Ponatinib in Chronic-Phase Chronic Myeloid Leukemia Patients: Final Report From a Phase 1 Trial

Abstract 3063

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INTRODUCTION

- Ponatinib is an oral tyrosine kinase inhibitor (TKI) with potent activity against native and mutant BCR-ABL1, including T315I[1]
- Ponatinib is approved for the treatment of adult patients with chronic myeloid leukemia (CML) or Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other TKI therapy is indicated or for those with the T315I mutation[2,3]
- A phase 1, dose-escalation study evaluated the safety, tolerability, and pharmacokinetics of ponatinib in patients with relapsed/refractory hematologic malignancies (N=81), and evaluated antileukemic activity in patients with Ph+ leukemias (n=65)[4]
- In the initial report of this phase 1 study, with a median follow-up of 12.9 months, ponatinib demonstrated robust clinical activity in heavily pretreated patients with Ph+ leukemias[4]
  - In chronic-phase CML (CP-CML) patients (n=43), the rates of major cytogenetic response (MCyR) and major molecular response (MMR) were 72% and 44%, respectively
  - In patients with accelerated-phase CML (AP-CML), blast-phase CML (BP-CML), or Ph+ ALL (n=22), the rates of major hematologic response and MCyR were 36% and 32%, respectively

OBJECTIVE

- To report final follow-up data on the efficacy and safety of ponatinib in CP-CML patients in the phase 1 clinical trial (NCT00660920)
  - Longest follow-up (median, 4.6 years) of ponatinib-treated patients to date

STUDY DESIGN

Open-label Dose-Escalation Phase 1 Study[4]

Patients	• Resistant/refractory hematologic malignancies (N=81) – Ph+ leukemias, n=65 (CP-CML, n=43; AP-CML, n=9; BP-CML, n=8; Ph+ ALL, n=5)
Ponatinib starting dose	• 2–60 mg/d • Intra-patient dose escalation was permitted
Ponatinib dose-reduction instructions post Oct 2013[a]	• 15 mg/d for CP-CML patients with MCyR • 30 mg/d for CP-CML patients without MCyR • 30 mg/d for AP-CML, BP-CML, or Ph+ ALL patients
Data analysis cut-off (final data from study)	• October 18, 2016
Patients in this analysis	• Patients with resistant/refractory CP-CML (n=43)
Median follow-up, CP-CML	• 55.4 (1.7–91.3) months

[a] Unless benefit-risk analysis justified treatment with a higher dose, dose reductions were instructed post Oct 2013 in response to an observed accumulation of arterial occlusive events (AEOs) with longer follow-up across the ponatinib clinical program[2]

RESULTS

Baseline Characteristics

Characteristics	CP-CML Patients, n=43
Median age, years (range)	55 (27–85)
Median time from diagnosis to first dose, years (range)	6.6 (0.8–23.5)
ECOG performance status, n (%)	
0	19 (44)
1	22 (51)
2	2 (5)
No. of prior TKIs, n (%)	
2	16 (37)
≥3	26 (60)
Mutation status,[a,b] n (%)	
No mutation	13 (30)
T315I	12 (28)
Mutation(s) other than T315I[c]	15 (35)

[a] Mutation status was assessed at a central laboratory; [b] 3 CP-CML patients had unknown mutation status; [c] Mutations other than T315I occurring in >5% of CP-CML patients included F317L (in 5 [12%] patients) and G250E (in 4 [9%] patients); 1 patient had both F317L and G250E mutations and is represented more than once in these percentages
ECOG, Eastern Cooperative Oncology Group

- Baseline characteristics for CP-CML patients were broadly similar to those of the overall study population[4]
- 42/43 (98%) CP-CML patients had received at least 2 prior TKIs

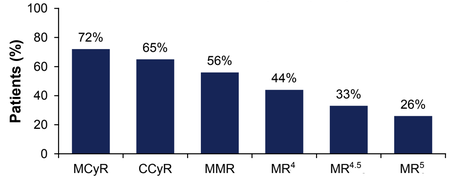
Patient Disposition and Exposure

	CP-CML Patients, n=43
Median follow-up on study, months (range)	55.4 (1.7–91.3)
Discontinued, n (%)	43 (100)
Primary reason for discontinuation, n (%)	
Administrative decision[a]	20 (47)
AEs[b]	11 (26)
Progressive disease	6 (14)
Consent withdrawn	4 (9)
Lost to follow-up	1 (2)
Death[c]	1 (2)
Median dose intensity, mg/d (range)	26.4 (4.0–53.6)

[a] Includes patients who were ongoing until study termination (n=18); patients who continued to have clinical benefit from the treatment had the option to receive ponatinib through alternative mechanisms; [b] AEs leading to discontinuation in CP-CML patients were (n=1 for each): pancreatitis; visceral arterial ischemia; central nervous system (CNS) infarction; myocardial infarction; cardiomyopathy, congestive heart failure, rapid atrial fibrillation, decreased left ventricular ejection fraction (all in 1 patient); worsening of peripheral vascular disease; recurrent peripheral arterial ischemia of the right leg; fever and disease progression with CNS involvement; intermittent headache; increased creatinine; and renal failure; [c] Cause of death: bilateral pneumonia and shortness of breath
AEs, adverse events

- Of the 11 CP-CML patients who discontinued as a result of AEs, 6 were in MCyR and, of those, 5 were in complete cytogenetic response (CCyR); 2 patients with CCyR were also in MMR
- Of the 18 patients who discontinued due to study termination, 15 patients were in MMR or better as of data cut-off (MMR, n=3; MR[4], n=1; MR[4.5], n=5; MR[5], n=6); MCyR or MMR was not reported in 3 patients, who achieved complete hematologic response as their best response

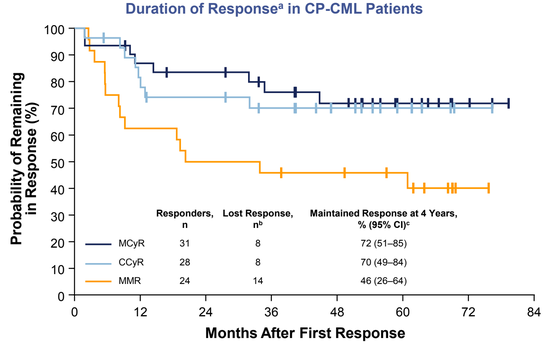
Cumulative Response Rates in CP-CML Patients (n=43; median follow-up, 4.6 years)



MCyR, 0%–35% Ph+ metaphases; CCyR, 0% Ph+ metaphases; MMR, ≤0.1% BCR-ABL[IS] or undetectable disease in cDNA with ≥1000 ABL transcripts; MR[4], detectable disease ≤0.01% BCR-ABL[IS] or undetectable disease in cDNA with ≥10,000 ABL transcripts; MR[4.5], detectable disease ≤0.0032% BCR-ABL[IS] or undetectable disease in cDNA with ≥32,000 ABL transcripts; MR[5], detectable disease ≤0.001% BCR-ABL[IS] or undetectable disease in cDNA with ≥100,000 ABL transcripts

- Median time to response was 2.8 (MCyR), 5.5 (CCyR), and 7.4 (MMR) months
- In 12 patients with the T315I mutation, MCyR was reported in 11 (92%) patients, CCyR in 10 (83%) patients, and MMR in 9 (75%) patients (see Jabbour et al. ASH 2016. Abstract 3067)
- In 15 patients with other mutations, MCyR was reported in 10 (67%) patients, CCyR in 10 (67%) patients, and MMR in 8 (53%) patients

Duration of Response[a] in CP-CML Patients



[a] Patients remaining on study were required to undergo cytogenetic assessments once per year and molecular assessments every 3 months; [b] Failed to meet criteria for response at any single time point after initial response; [c] Kaplan-Meier estimate
CI, confidence interval

- Of the patients who achieved cytogenetic response, 72% and 70% were estimated to maintain MCyR and CCyR, respectively, for at least 4 years (median durations not reached)
- Median duration of MMR was 27.1 months (range, 8.0–not reached)

Cumulative Response Rates in CP-CML Patients by Starting Dose Lower Than 45 mg

	Starting Dose	n (%)	Dose Intensity, mg/d[a] Median (range)[b]
MCyR	Any (n=43)	31 (72)	30.7 (3.5–59.3)
	≤30 mg/d (n=15)	10 (67)	14.8 (3.5–29.6)
	4 mg/d (n=3)	2 (67)	3.7 (3.5–3.9)
	15 mg/d (n=7)	5 (71)	14.8 (14.7–23.7)
	30 mg/d (n=5)	3 (60)	27.4 (10.6–29.6)
CCyR	Any (n=43)	28 (65)	38.3 (3.5–59.3)
	≤30 mg/d (n=15)	8 (53)	14.9 (3.5–35.2)
	4 mg/d (n=3)	1 (33)	3.5 (3.5–3.5)
	15 mg/d (n=7)	4 (57)	14.9 (14.7–35.2)
	30 mg/d (n=5)	3 (60)	27.4 (12.1–29.8)
MMR	Any (n=43)	24 (56)	40.3 (14.3–59.5)
	≤30 mg/d (n=15)	7 (47)	15.0 (14.3–36.6)
	4 mg/d (n=3)	1 (33)	14.3 (14.3–14.3)
	15 mg/d (n=7)	4 (57)	15.0 (14.7–36.6)
	30 mg/d (n=5)	2 (40)	28.9 (27.8–29.9)

[a] Dose intensity until time of response for responders only; [b] Median daily dose between first dose date and last dose date through date of first response

- The MCyR, CCyR, and MMR rates in CP-CML patients who received a ponatinib starting dose of ≤30 mg/d are consistent with the corresponding response rates in the overall CP-CML population

Treatment-Emergent AEs in ≥25% of CP-CML Patients (n=43)

	Any Grade, %	Grade ≥3, %
Nonhematologic		
Rash	65	2
Fatigue	63	7
Abdominal pain	58	16
Headache	58	2
Arthralgia	53	2
Constipation	51	2
Hypertension	49	12
Nausea	49	0
Vomiting	47	0
Dry skin	44	0
Hypertriglyceridemia	42	2
Upper respiratory tract infection	40	0
Back pain	37	2
Increased lipase	37	19
Muscle spasms	37	0
Myalgia	35	0
Peripheral edema	35	0
Pyrexia	35	0
Cough	33	0
Pain in extremity	30	5
Urinary tract infection	30	5
Bone pain	28	0
Chills	28	2
Diarrhea	26	0
Dizziness	26	5
Nasopharyngitis	26	0
Hematologic		
Thrombocytopenia	44	33

- Most treatment-emergent AEs were grades 1 or 2 and, as reported previously, most occurred in the first year of treatment[5]
- The most common serious treatment-emergent AEs were abdominal pain, atrial fibrillation, dehydration, malignant melanoma, myocardial infarction, and pancreatitis (n=4 each)

Cumulative and Exposure-Adjusted Incidences of Treatment-Emergent AOEs and VTEs in CP-CML Patients

	CP-CML Patients n=43	
Category[a]	AE	SAE
AOEs,[b] n (%)	19 (44)	16 (37)
Cardiovascular	14 (33)	10 (23)
Cerebrovascular	5 (12)	4 (9)
Peripheral vascular	8 (19)	6 (14)
Exposure-adjusted AOEs, no. of patients with events per 100 patient-years	10.5	8.8
VTEs, n (%)	3 (7)	1 (2)
Exposure-adjusted VTEs, no. of patients with events per 100 patient-years	1.7	0.6

[a] Categorization of AOEs/VTEs is based on a broad collection of >400 Medical Dictionary for Regulatory Activities (MedDRA) preferred terms related to vascular ischemia or thrombosis; [b] Some patients experienced >1 AOE
AE, total AEs (including SAEs); SAE, serious AEs only (designated as serious by the investigator, in accordance with standard regulatory criteria)
VTEs, venous thromboembolic events

- Median time to onset of AOEs and VTEs was 13.8 (0.03–57.9) months and 27.2 (9.7–50.2) months, respectively, in CP-CML patients with events; these results are similar to those observed in the phase 2 PACE trial[6]
- Most AOEs and VTEs were medically managed; 4/43 CP-CML patients (9%) discontinued therapy as a result of an AOE (n=4) or VTE (n=0), and no patient death was attributed to an AOE or VTE

SUMMARY

- In this final report from the phase 1 study of ponatinib with median follow-up of 4.6 years, ponatinib treatment demonstrated deep, long-lasting response in heavily pretreated CP-CML patients who had limited treatment options at the time of entry to the trial:
  - Cumulative rates of MCyR, CCyR, and MMR were 72%, 65%, and 56%, respectively
  - By Kaplan-Meier estimate, the probability of remaining in MCyR, CCyR, and MMR at 4 years was 72%, 70%, and 46%, respectively
- Among CP-CML patients treated with ponatinib in this phase 1 population, the cumulative incidence of treatment-emergent AOEs and VTEs, which are categorized based on a broad collection of >400 terms related to vascular ischemia or thrombosis, was 44% and 7%, respectively; when adjusted for exposure to ponatinib, the incidence was 10.5 and 1.7 events per 100 patient-years, respectively
  - Most AOEs/VTEs were medically managed; 9% of CP-CML patients discontinued as a result of an AOE (9%) or VTE (0%)
- The most common treatment-emergent AEs were consistent with the AE profile of ponatinib across the clinical program
- In this longest clinical evaluation of ponatinib to date, ponatinib provided long-term clinical benefit to CP-CML patients, regardless of mutation status. Observed AOE rates should be considered in the context of the potential benefit (including rate, depth, and duration of response) in this heavily pretreated patient population

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DISCLOSURES

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