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J. DiPersio
Washington University School of Medicine in St. Louis

et al

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A Phase 2 Trial of Ponatinib in Philadelphia Chromosome–Positive Leukemias

J.E. Cortes, D.-W. Kim, J. Pinilla-Ibarz, P. le Coutre, R. Paquette, C. Chuah, F.E. Nicolini, J.F. Apperley, H.J. Khoury, M. Talpaz, J. DiPersio, D.J. DeAngelo, E. Abruzzese, D. Rea, M. Baccarani, M.C. Müller, C. Gambacorti-Passerini, S. Wong, S. Lustgarten, V.M. Rivera, T. Clackson, C.D. Turner, F.G. Haluska, F. Guilhot, M.W. Deininger, A. Hochhaus, T. Hughes, J.M. Goldman, N.P. Shah, and H. Kantarjian, for the PACE Investigators*

ABSTRACT

BACKGROUND

Ponatinib is a potent oral tyrosine kinase inhibitor of unmutated and mutated BCR-ABL, including BCR-ABL with the tyrosine kinase inhibitor–refractory threonine-to-isoleucine mutation at position 315 (T315I). We conducted a phase 2 trial of ponatinib in patients with chronic myeloid leukemia (CML) or Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph-positive ALL).

METHODS

We enrolled 449 heavily pretreated patients who had CML or Ph-positive ALL with resistance to or unacceptable side effects from dasatinib or nilotinib or who had the BCR-ABL T315I mutation. Ponatinib was administered at an initial dose of 45 mg once daily. The median follow-up was 15 months.

RESULTS

Among 267 patients with chronic-phase CML, 56% had a major cytogenetic response (51% of patients with resistance to or unacceptable side effects from dasatinib or nilotinib and 70% of patients with the T315I mutation), 46% had a complete cytogenetic response (40% and 66% in the two subgroups, respectively), and 34% had a major molecular response (27% and 56% in the two subgroups, respectively). Responses were observed regardless of the baseline BCR-ABL kinase domain mutation status and were durable; the estimated rate of a sustained major cytogenetic response of at least 12 months was 91%. No single BCR-ABL mutation conferring resistance to ponatinib was detected. Among 83 patients with accelerated-phase CML, 55% had a major hematologic response and 39% had a major cytogenetic response. Among 62 patients with blast-phase CML, 31% had a major hematologic response and 23% had a major cytogenetic response. Among 32 patients with Ph-positive ALL, 41% had a major hematologic response and 47% had a major cytogenetic response. Common adverse events were thrombocytopenia (in 37% of patients), rash (in 34%), dry skin (in 32%), and abdominal pain (in 22%). Serious arterial thrombotic events were observed in 9% of patients; these events were considered to be treatment-related in 3%. A total of 12% of patients discontinued treatment because of an adverse event.

CONCLUSIONS

Ponatinib had significant antileukemic activity across categories of disease stage and mutation status. (Funded by Ariad Pharmaceuticals and others; PACE ClinicalTrials.gov number, NCT01207440.)

The authors' full names, degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Cortes at the Department of Leukemia, University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, or at jcortes@mdanderson.org.

*A complete list of investigators in the Ponatinib Ph+ ALL and CML Evaluation (PACE) trial is provided in the Supplementary Appendix, available at NEJM.org.

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Patients with newly diagnosed chronic myeloid leukemia (CML) frequently receive imatinib. Although initial response rates are high, imatinib fails in up to 40% of patients because of disease resistance, frequently because of BCR-ABL kinase domain mutations or unacceptable side effects.[1,2] Patients who discontinue imatinib may have a response to second-generation tyrosine kinase inhibitors. However, 37 to 52% of patients do not have a response,[3-8] and 23 to 26% of patients have an initial major cytogenetic response that is lost by 2 years.[3,9] The prognosis for these patients is very poor. With the exception of the small number of patients who are candidates for allogeneic stem-cell transplantation, patients are likely to die from the leukemia.

Ponatinib is a potent oral tyrosine kinase inhibitor that is active against unmutated and mutated BCR-ABL, including the threonine-to-isoleucine mutation at position 315 (T315I), which is present in up to 20% of patients with tyrosine kinase inhibitor–resistant disease and confers resistance to all other approved BCR-ABL tyrosine kinase inhibitors.[10-17] In preclinical experiments, 40 nM of ponatinib (a concentration that can be achieved in patients who receive daily doses of ≥30 mg[18]) suppressed the emergence of any single mutation.[19] In a phase 1 study, ponatinib showed substantial antileukemic activity in patients with Philadelphia chromosome (Ph)–positive disease who had resistance to or unacceptable side effects from previous treatment with tyrosine kinase inhibitors.[18] Here we describe the initial results of the phase 2 PACE (Ponatinib Ph-positive acute lymphoblastic leukemia [ALL] and CML Evaluation) clinical trial of ponatinib in patients who had chronic-phase CML, accelerated-phase CML, blast-phase CML, or Ph-positive ALL with resistance to or unacceptable side effects from dasatinib or nilotinib or with the T315I mutation.

Methods

Study Oversight

The study was developed jointly by the sponsor, Ariad Pharmaceuticals, and the PACE steering committee (see Appendix A in the Supplementary Appendix, available with the full text of this article at NEJM.org). The protocol (available 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 collaboration with the investigators. All the authors contributed to and 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 the authors reviewed, edited, and approved the final manuscript and made the decision to submit the manuscript for publication. Professional medical-writing assistance was provided by the sponsor.

Patients

Patients were eligible if they were at least 18 years of age and had CML or Ph-positive ALL. CML phases were defined according to the criteria described by Talpaz et al.[20] Ph-positive ALL was defined as more than 30% lymphoid blasts in blood or bone marrow at diagnosis and no history of CML. Additional eligibility criteria were resistance to dasatinib or nilotinib (for definitions, see Appendix B in the Supplementary Appendix), unacceptable side effects of these agents, or development of the T315I mutation after any tyrosine kinase inhibitor therapy. Patients had 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 asymptomatic and higher numbers indicate increasing disability), adequate renal and hepatic function, normal pancreatic status, no history of pancreatitis, and a normal QT interval corrected with the use of Fridericia's formula. All patients provided written informed consent.

Study Design and Treatment

This was an open-label, multinational trial involving 66 sites. Patients received an initial dose of 45 mg of ponatinib orally once daily. Patients were grouped into six cohorts (Fig. S1 in the Supplementary Appendix): patients with chronic-phase CML with resistance to or unacceptable side effects of dasatinib or nilotinib, patients with chronic-phase CML and the T315I mutation, patients with accelerated-phase CML with resistance to or unacceptable side effects of dasatinib or nilotinib, patients with accelerated-phase CML and the T315I mutation, patients with blast-phase CML or Ph-positive ALL with resistance to or unacceptable side effects of dasatinib or nilotinib, and patients with blast-phase CML or Ph-

positive ALL with the T315I mutation. Assignment to a T315I cohort required confirmation of T315I by a central laboratory (MolecularMD) at baseline. Treatment was continued until there was evidence of disease progression, an adverse event occurred that was deemed to necessitate treatment cessation, the patient withdrew consent, or the investigator decided to terminate treatment.

END POINTS

The primary end point was a major cytogenetic response at any time within the first 12 months (in patients with chronic-phase CML) and a major hematologic response at any time within the first 6 months (in patients with accelerated-phase CML, blast-phase CML, or Ph-positive ALL). Patients with a partial cytogenetic response at enrollment who then had a complete cytogenetic response were classified as having a major cytogenetic response during the trial. Secondary end points for chronic-phase CML included a complete hematologic response (confirmed ≥28 days after the patient first met the criteria for a complete hematologic response). Secondary end points for accelerated- and blast-phase CML and Ph-positive ALL included a complete or partial cytogenetic response and a confirmed major cytogenetic response. Secondary end points for all diagnoses included a major molecular response, the time to the response, the duration of the response, progression-free survival, overall survival, and safety. End-point definitions and response criteria are described in Appendixes B and C, respectively, in the Supplementary Appendix.

ASSESSMENTS OF EFFICACY AND SAFETY

Response assessments were performed every 3 months (in patients with chronic-phase CML) or at the end of cycle 1 (for a hematologic and cytogenetic response only; 1 cycle was 28 days), cycle 2, and every 2 months thereafter (in patients with accelerated-phase CML, blast-phase CML, or Ph-positive ALL). Molecular response and mutations were assessed by a central laboratory with the use of Sanger sequencing (Appendix B in the Supplementary Appendix).

We assessed adverse events continuously and graded them according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). Laboratory evaluations occurred weekly during cycle 1, every other week during cycles 2 and 3, and monthly thereafter.

STATISTICAL ANALYSIS

The efficacy population included all 444 patients who were assigned to a cohort. The safety population included all 449 patients who received 1 or more doses of ponatinib. The planned sample sizes for the cohorts were estimated to rule out prespecified null response rates with the use of 95% confidence intervals as specified in Appendix B in the Supplementary Appendix. Two-sided, exact 95% confidence intervals were calculated for rates of a major cytogenetic response, major hematologic response, complete hematologic response, and major molecular response. The duration of response, progression-free survival, and overall survival were estimated with the use of the Kaplan–Meier method. Fisher's exact test was used for subgroup comparisons.

RESULTS

PATIENTS

From September 2010 to October 2011, we enrolled 449 patients: 203 with chronic-phase CML and resistance to or unacceptable side effects of dasatinib or nilotinib and 64 with chronic-phase CML and the T315I mutation, 65 with accelerated-phase CML and resistance to or unacceptable side effects of dasatinib or nilotinib and 18 with accelerated-phase CML and the T315I mutation, and 48 with blast-phase CML or Ph-positive ALL and resistance to or unacceptable side effects of dasatinib or nilotinib and 46 with blast-phase CML or Ph-positive ALL and the T315I mutation. Five patients (3 with chronic-phase CML and 2 with accelerated-phase CML) who had a history of the T315I mutation were enrolled and treated but were not assigned to a cohort because the T315I mutation was not confirmed at baseline and the patients had not received nilotinib or dasatinib; these patients were excluded from the efficacy population.

Demographic and baseline characteristics of the patients are summarized in Table 1, and in Table S1 in the Supplementary Appendix. Thirty-seven percent of the patients had received two tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib, or bosutinib), and 55% had received three or more. Other previous therapies included cytarabine (in 23%) and interferon alfa (in 34%).

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Chronic-Phase CML (N=270)	Accelerated- Phase CML (N=85)	Blast-Phase CML (N=62)	Ph-Positive ALL (N=32)	Total (N=449)
Age					
Median (range) — yr	60 (18–94)	60 (23–82)	53 (18–74)	62 (20–80)	59 (18–94)
≥65 yr — no. (%)	101 (37)	27 (32)	14 (23)	13 (41)	155 (35)
Previous use of tyrosine kinase inhibitors — no. (%)†					
≥2 drugs	252 (93)	80 (94)	59 (95)	26 (81)	417 (93)
≥3 drugs	161 (60)	51 (60)	37 (60)	13 (41)	262 (58)
No. of previous approved tyrosine kinase inhibitors — no. (%)					
1	19 (7)	5 (6)	3 (5)	6 (19)	33 (7)
2	98 (36)	33 (39)	22 (35)	14 (44)	167 (37)
3	141 (52)	44 (52)	34 (55)	12 (38)	231 (51)
4	12 (4)	3 (4)	3 (5)	0	18 (4)
Median duration of previous treatment with tyrosine kinase inhibitors (range) — yr†	5.4 (0.4–13.3)	5.1 (0.3–12.1)	2.0 (0.1–11.6)	1.2 (0.1–8.2)	4.6 (0.1–13.3)
Resistance to or unacceptable side effects of dasatinib or nilotinib at any time — no. (%)‡§					
Resistance¶	214 (84)	74 (92)	59 (97)	27 (90)	374 (88)
Unacceptable side effects only‖	40 (16)	6 (8)	2 (3)	2 (7)	50 (12)
Not specified	2 (1)	0	0	1 (3)	3 (1)
Cytogenetic status at enrollment — no. (%)					
Complete cytogenetic response**	0	1 (1)	3 (5)	2 (6)	6 (1)
Partial cytogenetic response††	53 (20)	1 (1)	3 (5)	8 (25)	65 (14)
Less than partial cytogenetic response	215 (80)	80 (94)	51 (82)	20 (62)	366 (82)
Missing or <20 metaphases examined	2 (1)	3 (4)	5 (8)	2 (6)	12 (3)
Best response to most recent regimen containing dasatinib or nilotinib — no. (%)§					

Major hematologic response or better‡‡	NA	17 (21)	9 (15)	13 (43)
Major cytogenetic response or better§§	66 (26)	12 (15)	7 (11)	8 (27)
Major molecular response	8 (3)	2 (2)	1 (2)	5 (17)

* ALL denotes acute lymphoblastic leukemia, CML chronic myeloid leukemia, NA not applicable, and Ph Philadelphia chromosome.
† This category includes approved tyrosine kinase inhibitors (imatinib, nilotinib, dasatinib, and bosutinib) and investigational tyrosine kinase inhibitors. Previous investigational tyrosine kinase inhibitors received by at least 1% of patients included radotinib (in 2% of patients), bafetinib (in 2%), DCC-2036 (in 2%), and XL228 (in 2%).
‡ To be eligible for enrollment, patients with unacceptable side effects had to have active disease (e.g., they could not have a complete cytogenetic response [in patients with chronic-phase CML] or a major hematologic response [in patients with accelerated-phase CML, blast-phase CML, or Ph-positive ALL]).
§ Percentages were calculated according to the number of patients who received previous dasatinib or nilotinib: 256 patients with chronic-phase CML, 80 patients with accelerated-phase CML, 61 patients with blast-phase CML, and 30 patients with Ph-positive ALL.
¶ Patients with resistance to one tyrosine kinase inhibitor and unacceptable side effects of the other were classified as having resistance.
‖ Patients may have had resistance to or unacceptable side effects of tyrosine kinase inhibitors other than nilotinib or dasatinib.
** Patients who had a complete cytogenetic response at study entry were classified as not having a cytogenetic response during the study.
†† Patients who had a partial cytogenetic response at study entry who then had a complete cytogenetic response were considered as having a major cytogenetic response.
‡‡ This category includes a major hematologic response, partial cytogenetic response, complete cytogenetic response, and major molecular response.
§§ This category includes a partial cytogenetic response, complete cytogenetic response, and major molecular response.

Among the 427 patients who had previously received dasatinib or nilotinib, 88% had resistance and 12% had unacceptable side effects. Responses to the most recent nilotinib or dasatinib therapy were generally poor (e.g., among patients with chronic-phase CML, only 26% had had a major cytogenetic response and only 3% had had a major molecular response) (Table 1). Among patients assigned to cohorts with resistance to or unacceptable side effects of these agents, BCR-ABL mutations were undetectable in 67% of patients with chronic-phase CML, 60% of patients with accelerated-phase CML, 45% of patients with blast-phase CML, and 30% of patients with Ph-positive ALL. Two or more mutations were detectable at baseline in 10% of patients with chronic-phase CML, 7% of patients with accelerated-phase CML, 16% of patients with blast-phase CML, and 28% of patients with Ph-positive ALL (Table S2 in the Supplementary Appendix).

At the time of the analysis (November 9, 2012), the median follow-up was 15 months (range, <1 to 25), and 222 patients (49%) were still receiving therapy (minimum follow-up, 12 months) (Table 2). In total, 227 patients (51%) discontinued treatment; most of these patients had advanced disease. The most common reasons for discontinuation were progressive disease (in 7% of patients with chronic-phase CML and in 37% of patients with advanced disease) and adverse events (in 13% of patients with chronic-phase CML and in 12% of patients with advanced disease) (Table 2).

EFFICACY

Chronic-Phase CML

Among patients with chronic-phase CML, 56% (95% confidence interval [CI], 50 to 62) had a major cytogenetic response by 12 months, which was the primary end point (51% of those with resistance to or unacceptable side effects of dasatinib or nilotinib and 70% of those with the T315I mutation). A total of 46% of patients with chronic-phase CML had a complete cytogenetic response (40% of those with resistance to or unacceptable side effects of dasatinib or nilotinib and 66% of those with the T315I mutation), and 34% had a major molecular response (27% of those with resistance to or unacceptable side effects of dasatinib or nilotinib and 56% of those with the T315I mutation). A deeper molecular response (i.e., a transcript ratio of BCR-ABL to ABL of 0.0032%

Table 2. Treatment Status of the Study Patients at the Data Cutoff Point.

Treatment Status	Chronic-Phase CML (N=270)	Accelerated-Phase CML (N=85)	Blast-Phase CML (N=62)	Ph-Positive ALL (N=32)	Total (N=449)
Continued to receive treatment — no. (%)	171 (63)	45 (53)	5 (8)	1 (3)	222 (49)
Discontinued treatment — no. (%)*					
Had progressive disease	20 (7)	18 (21)	31 (50)	17 (53)	86 (19)
Had adverse event†	35 (13)	9 (11)	10 (16)	2 (6)	56 (12)
Died‡	5 (2)	2 (2)	6 (10)	5 (16)	18 (4)
Withdrew consent	14 (5)	0	3 (5)	1 (3)	18 (4)
Had other reasons§	5 (2)	6 (7)	6 (10)	1 (3)	18 (4)
Lack of efficacy	11 (4)	3 (4)	0	4 (12)	18 (4)
Physician's decision	8 (3)	2 (2)	1 (2)	1 (3)	12 (3)
Noncompliance	1 (<1)	0	0	0	1 (<1)
Median follow-up (range) — mo	15 (0.1–25)	16 (3.6–25)	6 (0.1–21)	6 (0.1–19)	15 (0.1–25)

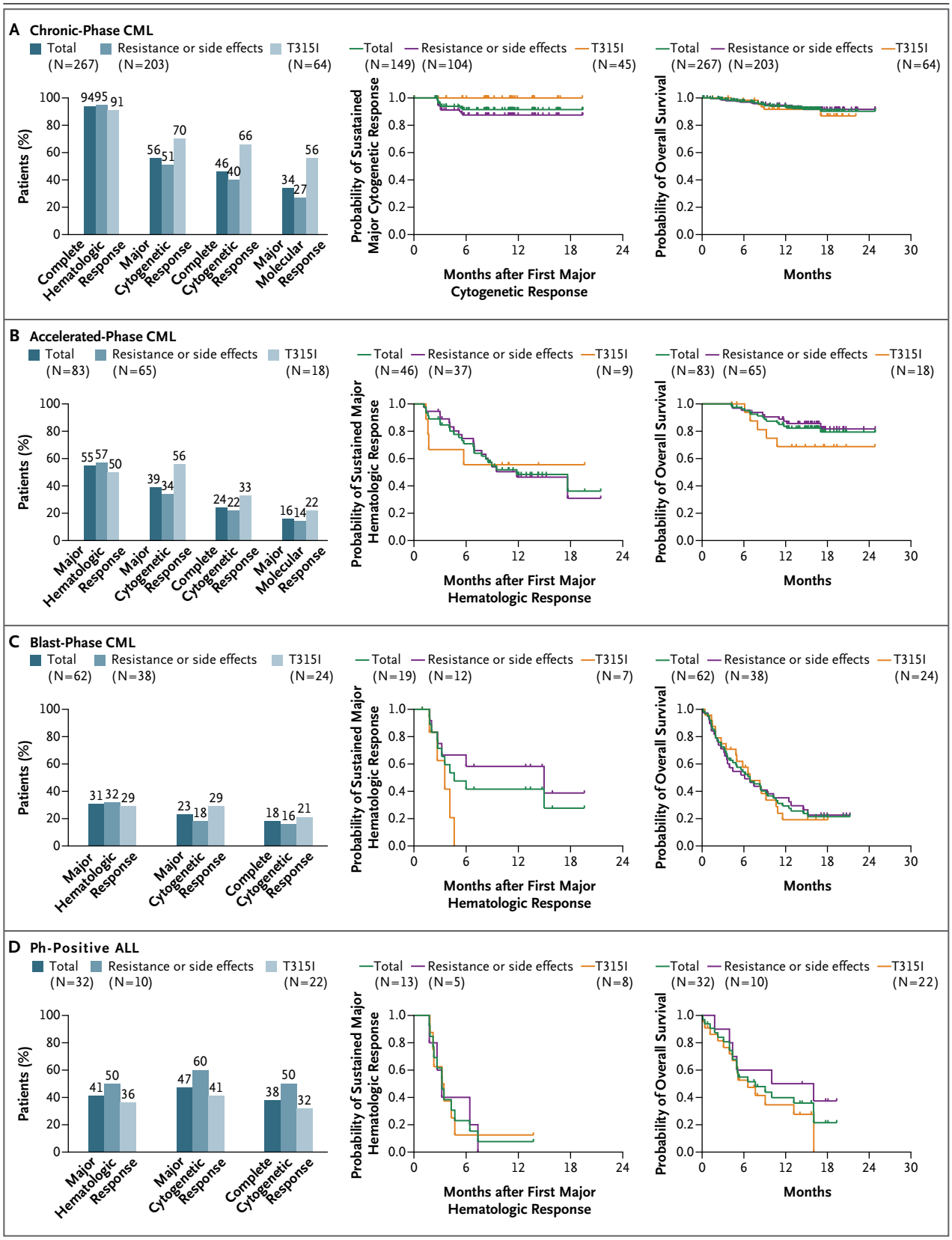
* The primary reasons for discontinuation are listed.
† Adverse events leading to discontinuation in more than 1 patient were thrombocytopenia in 18 patients (4.0%), myelodysplastic syndrome in 2 (0.4%), sepsis in 2 (0.4%), pneumonia in 2 (0.4%), cerebral infarction in 2 (0.4%), and cardiac failure in 2 (0.4%).
‡ Five deaths were assessed by the investigators as being possibly or probably related to ponatinib: one patient with chronic-phase CML had pneumonia and one patient with chronic-phase CML had an acute myocardial infarction, one patient with accelerated-phase CML had fungal pneumonia, one patient with blast-phase CML had a gastric hemorrhage, and one patient with Ph-positive ALL had a cardiac arrest. Other reasons for death were: sepsis or septic shock (in four patients), cardiac arrest (in two patients), congestive cardiac failure (in two patients), cardiopulmonary failure (in one patient), dehydration (in one patient), the hyperviscosity syndrome (in one patient), neoplasm progression (in one patient), and small intestinal obstruction (in one patient).
§ This category includes transplantation (in five patients with chronic-phase CML, five with accelerated-phase CML, six with blast-phase CML, and one with Ph-positive ALL).

or less [with the ratio expressed as a percentage on the International Scale], referred to as a molecular response 4.5) was observed in 15% of patients with chronic-phase CML (12% of those with resistance to or unacceptable side effects of dasatinib or nilotinib and 23% of those with the T315I mutation (Fig. 1A, and Table S3 in the Supplementary Appendix).

The median time to a major cytogenetic response in patients who had a response was 2.8 months (range, 1.6 to 11.3), and the duration ranged from 1 day to 19.4 months or more (the median was not reached). Among patients who had a major cytogenetic response, the estimated rate of a sustained response of at least 12 months was 91% (95% CI, 85 to 95) (Fig. 1A). Rates of

Figure 1 (facing page). Response to Ponatinib According to Type of Leukemia, Resistance to or Unacceptable Side Effects from Previous Treatment with Dasatinib or Nilotinib, and T3151 Mutation Status.

Panel A shows the percentages of patients with chronic-phase CML who had a complete hematologic response, major cytogenetic response, complete cytogenetic response, or major molecular response. It was estimated that 91% (95% confidence interval [CI], 85 to 95) of the patients with a major cytogenetic response would have a sustained response of at least 12 months. Overall survival was estimated to be 94% at 12 months. Panel B shows the percentages of the patients with accelerated-phase CML who had a major hematologic response, major cytogenetic response, complete cytogenetic response, or major molecular response. It was estimated that 48% (95% CI, 32 to 63) of the patients with a major hematologic response would have a sustained response of at least 12 months. Overall survival was estimated to be 84% at 12 months. Panel C shows the percentages of patients with blast-phase CML who had a major hematologic response, major cytogenetic response, or complete cytogenetic response. It was estimated that 42% (95% CI, 19 to 63) of the patients with a major hematologic response would have a sustained response of at least 12 months. Overall survival was estimated to be 29% at 12 months (median, 7 months). Panel D shows the percentages of patients with Ph-positive ALL who had a major hematologic response, major cytogenetic response, or complete cytogenetic response. It was estimated that 8% (95% CI, 0.5 to 29) of the patients with a major hematologic response would have a sustained response of at least 12 months. Overall survival was estimated to be 40% at 12 months (median, 8 months).



progression-free and overall survival (Fig. 1A) were estimated to be 80% and 94%, respectively, at 12 months. Three patients with chronic-phase CML had progression to accelerated-phase CML or blast-phase CML; accelerated-phase CML developed in two additional patients with a history of this condition.

Prespecified subgroup analyses were conducted to evaluate the effect of clinical factors on response rates. Patients who received fewer previous tyrosine kinase inhibitors, were younger, and had a shorter interval between diagnosis and enrollment in the study tended to have higher response rates (Table 3, and Table S4 in the Supplementary Appendix). Despite the higher response rates observed in the T315I cohorts as compared with the cohorts with resistance to or unacceptable side effects of dasatinib or nilotinib, a post hoc multivariate analysis indicated that T315I was not a significant predictor of a major cytogenetic response. Other features, especially higher dose intensity and younger age in patients with the T315I mutation (Table S5 in the Supplementary Appendix), explain the higher response rates.[21] High response rates were observed among patients with chronic-phase CML regardless of mutation status (Table S6 in the Supplementary Appendix), and responses were observed for each of the 15 mutations present in more than one patient at baseline (Table S7 in the Supplementary Appendix). At the time of the analysis, six patients had an unsustained major cytogenetic response and discontinued treatment; end-of-treatment samples were available for four of these patients. No change in BCR-ABL mutation status was observed in these patients (Appendix D in the Supplementary Appendix). No single BCR-ABL mutation conferring resistance to ponatinib was observed (Appendix D in the Supplementary Appendix).

Accelerated-Phase CML

Among patients with accelerated-phase CML, 55% (95% CI, 44 to 66) had a major hematologic response by 6 months (the primary end point). A major cytogenetic response was seen in 39%, 24% had a complete cytogenetic response, and 16% had a major molecular response (Fig. 1B, and Table S3 in the Supplementary Appendix).

The median time to a major hematologic response was 3 weeks (range, 2 to 25), and the duration ranged from 1 month to 21 months or more (median, 12 months); the estimated rate of a sustained response of at least 12 months was 48% (Fig. 1B). The median time to a major cytogenetic response was 3.7 months (range, 0.8 to 9.7), and the estimated rate of a sustained response of at least 12 months was 73%. The rate of progression-free survival was estimated to be 55% at 12 months (median, 18 months), and the rate of overall survival (Fig. 1B) was estimated to be 84% at 12 months.

Like the patients with chronic-phase CML, the patients with accelerated-phase CML who received fewer previous tyrosine kinase inhibitors tended to have higher response rates (Table S8 in the Supplementary Appendix). High response rates were observed among patients with BCR-ABL mutations, including those with the T315I mutation, and among those without BCR-ABL mutations (Table S6 in the Supplementary Appendix), and no single mutation conferring resistance to ponatinib was observed (Appendix D in the Supplementary Appendix).

Blast-Phase CML and Ph-Positive ALL

Among patients with blast-phase CML, 31% (95% CI, 20 to 44) had a major hematologic response by 6 months (the primary end point), 23% had a major cytogenetic response, and 18% had a complete cytogenetic response (Fig. 1C). Table S9 in the Supplementary Appendix shows outcomes in patients with myeloid blast-phase CML and those with lymphoid blast-phase CML. Among patients with Ph-positive ALL, 41% (95% CI, 24 to 59) had a major hematologic response, 47% had a major cytogenetic response, and 38% had a complete cytogenetic response (Fig. 1D).

The median time to a major hematologic response in patients with blast-phase CML who had a response was 4.1 weeks (range, 1.7 to 16.1), the duration ranged from 1 month to 20 months or more (median, 5 months), and the estimated rate of a sustained response of at least 12 months was 42% (Fig. 1C). The median time to a major hematologic response in patients with Ph-positive ALL was 2.9 weeks (range, 1.6 to 24), the duration was 2 months to 14 months or more (median, 3 months), and the estimated rate of a sustained response of at least 12 months was 8% (Fig. 1D). The median time to a major cytogenetic response in patients with blast-phase CML who had a response was 1.9 months (range, 0.9 to 5.5), and the estimated rate of a sustained

Table 3. Response According to Previous Therapy in Patients with Chronic-Phase CML.

Variable	All Patients		Patients with Resistance or Unacceptable Side Effects		T315I Mutation	
	no.	*% (95% CI)*	*no.*	*% (95% CI)*	*no.*	*% (95% CI)*
One previous approved tyrosine kinase inhibitor*	19†		4		12	
Major cytogenetic response‡		79 (54–94)		50 (7–93)		83 (52–98)
Complete cytogenetic response		74 (49–91)		50 (7–93)		75 (43–95)
Major molecular response		47 (24–71)		0		67 (35–90)
Two previous approved tyrosine kinase inhibitors*	98		68		30	
Major cytogenetic response‡		67 (57–76)		63 (51–75)		77 (58–90)
Complete cytogenetic response		56 (46–66)		49 (36–61)		73 (54–88)
Major molecular response		36 (26–46)		28 (18–40)		53 (34–72)
Three previous approved tyrosine kinase inhibitors*	141		119		22	
Major cytogenetic response‡		45 (37–54)		44 (35–53)		55 (32–76)
Complete cytogenetic response		39 (31–48)		37 (28–46)		50 (28–72)
Major molecular response		33 (26–42)		29 (21–38)		55 (32–76)
Four previous approved tyrosine kinase inhibitors*	12		12			
Major cytogenetic response‡		58 (28–85)		58 (28–85)		—
Complete cytogenetic response		25 (5–57)		25 (5–57)		—
Major molecular response		8 (0.2–38)		8 (0.2–38)		—

* Patients may have received other, nonapproved tyrosine kinase inhibitors.
† This category includes the three patients who were not assigned to a cohort; they were T315I-negative at baseline and had not previously received dasatinib or nilotinib, but they had received imatinib.
‡ A major cytogenic response consists of a partial cytogenic response plus a complete cytogenic response.

response of at least 12 months was 66%. The median time to a major cytogenetic response in patients with Ph-positive ALL was 1 month (range, 0.9 to 3.7), the median duration was 3.7 months, and the estimated rate of a sustained response of at least 12 months was 32%. Among patients with blast-phase CML, the rate of progression-free survival at 12 months was estimated to be 19% (median, 4 months), and among patients with Ph-positive ALL, the rate of progression-free survival was estimated to be 7% (median, 3 months). The overall survival rate at 12 months was estimated to be 29% (median, 7 months) among patients with blast-phase CML and 40% (median, 8 months) among patients with Ph-positive ALL (Fig. 1C and 1D). No single mutation was associated with resistance to ponatinib. However, the acquisition of compound mutations (≥2 mutations in the same BCR-ABL allele) was sometimes observed in patients with an unsustained major hematologic response; all these patients had one of the mutations at study entry (Appendix D in the Supplementary Appendix).

SAFETY

The median duration of ponatinib treatment was 12.8 months (range, 1 day to >24.8 months). The median relative dose intensity (the proportion of administered doses relative to planned doses) was 0.84. Dose reductions occurred in 55% of the patients (median time to dose reduction, 2.3 months; range, 1 day to 19 months), and 67% of the patients had at least one dose interruption.

The most common nonhematologic adverse events that were considered by the site investigator to be at least possibly related to treatment were rash (in 34% of the patients), dry skin (in 32%), and abdominal pain (in 22%). These events were primarily grade 1 or 2 in severity (Table 4, and Table S10 in the Supplementary Appendix, which lists events in each of the six study cohorts). The

Table 4. Treatment-Related Adverse Events.*

Event	Chronic-Phase CML (N=270)		Accelerated-Phase CML (N=85)		Blast-Phase CML (N=62)		Ph-Positive ALL (N=32)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)							
Nonhematologic events								
Rash†	107 (40)	10 (4)	25 (29)	3 (4)	15 (24)	2 (3)	6 (19)	1 (3)
Dry skin	104 (39)	5 (2)	21 (25)	1 (1)	10 (16)	1 (2)	7 (22)	0
Abdominal pain	74 (27)	20 (7)	15 (18)	4 (5)	6 (10)	1 (2)	6 (19)	2 (6)
Headache	63 (23)	5 (2)	10 (12)	0	7 (11)	1 (2)	4 (12)	0
Increased lipase	57 (21)	27 (10)	12 (14)	11 (13)	8 (13)	7 (11)	3 (9)	2 (6)
Fatigue	51 (19)	4 (1)	17 (20)	1 (1)	7 (11)	2 (3)	3 (9)	0
Constipation	53 (20)	3 (1)	11 (13)	1 (1)	3 (5)	0	6 (19)	1 (3)
Myalgia	46 (17)	3 (1)	16 (19)	0	7 (11)	0	2 (6)	0
Arthralgia	45 (17)	6 (2)	16 (19)	1 (1)	8 (13)	0	1 (3)	0
Nausea	38 (14)	1 (<1)	9 (11)	0	12 (19)	0	1 (3)	0
Increased alanine aminotransferase	31 (11)	9 (3)	10 (12)	2 (2)	5 (8)	2 (3)	1 (3)	1 (3)
Pancreatitis	19 (7)	17 (6)	7 (8)	5 (6)	3 (5)	2 (3)	0	0
Hypertension	25 (9)	6 (2)	6 (7)	3 (4)	1 (2)	1 (2)	1 (3)	1 (3)
Increased aspartate aminotransferase	24 (9)	5 (2)	8 (9)	3 (4)	4 (6)	1 (2)	1 (3)	1 (3)
Increased blood amylase	16 (6)	4 (1)	6 (7)	3 (4)	3 (5)	2 (3)	1 (3)	0
Increased γ-glutamyltransferase	11 (4)	4 (1)	7 (8)	2 (2)	2 (3)	1 (2)	0	0
Dyspnea	13 (5)	4 (1)	6 (7)	0	4 (6)	1 (2)	0	0
Cardiac failure	3 (1)	2 (<1)	1 (1)	1 (1)	2 (3)	2 (3)	0	0
Hematologic events								
Thrombocytopenia	111 (41)	86 (32)	36 (42)	28 (33)	17 (27)	16 (26)	3 (9)	2 (6)
Neutropenia	44 (16)	38 (14)	22 (26)	22 (26)	14 (23)	11 (18)	4 (12)	4 (12)
Anemia	27 (10)	15 (6)	14 (16)	8 (9)	14 (23)	13 (21)	5 (16)	4 (12)
Decreased white-cell count	11 (4)	7 (3)	7 (8)	5 (6)	0	0	1 (3)	1 (3)
Pancytopenia	2 (1)	2 (1)	3 (4)	2 (2)	3 (5)	3 (5)	0	0
Febrile neutropenia	1 (<1)	1 (<1)	2 (2)	2 (2)	2 (3)	2 (3)	2 (6)	2 (6)

* Treatment-related adverse events were defined as events that the site investigators deemed to have a possible, probable, or definite relationship to ponatinib. Listed are the treatment-related adverse events that were reported in at least 10% of the patients, along with any incidence of grade 3 or 4 events in more than 1% of the total study population.
† Rash includes erythematous and papular rash.

most common hematologic adverse events were thrombocytopenia (in 37% of patients), neutropenia (in 19%), and anemia (in 13%) (Table 4).

Nonhematologic serious adverse events that occurred in at least 1% of patients were pancreatitis (in 5%), abdominal pain (in 2%), increased lipase levels (in 2%), diarrhea (in 1%), pyrexia (in 1%), and myocardial infarction (in 1%). Hematologic serious adverse events that occurred in at least 1% of patients were thrombocytopenia (in 2%), anemia (in 1%), neutropenia (in 1%), febrile neutropenia (in 1%), and pancytopenia (in 1%). Eighteen patients died during the study. The most common cause of death was sepsis or septic shock in four patients (one patient with accelerated-phase CML, one with blast-phase CML, and two with Ph-positive ALL). Five deaths were attributable to ponatinib (Table 2).

Thrombocytopenia, the most common adverse event, usually occurred early in the course of treatment (within the first 3 months). Pancreatitis, the most common serious adverse event, tended to occur early (median time to first onset, 14 days; 69% of cases occurred in the first month and 17% of cases occurred in the second month) and was reversible (most cases resolved within 1 week). All 29 patients with pancreatitis resumed treatment with ponatinib, and 3 patients had recurrent events (multiple events occurred in 1 patient). Only 1 patient (with chronic-phase CML) discontinued treatment because of pancreatitis. Clinical management of thrombocytopenia and pancreatitis was consistent with protocol-stipulated dose modifications (Appendix B in the Supplementary Appendix).

Arterial thrombotic events were observed. Cardiovascular, cerebrovascular, and peripheral vascular events that were considered by the site investigator to be at least possibly related to treatment were observed in 2.2%, 0.7%, and 1.6% of patients, respectively. Regardless of the relationship of the events to treatment, as ascribed by the investigators, 7.1% of patients had cardiovascular events, 3.6% had cerebrovascular events, and 4.9% had peripheral vascular events. Two patients discontinued ponatinib after the occurrence of one event. Of the remaining patients, 36% had one or more additional events. Cardiovascular, cerebrovascular, and peripheral vascular serious adverse events that were related to treatment were observed in 2.0%, 0.4%, and 0.4% of patients, respectively. Regardless of the relationship to treatment, 5.1% of the patients had cardiovascular serious adverse events, 2.4% had cerebrovascular serious adverse events, and 2.0% had peripheral vascular serious adverse events. Fifty-five percent of these patients had a history of ischemic disease at study enrollment, and 95% had one or more risk factors (hypertension, diabetes, hypercholesterolemia, or obesity) with or without a history of ischemic disease, nonischemic cardiac disease, or venous thromboembolism.

DISCUSSION

Many patients with a new diagnosis of Ph-positive leukemia have a prolonged clinical benefit from targeted therapy with imatinib or second-generation drugs.[2,14,22,23] However, resistance to therapy eventually develops in many patients. Once available treatment options are exhausted, the prognosis is poor.[24]

Response rates to previous therapy, a major predictor of response to subsequent therapy,[25] provide reasonable estimates of expected responses to the best available therapy. In this study, ponatinib was associated with robust antileukemic activity in heavily pretreated patients with CML or Ph-positive ALL, and the response rates were substantially higher than those reported for the most recent course of nilotinib or dasatinib treatment received before the study treatment.

At concentrations that are "clinically achievable" (i.e., blood concentrations of 40 nM of ponatinib observed in patients who receive daily doses of ≥30 mg), ponatinib has shown preclinical activity against all BCR-ABL mutants tested and has uniformly suppressed the emergence of single-mutant clones in a mutagenesis assay.[19] In this trial, among patients with chronic-phase CML, responses were observed against all mutants present in more than 1 patient. Among patients in whom the response was not sustained, end-of-treatment analyses did not reveal the emergence of single mutations. Compound mutations developed in 21 patients, primarily those with blast-phase CML or Ph-positive ALL who entered the study with one or more mutations, mainly T315I. In particular, the development of E255K/T315I, E255V/F317I, or T315I/F359V compound mutations was observed in more than 1 patient (Appendix D in the Supplementary Appendix). This is consistent with the genetic instability associated with advanced disease,[26,27] and it is also consistent with preclinical data showing emergence of certain compound mutations on a background of T315I or E255V single mutations at concentrations of ponatinib that are clinically achievable.[19] Compound mutations in BCR-ABL may develop sequentially and have been associated with resistance to other tyrosine kinase inhibitors.[28-31] Data from this study, together with the phase 1 data,[18] did not show a single mutation conferring resistance to ponatinib. We speculate that the use of ponatinib at earlier stages of disease could prevent the emergence of resistance caused by mutations. Mechanisms of resistance to ponatinib in the absence of mutations remain to be identified.

Response rates were high among patients with chronic-phase CML who did not have de-

tectable BCR-ABL mutations, as well as among patients with mutations other than T315I. Response rates were higher among patients with T315I, which is resistant to all other targeted therapies. However, a multivariate analysis showed that the presence of T315I itself is not a predictor of response; rather, the differences in response rates are explained by the clinical features of these patients. Younger, less heavily pretreated patients were able to receive higher doses of ponatinib without unacceptable adverse effects and had higher response rates, irrespective of their T315I mutation status.[21] Since responses were observed regardless of the presence or absence and type of mutations, mutation analysis might not be necessary in every case. Certainly, a patient can be properly treated with ponatinib without undergoing prior mutation testing, if it is not available. However, knowledge of any mutations present at the start of therapy, as a baseline, may be useful for recognizing the emergence of preexisting mutations or of compound mutations that might lead to ponatinib resistance. Thus, mutation analysis is still important for the treatment of patients with CML.[32,33]

Response rates in our study tended to be higher among patients treated with fewer previous tyrosine kinase inhibitors. Among patients with chronic-phase CML who received one previous tyrosine kinase inhibitor, 15 of 19 (79%) had a major cytogenetic response, whereas 66 of 98 (67%) had a major cytogenetic response after two previous tyrosine kinase inhibitors. In studies involving patients with resistance to or side effects of imatinib who were treated with nilotinib, dasatinib, or bosutinib, the reported major cytogenetic response rates were 48 to 63%.[3-8] Few data are available on the activity of second-generation tyrosine kinase inhibitors in patients who had treatment failure with imatinib and either nilotinib or dasatinib, but patients with chronic-phase CML have been reported to have major cytogenetic response rates ranging from 32 to 50%, with a limited duration of response.[34-37]

In our study, serious-grade arterial thrombotic events (including cardiovascular, cerebrovascular, and peripheral vascular events) were seen in only 8.9% of the patients who received ponatinib (treatment-related events, 2.9%). However, the United States Prescribing Information (USPI) for ponatinib recently included a boxed warning for arterial thrombotic events. The rates of these events that were initially reported in the USPI in December 2012 were 7.6% for serious adverse events and 11.4% for all adverse events, serious or not (median duration of exposure, 11 months among all patients in the trial). Data on an additional 13 months of exposure in patients who continued in the trial, which were available after submission and acceptance of our manuscript, showed that the cumulative incidence of serious arterial thrombotic events was 11.8%; the incidence of all arterial thrombotic events, serious or not, was 17.1%. When longer patient exposure is taken into account, the rates of these events per unit of time have not changed with time. However, the accumulation of adverse events has prompted a partial clinical hold on ongoing trials of ponatinib and the termination by the sponsor of the frontline randomized trial of ponatinib versus imatinib (Ponatinib in Newly Diagnosed Chronic Myeloid Leukemia [CML] [EPIC]). Awareness of these ponatinib-associated events is critical in the treatment of patients who are receiving ponatinib. In this study, arterial thrombotic events were observed predominantly in patients with either a documented ischemic condition or one or more risk factors at baseline. Patients with these clinical features should be carefully monitored. More data are needed to determine the cardiovascular risk attributable to ponatinib and the mechanism of action underlying these events. It is also important to investigate whether interventions, such as the use of aspirin or other drugs that inhibit platelet aggregation, may reduce the risk of these events. However, ponatinib has been reported to have a mild inhibitory effect on platelet aggregation.[38] Cardiovascular adverse events have also been observed in patients treated with other BCR-ABL–targeted tyrosine kinase inhibitors, including peripheral arterial occlusive disease in patients treated with nilotinib.[39-41]

In conclusion, ponatinib showed clinically significant activity in patients with CML and those with Ph-positive ALL.

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APPENDIX

The authors' full names and academic degrees are as follows: Jorge E. Cortes, M.D., Dong-Wook Kim, M.D., Ph.D., Javier Pinilla-Ibarz, M.D., Ph.D., Philipp le Coutre, M.D., Ronald Paquette, M.D., Charles Chuah, M.D., Franck E. Nicolini, M.D., Ph.D., Jane F. Apperley, M.D., Hanna J. Khoury, M.D., Moshe Talpaz, M.D., John DiPersio, M.D., Ph.D., Daniel J. DeAngelo, M.D., Ph.D., Elisabetta Abruzzese, M.D., Ph.D., Delphine Rea, M.D., Ph.D., Michele Baccarani, M.D., Martin C. Müller, M.D., Carlo Gambacorti-Passerini, M.D., Stephane Wong, Ph.D., Stephanie Lustgarten, Ph.D., Victor M. Rivera, Ph.D., Tim Clackson, Ph.D., Christopher D. Turner, M.D., Frank G. Haluska, M.D., Ph.D., François Guilhot, M.D., Michael W. Deininger, M.D., Ph.D., Andreas Hochhaus, M.D., Timothy Hughes, M.D., John M. Goldman, D.M., Neil P. Shah, M.D., Ph.D., and Hagop Kantarjian, M.D.

The authors' affiliations are as follows: the Department of Leukemia, University of Texas M.D. Anderson Cancer Center, Houston (J.E.C., H.K.); Seoul St. Mary's Hospital, Catholic University of Korea, Seoul, South Korea (D.-W.K.); H. Lee Moffitt Cancer Center, Tampa, FL (J.P.-I.); Charité–Universitätsmedizin Berlin, Berlin (P.C.), III. Medizinische Klinik, Universitätsmedizin Mannheim, Mannheim (M.C.M.), and Abteilung Hämatologie und Onkologie, Universitätsklinikum Jena, Jena (A.H.) — all in Germany; Ronald Reagan UCLA Medical Center, University of California, Los Angeles (R.P.); Singapore General Hospital, Duke–National University of Singapore Graduate Medical School, Singapore (C.C.); Centre Hospitalier Lyon Sud, Pierre Bénite (F.E.N.), Service des Maladies du Sang and Clinical Investigation Center (CIC), Hôpital Saint-Louis, Paris (D.R.), and INSERM CIC, Centre Hospitaliere Universitaire de Poitiers, Poitiers (F.G.) all in France; Centre for Haematology, Imperial College London, London (J.F.A., J.M.G.); Winship Cancer Institute of Emory University, Atlanta (H.J.K.); Comprehensive Cancer Center, University of Michigan, Ann Arbor (M.T.); Washington University School of Medicine, St. Louis (J.D.); Dana–Farber Cancer Institute, Boston (D.J.D.); Hematology, S. Eugenio Hospital, Tor Vergata University, Rome (E.A.), the Department of Hematology and Oncology L. and A. Seragnoli, S. Orsola–Malpighi University Hospital, Bologna (M.B.), and Unità di Ricerca Clinica–Ematologia, Azienda Ospedaliera San Gerardo/University of Milano Bicocca, Monza (C.G.-P.) — all in Italy; MolecularMD, Portland, OR (S.W.); Ariad Pharmaceuticals, Cambridge, MA (S.L., V.M.R., T.C., C.D.T., F.G.H.); Huntsman Cancer Institute, University of Utah, Salt Lake City (M.W.D.); Institute of Medicine and Veterinary Science, Adelaide, SA, Australia (T.H.); and University of California San Francisco, San Francisco (N.P.S.).

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