Long-term Follow-up of the Efficacy and Safety of Ponatinib in Philadelphia Chromosome–Positive Leukemia Patients With the T315I Mutation

Abstract 3067

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INTRODUCTION

- Mutations in the BCR-ABL kinase domain that impair inhibitor binding are a primary cause of acquired resistance to tyrosine kinase inhibitors (TKIs) in patients with chronic myeloid leukemia (CML) and Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL)[1,2]
- The BCR-ABL T315I mutation, one of the most frequently detected BCR-ABL kinase domain mutations, is associated with poor prognosis, high rates of disease progression, and poor survival[2-7]
  - In an epidemiologic study of survival in chronic-phase CML (CP-CML) patients with the T315I mutation (T315I+) prior to the availability of ponatinib (n=82), median overall survival (OS) from time of T315I mutation detection was <2 years (22.4 months), with 3 of 82 patients alive at 4 years after T315I mutation detection[6]
- Ponatinib is approved for the treatment of adult patients with CML or Ph+ ALL for whom no other TKI therapy is indicated or for those with the T315I mutation[8,9]
- The primary publications of the phase 1 trial (NCT00660920) and the phase 2 PACE trial (NCT01207440) reported robust clinical activity of ponatinib in leukemia patients in whom prior TKIs had failed[10,11]
  - In the phase 1 trial, 92% of T315I+ CP-CML patients (n=12) achieved major cytogenetic response (MCyR) by 12 months[10]
  - In the phase 2 PACE trial, 70% of T315I+ CP-CML patients (n=64) achieved MCyR by 12 months[11]

OBJECTIVE

- To evaluate the efficacy and safety of ponatinib in CP-CML patients with the T315I mutation at baseline based on pooled data from the phase 1 trial and phase 2 PACE trial

METHODS

Analysis summary	• Pooled analysis of the efficacy and safety of ponatinib in patients with the T315I mutation detected at baseline in the phase 1 trial and PACE trial
Study design	
Phase 1 trial[10]	• Open-label, dose-escalation study of ponatinib (starting dose 2–60 mg once daily) in 81 adults with relapsed/ refractory hematologic malignancies – CP-CML, n=43; T315I+ CP-CML, n=12
Phase 2 PACE trial[11]	• Open-label, single-arm trial of ponatinib (starting dose 45 mg/d) in 449 adults with CML or Ph+ ALL resistant or intolerant to dasatinib or nilotinib or with the T315I mutation – CP-CML, n=270; T315I+ CP-CML, n=64
Patients	• Overall, N=76; phase 1, n=12; PACE, n=64
Ponatinib dose reduction	• Ponatinib dose reduction instructions post Oct 2013[8,a]: – 15 mg/d for CP-CML patients with MCyR – 30 mg/d for CP-CML patients without MCyR – 30 mg/d for accelerated-phase CML, blast-phase CML, or Ph+ ALL patients
BCR-ABL1 mutation status	• Detected in a central laboratory by Sanger sequencing at baseline
Response assessments (phase 1 and PACE)	• MCyR • Complete cytogenetic response (CCyR) • Major molecular response (MMR)[b] • Molecular response 4.5 (MR$^{4.5}$)[b]
Survival assessments (PACE only)	• Progression-free survival (PFS) and OS
Landmark analysis (PACE only)	• Impact of long-term ponatinib treatment at a 2-year landmark time point assessed in T315I+ CP-CML patients
Exposure-adjusted incidence rates of arterial occlusive events (AOEs; phase 1 and PACE)	• Reported as number of events/100 patient-years
Data cut-off	• Phase 1: October 18, 2016 • PACE: August 3, 2015

[a] In response to an observed accumulation of AOEs with longer follow-up across the ponatinib clinical program, dose reductions were instructed in Oct 2013 unless benefit-risk analysis justified treatment with a higher dose; [b] Assessed in a central laboratory

RESULTS

Baseline Characteristics

Characteristics	Pooled Phase 1 and PACE T315I+ CP-CML Patients, N=76
Median age, years (range)	50.0 (18.0–87.0)
Male, n (%)	56 (74)
Median time from diagnosis to first dose, years (range)	4.6 (0.8–19.0)
Prior TKI therapy,[a] n (%)	
1 TKI	17 (22)
2 TKIs	38 (50)
≥3 TKIs	20 (26)

[a] Includes approved and investigational TKIs

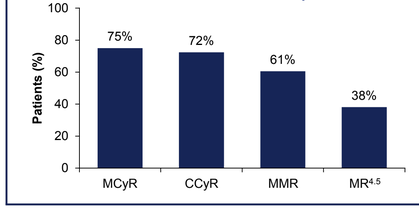
Patient Disposition

	Pooled Phase 1 and PACE T315I+ CP-CML Patients, N=76
Median follow-up,[a] months (range)	40.3 (1.5–91.4)
Remain on study,[b] n (%)	26 (34)
Discontinued, n (%)	50 (66)
Primary reason for discontinuation, n (%)	
Disease progression[c]	12 (16)
Lack of efficacy	2 (3)
AEs[d]	9 (12)
Consent withdrawn	5 (7)
Physician/administrative decision[e]	13 (17)
Death[f]	3 (4)
Other	6 (8)
Median ponatinib dose intensity, mg/d (range)	31.6 (4.9–50.0)
	PACE T315I+ CP-CML Patients Ongoing as of Data Cut-off, N=26
Current dose as of data cut-off, n (%)	
15 mg/d	19 (73)
30 mg/d	4 (15)
45 mg/d	3 (12)

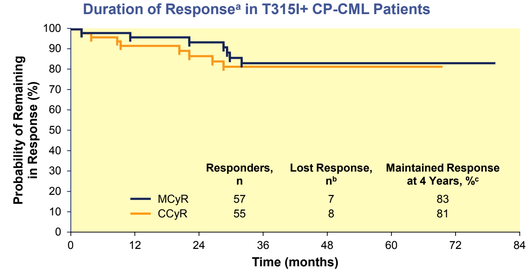
[a] For phase 1, median follow-up pertains only to time on study; for PACE, patients were followed up after discontinuation from study for survival analysis; [b] Phase 1 study is no longer ongoing; [c] Criteria for disease progression included death, development of advanced phase CML, loss of CHR (complete hematologic response) (in absence of cytogenetic response) and loss of MCyR; [d] AEs leading to discontinuation include coronary artery disease (n=3) and pain, recurrent large lung cell, cerebral infarction, cerebral infarction/cerebral artery stenosis, systemic inflammatory response syndrome, and lacunar infarction (all n=1); 6 patients in PACE and no patients in the phase 1 trial had an AOE leading to discontinuation; [e] Includes 8 phase 1 patients who were ongoing until study termination; patients who continued to have clinical benefit from the treatment had the option to receive ponatinib through alternative mechanisms; [f] Reasons for death include congestive cardiac failure, cardiac arrest, and cerebrovascular accident (all n=1)
AEs, adverse events

- Overall, CP-CML patients with T315I at baseline in PACE were younger, less heavily treated, and had a shorter time since diagnosis, compared with the non-T315I CP-CML population in PACE[11,12]

Cumulative Response Rates in T315I+ CP-CML Patients With 4 Years of Follow-up



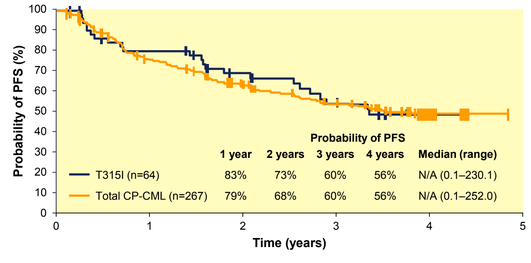
Duration of Response[a] in T315I+ CP-CML Patients



[a] Patients remaining on study are required to undergo cytogenetic assessments once per year in the phase 1 trial and at least once per year in PACE trial; [b] Failed to meet criteria for response at any single time point after initial response (phase 1), or failed to meet criteria for response in 2 consecutive assessments ≥28 days apart or discontinued after a single assessment in which the criteria for response were not met (PACE); [c] Kaplan-Meier estimate

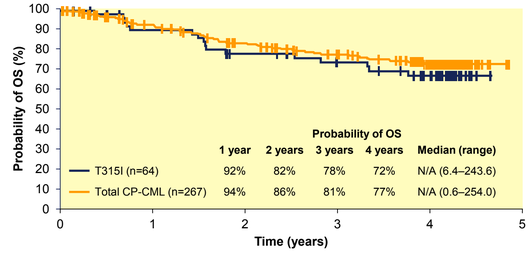
- MCyR and CCyR were durable in CP-CML patients with the T315I mutation at baseline, with 83%/81% of patients who achieved response estimated to maintain MCyR/CCyR at 4 years
- 75% (57/76) of T315I+ CP-CML patients achieved MCyR; 24 patients discontinued treatment after achieving MCyR
  - Primary reasons for discontinuation following achievement of MCyR included AEs (n=7), physician decision (n=5), intended to proceed to transplant (n=4), progressive disease (n=4), withdrawal by subject/consent withdrawn (n=3), and death (n=1)

PFS in T315I+ CP-CML Patients in the PACE Trial



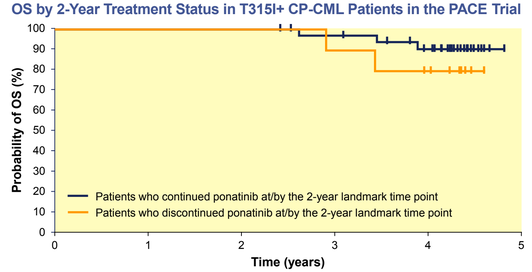
Progression was defined as death, development of AP- or BP-CML, loss of complete hematologic response (CHR) in the absence of cytogenetic response, loss of MCyR, or increasing white blood cell count without CHR. Patients who do not demonstrate progression or loss of response are censored at the last response assessment date
N/A, not applicable

OS in T315I+ CP-CML Patients in the PACE Trial



- In T315I+ CP-CML patients, the probability of survival at 4 years was 72%

OS by 2-Year Treatment Status in T315I+ CP-CML Patients in the PACE Trial



1-Year OS by Treatment Status at the 2-Year Landmark Time Point in T315I+ CP-CML Patients in the PACE Trial

	Patients Who Continued Ponatinib	Patients Who Discontinued Ponatinib	*P* Value
Patients with OS at/past landmark, n	36	10	
1-year OS past landmark, %	97	90	0.34

- Although patient numbers are limited for the landmark analysis, continuation of ponatinib treatment at 2 years was associated with a trend for improved OS (data will continue to mature)

Treatment-Emergent AEs in ≥25% of T315I+ CP-CML Patients

	Pooled Phase 1 and PACE, N=76	
	Any Grade, n (%)	Grade ≥3, n (%)
Nonhematologic		
Rash	42 (55)	4 (5)
Dry skin	37 (49)	2 (3)
Headache	35 (46)	2 (3)
Abdominal pain	33 (43)	8 (11)
Fatigue	31 (41)	2 (3)
Nausea	31 (41)	1 (1)
Constipation	27 (36)	4 (5)
Arthralgia	26 (34)	2 (3)
Hypertension	26 (34)	11 (14)
Myalgia	26 (34)	1 (1)
Upper respiratory tract infection	23 (30)	1 (1)
Increased lipase	21 (28)	9 (12)
Pyrexia	20 (26)	0
Hematologic		
Thrombocytopenia	25 (33)	17 (22)

- The majority of common treatment-emergent AEs were grade 1 or 2 in severity
- The most frequently observed grade ≥3 AEs were thrombocytopenia (22%), hypertension (14%), and increased lipase (12%)

Serious Treatment-Emergent AEs in ≥5% of T315I+ CP-CML Patients

	Pooled Phase 1 and PACE, N=76	
	Any Grade, n (%)	Grade ≥3, n (%)
Nonhematologic		
Pancreatitis	7 (9)	7 (9)
Acute myocardial infarction/myocardial infarction	6 (8)	6 (8)
Coronary artery disease	5 (7)	5 (7)
Angina pectoris	4 (5)	2 (3)
Atrial fibrillation	4 (5)	3 (4)
Pneumonia	4 (5)	3 (4)

Cumulative and Exposure-Adjusted Incidences of Treatment-Emergent AOEs and VTEs for T315I+ CP-CML Patients (Any Grade)[a]

	Pooled Phase 1 and PACE, N=76
AOEs,[b] n (%)	25 (33)
Cardiovascular	15 (20)
Cerebrovascular	10 (13)
Peripheral vascular	10 (13)
Exposure-adjusted AOEs, no. of patients with events per 100 patient-years	11.1
VTEs, n (%)	5 (7)
Exposure-adjusted VTEs, no. of patients with events per 100 patient-years	2.2

[a] Categorization of AOEs and 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
VTEs, venous thromboembolic events

SUMMARY & CONCLUSIONS

- Ponatinib continues to provide deep and durable responses with 4 years follow-up in T315I+ CP-CML patients from the phase 1 and PACE studies
  - 75% and 72% of T315I+ CP-CML patients achieved MCyR and CCyR, respectively
  - 83% and 81% of T315I+ CP-CML patients who achieved MCyR and CCyR, respectively, were estimated to maintain response at 4 years
- The safety profile of ponatinib in CP-CML patients with the T315I mutation was comparable to that observed among all CP-CML patients in the phase 1 and PACE trials[10,11]
- In this analysis, survival outcomes were high for T315I+ CP-CML patients, with median OS not yet reached and estimated 4-year OS of 72% in the PACE trial
  - Historically, outcomes for T315I+ CP-CML patients were poor; in an epidemiologic study reported in 2009 prior to the availability of ponatinib, among 82 T315I+ CP-CML patients, median OS was 22.4 months from the time of T315I detection, with 3 of 82 patients alive at 4 years after detection of the mutation[6]

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DISCLOSURES

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