because of death. Of all deaths, 9 occurred more than 7 days after the last dose was administered. All deaths were deemed to be unrelated to ponatinib by the investigators. Seven of the deaths were due to progressive disease. Among the 17 deceased patients, 3 had Ph-positive ALL, 7 had AML, and 6 of the 7 patients with CML were in advanced phases of disease.

kinase 3 (FLT3) (Appendix G in the Supplementary Appendix).[32,33] Data from these patients are not included in this report. The remaining 65 patients had Ph-positive disease: 43 with chronic-phase CML, 9 with accelerated-phase CML, 8 with blast-phase CML, and 5 with ALL. The characteristics of the patients with Ph-positive disease are presented in Table 2. Median follow-up for Ph-positive patients at the time of analysis was 66 weeks (range, 2 to 140).

SAFETY PROFILE

Seven dose levels were investigated: 2 mg (in 3 patients), 4 mg (in 6 patients), 8 mg (in 7 patients), 15 mg (in 8 patients), 30 mg (in 7 patients), 45 mg (in 31 patients), and 60 mg (in 19 patients). No dose-limiting toxic effects were observed in cohorts receiving up to 30 mg. At 45 mg, grade 3 rash constituting a dose-limiting toxicity was reported in a patient with chronic-phase CML. At 60 mg, dose-limiting toxic effects were reported in 6 patients in two separate cohorts. An elevation in pancreatic enzymes (amylase, lipase, or both) and clinical pancreatitis were reported in 4 patients. In addition, grade 3 fatigue (in a patient with chronic-phase CML) and grade 3 elevated levels of alanine aminotransferase and aspartate aminotransferase (in a patient with Ph-positive ALL) were observed.

The most common nonhematologic, treatment-related adverse events were skin disorders (e.g., rash, acneiform dermatitis, and dry skin) and constitutional symptoms (e.g., arthralgia, fatigue, and nausea), most of which were grade 1 or 2 (Table 3, and Table S2 in the Supplementary Appendix) and were managed with or without dose modification.

Pancreatitis occurred in 11 patients and was a serious adverse event in 8 patients (Table 3, and Table S3 in the Supplementary Appendix). Elevated levels of lipase or amylase without pancreatitis occurred in 7 additional patients. The onset of these symptoms was dose-related with regard to both incidence and timing. The median time to the first event of pancreatitis, elevated lipase, or elevated amylase was 22 days at a dose of 30 mg (in 5 patients), 40 days at a dose of 45 mg (in 8 patients), and 6.5 days at a dose of 60 mg (in 4 patients). One event occurred 15 days after a

patient started ponatinib at a dose of 8 mg. Most patients (9 of 11) had a single episode of pancreatitis (with 2 patients having 3 events each). Some patients had risk factors of previous pancreatitis (in 1 patient), alcohol use (in 3 patients), or diabetes (in 3 patients). None of the episodes of pancreatitis occurred in conjunction with liver-function abnormalities. Most events were self-limited; pancreatitis resolved in a median of 6 days in 13 of 15 events, and 2 events were ongoing at the time of this analysis. Rechallenge was generally successful, although 2 patients permanently discontinued ponatinib as a result of pancreatitis, and 1 patient permanently discontinued the drug as a result of an increased lipase level.

Treatment-related myelosuppression, mostly of grade 3 or 4, was common (Table 3) but was also frequently present at baseline, particularly in patients with accelerated- or blast-phase CML and Ph-positive ALL. In the 43 patients with chronic-phase CML, treatment-related thrombocytopenia of grade 3 or more occurred in 12 patients (28%), neutropenia in 6 patients (14%), and anemia in 1 patient (2%).

Table 2. Demographic and Clinical Characteristics of the Ph-Positive Patients at Baseline.*

Characteristic	Total Ph-Positive (N=65)	Chronic-Phase CML (N=43)	Accelerated-Phase CML (N=9)	Blast-Phase CML (N=8)	Ph-Positive ALL (N=5)
Age					
Median (range) — yr	55 (26–85)	55 (27–85)	61 (42–77)	51 (26–73)	36 (27–67)
≥65 yr — no. (%)	22 (34)	15 (35)	4 (44)	2 (25)	1 (20)
Sex — no. (%)					
Male	37 (57)	21 (49)	6 (67)	5 (62)	5 (100)
Female	28 (43)	22 (51)	3 (33)	3 (38)	0
ECOG performance status — no. (%)					
0	26 (40)	19 (44)	2 (22)	4 (50)	1 (20)
1	32 (49)	22 (51)	7 (78)	1 (12)	2 (40)
2	7 (11)	2 (5)	0	3 (38)	2 (40)
Median time from diagnosis to treatment (range) — yr	6.5 (0.8–23.5)	6.6 (0.8–23.5)	6.7 (2.7–16.2)	6.5 (1.6–19.8)	1.2 (0.8–1.9)
Hematologic analysis					
Median white-cell count (range) — $\times 10^{-3}$/mm^3	7.1 (0.2–212.7)	5.8 (0.6–65.2)	27.9 (1.6–212.7)	9.5 (1.5–36.9)	14.9 (0.2–92.7)
Median platelet count (range) — $\times 10^{-3}$/mm^3	188.5 (7–1400)	217.5 (28–900)	224.0 (28–1400)	22.0 (13–172)	14.0 (7–71)
Previous use of tyrosine kinase inhibitor — no. (%)					
≥2 drugs	61 (94)	42 (98)	9 (100)	8 (100)	2 (40)
≥3 drugs	41 (63)	27 (63)	8 (89)	6 (75)	0
Approved tyrosine kinase inhibitor					
Imatinib	63 (97)	43 (100)	9 (100)	8 (100)	3 (60)
Dasatinib	58 (89)	37 (86)	9 (100)	8 (100)	4 (80)
Nilotinib	36 (55)	24 (56)	7 (78)	5 (62)	0
Imatinib plus dasatinib or nilotinib	26 (40)	19 (44)	2 (22)	3 (38)	2 (40)
Imatinib plus dasatinib plus nilotinib	33 (51)	21 (49)	7 (78)	5 (62)	0
Other tyrosine kinase inhibitor					
XL-228	7 (11)	4 (9)	2 (22)	1 (12)	0
Bosutinib	6 (9)	5 (12)	1 (11)	0	0
MK-0457	3 (5)	1 (2)	1 (11)	1 (12)	0
INNO-406	2 (3)	1 (2)	1 (11)	0	0

Table 2. (Continued.)

Characteristic	Total Ph-Positive (N=65)	Chronic-Phase CML (N=43)	Accelerated-Phase CML (N=9)	Blast-Phase CML (N=8)	Ph-Positive ALL (N=5)
Other previous therapy — no. (%)					
Omacetaxine	11 (17)	7 (16)	3 (33)	1 (12)	0
Stem-cell transplantation	3 (5)	1 (2)	0	1 (12)	1 (20)
BCR-ABL mutation status — no. (%)					
No sequencing data	5 (8)	3 (7)	1 (11)	1 (12)	0
No mutations	18 (28)	13 (30)	4 (44)	1 (12)	0
≥1 mutation	42 (65)	27 (63)	4 (44)	6 (75)	5 (100)
2 mutations	5 (8)	3 (7)	1 (11)	1 (12)	0
Baseline mutation — no. (%)†					
T315I	19 (29)‡	12 (28)	1 (11)	2 (25)	4 (80)
F317L	7 (11)	5 (12)	1 (11)	1 (12)	0
G250E	4 (6)	4 (9)	0	0	0
F359V	2 (3)	1 (2)	1 (11)	0	0
H396R	2 (3)	1 (2)	0	1 (12)	0
M244V	2 (3)	2 (5)	0	0	0
M351T	2 (3)	2 (5)	0	0	0

* ECOG denotes Eastern Cooperative Oncology Group.
† These mutations occurred in at least 2% of Ph-positive patients. Patients may have had more than one mutation.
‡ A total of 27 patients entered the study with a history of having tested positive for the T315I mutation; of these patients, positivity was confirmed in 19 at baseline by centralized testing.

PHARMACOKINETICS

The relationships between the dose of ponatinib and both peak blood concentration and area under the curve (AUC) for each dose level on days 1 and 29 were approximately proportional to the dose. The half-life was approximately 22 hours for doses of 30 mg or more, suggesting that steady state may be achieved around day 7. There was an accumulation by a factor of 1.5 to 2.0 after repeated administration of ponatinib. At doses of 30 mg or more, trough blood concentrations surpassed the 40 nM concentration that was found to completely suppress the emergence of BCR-ABL mutations in preclinical studies (Fig. 1C, and Table S1 in the Supplementary Appendix).[20,21]

PHARMACODYNAMICS

Among the 43 Ph-positive patients who could be evaluated for pharmacodynamics assessment, a reduction of 50% or more in CRKL phosphorylation, a surrogate for BCR-ABL inhibition,[34] was observed in 4 of 6 patients (67%) receiving 8 mg of ponatinib. At doses of 15 mg or more, 32 of 34 patients (94%) had a reduction of 50% or more in CRKL phosphorylation, including 8 of 10 patients (80%) with the T315I mutation (Fig. 1D, and Appendix E in the Supplementary Appendix).

RECOMMENDED DOSE FOR FURTHER STUDY

On the basis of safety, pharmacokinetic, and pharmacodynamic data, 45 mg of ponatinib was determined to be the maximum tolerated dose. This dose was selected as the recommended dose for further clinical study.

PREVIOUS THERAPY AND MUTATION STATUS

In all Ph-positive patients, the disease was relapsed or resistant to approved tyrosine kinase inhibitors (imatinib, dasatinib, or nilotinib). Ninety-one percent of Ph-positive patients had received two or more approved tyrosine kinase inhibitors: 40% had received imatinib followed by dasatinib or nilotinib, and 51% had received imatinib followed by both dasatinib and nilotinib (Table 2).

At study entry, 42 of 65 patients (65%) carried at least one BCR-ABL kinase domain mutation; the most frequent mutation was T315I (in 19 patients, or 29%) (Table 2, and Table S4 in the Supplementary Appendix).

ANTILEUKEMIA ACTIVITY

Overall Group

Among 43 patients with chronic-phase CML, 42 (98%) had a complete hematologic response, 31 (72%) had a major cytogenetic response, and 27 (63%) had a complete cytogenetic response (Table 4, and Tables S4 and S5 in the Supplementary Appendix). Among patients who had a response, the median time until a major cytogenetic response was 12 weeks (range, 8 to 72), and the duration ranged from 8 to 117 or more weeks (median duration not reached). The rate of a major cytogenetic response to ponatinib was higher for patients in whom CML had been diagnosed within the past 5 years than in those with a longer disease history (86% for 14 patients with 0 to 5 years since diagnosis vs. 53% for 15 patients with 9 to 24 years since diagnosis), although the difference was not significant (P=0.11). At the time of analysis, 29 of 31 patients with chronic-phase CML who had a major cytogenetic response continued to participate in the study. One patient who was receiving a dose of 4 mg discontinued ponatinib because of disease progression, and 1 patient who was receiving a 30-mg dose and had a major cytogenetic response discontinued therapy because of an adverse event (congestive heart failure) while in complete cytogenetic response. It was estimated that 89% of patients with chronic-phase CML who had a major cytogenetic response would remain in response at 1 year (95% confidence interval [CI], 69 to 96 by Kaplan–Meier analysis).

Table 3. Most Frequent Treatment-Related Adverse Events.*

Treatment-Related Adverse Events	Total Study Population (N=81)		
	Any Grade	Grade ≥3	Serious
	number of patients (percent)		
Nonhematologic event			
Rash†	26 (32)	1 (1)	0
Arthralgia	14 (17)	1 (1)	0
Increased lipase	12 (15)‡	6 (7)	0
Fatigue	11 (14)	1 (1)	0
Acneiform dermatitis	11 (14)	1 (1)	0
Dry skin	11 (14)	0	0
Nausea	11 (14)	0	0
Headache	10 (12)	0	0
Hypertriglyceridemia	10 (12)	0	0
Myalgia	10 (12)	0	0
Pancreatitis§	11 (14)	4 (5)	8 (10)
Abdominal pain	8 (10)	1 (1)	0
Increased alanine aminotransferase	8 (10)	1 (1)	0
Increased aspartate aminotransferase	7 (9)	1 (1)	0
Abdominal distention	3 (4)	1 (1)	0
Increased amylase	3 (4)	2 (2)	0
Chills	3 (4)	1 (1)	0
Dyspnea	3 (4)	1 (1)	0
Prolonged QT interval	3 (4)	2 (2)	1 (1)
Erythema nodosum	2 (2)	1 (1)	0
Increased creatine kinase	1 (1)	1 (1)	0

Table 3. (Continued.)

Treatment-Related Adverse Events	Total Study Population (N=81)		
	Any Grade	Grade ≥3	Serious
	number of patients (percent)		
Congestive cardiac failure	1 (1)	1 (1)	1 (1)
Decreased ejection fraction	1 (1)	1 (1)	1 (1)
Fluid retention	1 (1)	1 (1)	0
Interstitial lung disease	1 (1)	1 (1)	1 (1)
Melanoma	1 (1)	1 (1)	0
Migraine	1 (1)	1 (1)	0
Pain	1 (1)	1 (1)	0
Accidental overdose	1 (1)	0	1 (1)
Cardiomyopathy	1 (1)	0	1 (1)
Hematologic event			
Thrombocytopenia	22 (27)	16 (20)	1 (1)
Neutropenia	10 (12)	8 (10)	0
Anemia	8 (10)	2 (2)	0
Lymphopenia	3 (4)	1 (1)	0
Decreased white-cell count	3 (4)	1 (1)	0

* Treatment-related adverse events were defined as events that investigators deemed to have a possible, probable, or definite relationship to ponatinib. Details on how relatedness was determined are provided in Appendix B in the Supplementary Appendix. Listed are treatment-related adverse events that were reported in at least 10% of patients, along with any incidence of events of grade 3 or higher or of events that were serious.
† Rash includes erythematous and papular rash.
‡ A grade 1 increase in the lipase level that was deemed probably not related to ponatinib occurred in one additional patient.
§ Included in this category is one patient who had three events of pancreatitis (all grade 2; all serious) that were deemed to be either not related or probably not related to ponatinib. One event was changed to grade 3 and possibly related to ponatinib after the database cutoff.

Among patients with chronic-phase CML, 19 (44%) had a major molecular response, including 9 (21%) who had a deeper molecular response, which was defined as at least a 4-log reduction, or a transcript ratio of BCR-ABL to ABL of 0.01% or less (with the ratio expressed as a percentage on the International Scale). The molecular response was related to dose (Fig. 1E). Fifteen patients were having an ongoing major molecular response at the time of this analysis, and 4 patients no longer had a major molecular response but continued to have a complete cytogenetic response. Among patients with a major molecular response, the median time to the response was 16 weeks (range, 8 to 97), and the duration ranged from 12 to 105 or more weeks (median not reached). Patients with a more recent diagnosis had increased rates of major molecular response: 79% for 14 patients with 0 to 5 years since diagnosis vs. 29% for 14 patients with more than 5 to 9 years since diagnosis ($P=0.02$) and 27% for 15 patients with more than 9 to 24 years since diagnosis ($P=0.009$). It was estimated that 82% of patients with chronic-phase CML who had a major molecular response would remain in response at 1 year (95% CI, 54 to 94 by Kaplan–Meier analysis).

Among the 19 patients with chronic-phase CML who were resistant to imatinib followed by either dasatinib or nilotinib, 17 (89%) had a major cytogenetic response, 15 (79%) had a complete cytogenetic response, and 13 (68%) had a major molecular response. Among the 21 patients with resistance to imatinib, dasatinib, and nilotinib, 12 (57%) had a major cytogenetic response, 10 (48%) had a complete cytogenetic response, and 5 (24%) had a major molecular response (Tables S4 and S5 in the Supplementary Appendix).

Table 4. Response to Ponatinib Treatment.*

Variable	Chronic-Phase CML (N=43)				Accelerated-Phase CML, Blast-Phase CML, and Ph-Positive ALL (N=22)			
	All Patients (N=43)†	T315I Mutation (N=12)	Other Mutation (N=15)	No Mutation (N=13)	All Patients (N=22)‡	T315I Mutation (N=7)	Other Mutation (N=8)	No Mutation (N=5)
Median follow-up (range) — wk	73 (7–140)				13 (2–121)			
Patients remaining in the study — no. (%)	33 (77)				2 (9)§			
Complete hematologic response — no. (%)	42 (98)¶	12 (100)	14 (93)	13 (100)	NA	NA	NA	NA
Major hematologic response — no. (%)	NA	NA	NA	NA	8 (36)	2 (29)	2 (25)	3 (60)
Major cytogenetic response — no. (%)	31 (72)‖	11 (92)	10 (67)	8 (62)	7 (32)	2 (29)	3 (38)	2 (40)
Complete cytogenetic response	27 (63)	9 (75)	10 (67)	6 (46)	3 (14)	1 (14)	0	2 (40)
Partial cytogenetic response	4 (9)	2 (17)	0	2 (15)	4 (18)	1 (14)	3 (38)	0
Major molecular response — no. (%)**	19 (44)	8 (67)	8 (53)	2 (15)	2 (9)	2 (29)	0	0
Molecular response 4	9 (21)	3 (25)	6 (40)	0	0	0	0	0
Molecular response 4.5	3 (7)	0	3 (20)	0	0	0	0	0

* NA denotes not applicable.
† Sequencing data were not available for three patients with chronic-phase CML; all three had a complete hematologic response, two had a major cytogenetic response (both complete), and one had a major molecular response.
‡ Sequencing data were not available for one patient with accelerated-phase CML and one patient with blast-phase CML; the former patient had a major hematologic response.
§ These two patients had accelerated-phase CML.
¶ Of these patients, 26 had a complete hematologic response at baseline, and all 26 remained in complete hematologic response during the study.
‖ At baseline, one patient had a complete hematologic response and a molecular relapse. This patient had a major molecular response during the study. Eight patients had a partial cytogenetic response at entry; of these patients, seven had a complete cytogenetic response during the study, and one maintained a partial cytogenetic response.
** Molecular response 4 was defined as at least a 4-log reduction, or a transcript ratio of BCR-ABL to ABL of 0.01% or less (expressed as a percentage on the International Scale) in peripheral blood, as measured on quantitative reverse-transcriptase–polymerase-chain-reaction assay. Molecular response 4.5 indicates that the ratio is 0.0032% or less. (Details are provided in Appendix F in the Supplementary Appendix.)

Of the 22 patients with advanced disease, 8 (36%) had a major hematologic response, 7 (32%) had a major cytogenetic response, and 2 (9%) had a major molecular response (Table 4). Among patients with a major hematologic response, the median time to response was 8 weeks (range, 2 to 92), and the duration ranged from 0.1 to 64 weeks (median, 16). It was estimated that 44% of patients with advanced disease who had a major hematologic response would remain in response at 1 year (95% CI, 7 to 79 by Kaplan–Meier analysis).

According to Baseline Mutational Status

All 12 patients with chronic-phase CML who had the T315I mutation had a complete hematologic response (100%), 11 (92%) had a major cytogenetic response, 9 (75%) had a complete cytogenetic response, and 8 (67%) had a major molecular response (Table 4). All patients with chronic-phase CML who had the T315I mutation remained in the study at the time of the analysis. Among patients with a major cytogenetic response, the median time to response was 12 weeks (range, 9 to 40), and the duration ranged from 8 to 117 or more weeks. It was estimated that 91% of patients with chronic-phase CML and the T315I mutation who had a major cytogenetic response would remain in response at 1 year (95% CI, 51 to 99 by Kaplan–Meier analysis). Of the 8 patients with a major molecular response, 6 were ongoing at the time of the analysis. Among patients with a major molecular response, the median time to response was 24 weeks (range, 8 to 97), and the duration ranged from 12 to 88 or more weeks. Of 7 patients with advanced disease who had the T315I mutation, 2 (29%) each had a major hematologic response, a major cytogenetic response, and a major molecular response.

Among the 15 patients with chronic-phase CML who were carrying a non-T315I mutation at baseline, 14 (93%) had a complete hematologic response, 10 (67%) had a major cytogenetic response (all with a complete cytogenetic response), and 8 (53%) had a major molecular response (Table 4, and Tables S4 and S5 in the Supplementary Appendix). Of the 13 patients with chronic-phase CML who had no detectable mutations, 13 (100%) had a complete hematologic response, 8 (62%) had a major cytogenetic response, and 2 (15%) had a major molecular response (Table 4, and Tables S4 and S5 in the Supplementary Appendix).

DISCUSSION

In this study, ponatinib showed significant clinical activity in a heavily pretreated population of patients with Ph-positive leukemias that were resistant to, or had relapsed during receipt of, currently available tyrosine kinase inhibitors. The most common treatment-related adverse events were skin disorders and constitutional symptoms, which were generally low-grade in severity and were manageable. Dose-limiting toxic effects included pancreatic events, with pancreatitis observed in 14% of patients. Myelosuppression, an expected adverse event in this heavily pretreated population, was also common. Among patients with chronic-phase CML, 93% had been treated with two or more approved tyrosine kinase inhibitors, and 49% had received all three approved tyrosine kinase inhibitors. The observed rate of major cytogenetic response in this group was 72%, the rate of complete cytogenetic response was 63%, and the rate of major molecular response was 44%. Clinically meaningful responses were also observed in patients with advanced disease. These findings identify ponatinib as a highly active agent for patients with CML who have shown resistance to multiple tyrosine kinase inhibitors.

Mutations in the BCR-ABL kinase domain that confer resistance to tyrosine kinase inhibitors have been shown to be responsible for 30 to 40% of resistance to imatinib.[35] Such mutations have been found to increase in frequency with the duration of exposure to tyrosine kinase inhibitors[13] and have been associated with an adverse prognosis.[11,36] Dasatinib and nilotinib are active against a number of imatinib-resistant mutants but are ineffective against subsets of mutants.[19,37] Imatinib, dasatinib, and nilotinib are all ineffective against the T315I mutant, a common mutation.[19,37] In addition, therapy with tyrosine kinase inhibitors fails in some patients who carry mutants that are sensitive to these drugs.[38] Moreover, mutations are undetectable in a substantial proportion of patients with imatinib failure.[39] In many of these patients, mechanisms of resistance that are not associated with BCR-ABL may be operative,[35,37] although this is poorly understood.

In our study, we found that ponatinib had activity in all of the following situations: against a spectrum of mutants in patients in whom previous therapy had failed, against the T315I mutant, and against disease that had been refrac-

tory to therapy with multiple tyrosine kinase inhibitors in the absence of detectable BCR-ABL mutations. The majority of patients with chronic-phase CML with non-T315I mutations had a complete cytogenetic response and a major molecular response. Similarly high rates of cytogenetic response were observed in patients with chronic-phase CML with the T315I mutation and in those with no detectable kinase domain mutations. Responses have been durable, with the median duration of response in patients with chronic-phase CML yet to be reached at the time of this analysis but exceeding 1 year. These data compare favorably with data regarding second-generation tyrosine kinase inhibitors that were used after imatinib failure (rate of major cytogenetic response, 35 to 63%)[7-10,40] or after the failure of two drugs (rate of major cytogenetic response, 32 to 50%).[41-44]

Ponatinib was rationally developed to address the limitations of currently available CML-directed tyrosine kinase inhibitors. It was designed for high-affinity, optimized binding to the active site of BCR-ABL, with an emphasis on very high potency and the ability to overcome BCR-ABL mutation-based resistance. Blood levels that occurred at the recommended dose in this study were above the threshold defined in preclinical cell-based mutagenesis assays as uniformly preventing the development of resistant clones (40 nM)[20] and were associated with high rates of cytogenetic and molecular responses. The high potency and relatively long half-life of ponatinib may contribute to its activity in this patient population. Ponatinib has also been shown to inhibit the activity of other clinically relevant kinases with 50% inhibitory concentrations of less than 20 nM and has shown cellular activity against RET, FLT3, KIT, and members of the FGFR and PDGFR families of kinases.[32,45,46]

In conclusion, once-daily ponatinib is a pan–BCR-ABL inhibitor with substantial and durable clinical activity in patients with Ph-positive leukemias with resistance to tyrosine kinase inhibitors.

Supported by Ariad Pharmaceuticals and by a grant (CA016672) to M.D. Anderson Cancer Center from the National Institutes of Health. Drs. Shah and Deininger are Scholars in Clinical Research of the Leukemia and Lymphoma Society.

Dr. Cortes reports receiving consulting fees from Ariad Pharmaceuticals, Novartis, Bristol-Myers Squibb, Pfizer, and Chemgenex and grant support (or grants pending) paid to his institution from Ariad Pharmaceuticals, Novartis, Bristol-Myers Squibb, Pfizer, Chemgenex, Deciphera, and Incyte; Dr. Kantarjian, receiving grant support (or grants pending) paid to his institution from Novartis and Bristol-Myers Squibb; Dr. Shah, receiving consulting fees from Bristol-Myers Squibb and Novartis and grant support (or grants pending) paid to his institution from Bristol-Myers Squibb, Ambit, and Plexxikon; Dr. Mauro, receiving consulting fees and lecture fees from Bristol-Myers Squibb, Novartis Oncology, and Pfizer; Drs. Hu, Narasimhan, Rivera, Clackson, Turner, and Haluska, being employees of and having an equity interest in Ariad Pharmaceuticals; Dr. Druker, serving on advisory boards for MolecularMD, Blueprint Medicines, Ambit Biosciences, Cylene Pharmaceuticals, Gilead Sciences, Hoffmann–La Roche, and Calistoga, receiving consulting fees from MolecularMD, Blueprint Medicines, Cylene Pharmaceuticals, Gilead Sciences, Millennium Pharmaceuticals, and Calistoga and grant support (or grants pending) paid to his institution from Novartis and Bristol-Myers Squibb, receiving royalties on patents (Mutated ABL Kinase Domains #0843 and Detection of Gleevec Resistant Mutations #0996) and from licensing monoclonal antiphosphotyrosine antibody 4G10 to Millipore, and having an equity interest in Blueprint Medicines and MolecularMD (technology used in this study has been licensed to MolecularMD, a potential conflict of interest that has been reviewed and managed by the Conflict of Interest in Research Committee and the Integrity Program Oversight Council at the Oregon Health and Science University); Dr. Deininger, serving as a board member for and receiving consulting fees from Bristol-Myers Squibb, Novartis, and Ariad Pharmaceuticals and receiving grant support (or grants pending) paid to his institution from Bristol-Myers Squibb, Celgene, and Genzyme; and Dr. Talpaz, receiving consulting fees from Ariad Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients and their caregivers for their participation in the trial; the members of the Ponatinib Phase 1 Study Team (Ariad); Ruth O'Halloran, Ph.D., and Holly Maier, Ph.D., of Ariad Pharmaceuticals for medical-writing assistance; and Anna Kohlmann, Ph.D., Xiaotian Zhu, Ph.D., and David C. Dalgarno, Ph.D., of Ariad Pharmaceuticals for their assistance in the preparation of earlier versions of the figures.

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