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Multicenter, prospective, and retrospective observational cohort study of ponatinib in patients with CML in Italy: Interim analysis of the OITI trial

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Background

- Ponatinib is a third-generation tyrosine kinase inhibitor (TKI) indicated for adult patients with second-generation TKI-resistant/intolerant chronic phase (CP), accelerated phase (AP), or blast phase (BP) chronic myeloid leukemia (CML), Philadelphia chromosome-positive acute lymphoblastic leukemia, or for patients carrying the T315I mutation.[1–3]
- In the real-world setting, there is a paucity of data regarding the use of ponatinib. The goal of the Observational study of Iclusig® (ponatinib) Treatment in patients with CML in Italy (OITI) is to evaluate treatment patterns and outcomes, including safety and efficacy, of ponatinib in patients with CML treated in hematology centers in Italy since January 2015, when ponatinib became commercially available.

Methods

- OITI is an ongoing, non-interventional cohort study that includes patients aged ≥18 years with a confirmed diagnosis of CP, AP, or BP CML who initiated ponatinib treatment in routine clinical practice across 40 centers (academic and hospital settings).
- The study population consists of:
  - A prospective cohort, including patients who started treatment with ponatinib after site activation during the ongoing enrollment period;
  - A retrospective cohort, including patients who started treatment with ponatinib but who died or were lost to follow-up prior to site activation;
  - A retrospective/prospective cohort, including patients who started treatment with ponatinib prior to site activation and are still on treatment.
- Demographic, efficacy, and safety data are collected from patients' medical charts at study entry and at routine care visits.
- Patients are enrolled into the study during the 24 months after the first patient enrollment (up to October 2020).
- The study aims to follow all prospective and retrospective/prospective patients for a minimum of 24 months.
- The observational period will be closed 24 months after the last patient is enrolled.
- The primary endpoint is the complete cytogenetic response (CCyR) rate in patients with CP CML 6 months after starting ponatinib treatment.
- Main secondary endpoints are major molecular response (MMR) (MR3.0), deep molecular response (DMR) (MR4.0 and MR4.5) over time, and the safety profile.
- An estimated 104 patients are required as a minimal sample size.
- Here, we present the first interim analysis after ≥6 months' observation for the retrospective and retrospective/prospective cohorts.

Results

Patient characteristics

- At the time of data analysis (July 02, 2019), 56 patients (53 CP, 1 AP, and 2 BP CML) had been enrolled across 21 Italian centers.
- Patient baseline characteristics are shown in **Table 1:**
  - Twenty-eight patients (50.0%) had received ponatinib as second-line treatment and 19 (33.9%) received ponatinib in third-line.
  - The reasons for switching to ponatinib included resistance (62.5%), intolerance (23.2%), and warning response (7.1%).
  - Twenty patients (35.7%) had a history of cardiovascular events and 23 (41.1%) had a history of hypertension.
  - Among patients with CP, AP, and BP CML, the median age at study entry was 59.1, 33.7, and 48.5 years, respectively.
  - Among 37 evaluable patients, 12 CP patients (32.4%), 1 AP patient (2.7%), and 1 BP patient (2.7%) had a confirmed *BCR-ABL1* mutation; 4 patients (10.8%) carried the T315I mutation.

Table 1. Patient baseline characteristics

Patient baseline characteristics (N=56)	
Median age, years (range)	59 (19–81)
Male, n (%)	32 (57.1)
CML phase at diagnosis, n (%)	
CP	53 (94.6)
AP	1 (1.8)
BP	2 (3.6)
Sokal score at diagnosis, n (%)	
Low	11 (21.2)
Intermediate	25 (48.1)
High	16 (30.8)
Transcript type, n (%)	
b2a2	23 (46.0)
b3a2	25 (50.0)
Other	2 (4.0)
Evaluable patients with confirmed *BCR-ABL1* mutation, n (%)	14 (37.8)
T315I mutation,[a] n (%)	4 (10.8)
Treatment line, n (%)	
2	28 (50.0)
3	19 (33.9)
4	7 (12.5)
5	2 (3.6)
Reasons for switching to ponatinib, n (%)	
Resistance	35 (62.5)
Intolerance	13 (23.2)
Warning response	4 (7.1)
Progression	1 (1.8)
Patient decision	2 (3.6)
Unknown	1 (1.8)
History of cardiovascular events, n (%)	20 (35.7)
Hypercholesterolemia, n (%)	7 (12.5)
Hypertension, n (%)	23 (41.1)
Diabetes Type I, n (%)	1 (1.8)
Diabetes Type II, n (%)	5 (8.9)
Patients receiving antithrombotic prophylaxis, n (%)	23 (41.1)

[a]37 evaluable patients.
AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukemia; CP, chronic phase.

Treatment

- The starting dose of ponatinib for patients with CP CML was 45 mg once daily in 41.5% of patients, 30 mg in 41.5% of patients, and 15 mg in 17.0% of patients (**Table 2**).
- Median treatment duration was 23.9 months (range, 3.3–49.9 months) at the time of analysis.

Table 2. Starting dose and duration of ponatinib treatment

	CP	AP	BP
Patients, n	53	1	2
Starting dose, n (%)			
45 mg	22 (41.5)	0	0
30 mg	22 (41.5)	0	1 (50.0)
15 mg	9 (17.0)	1 (100.0)	1 (50.0)
Median time on ponatinib, months (range)	23.85 (3.32–49.87)	6.22 (6.22–6.22)	12.89 (11.71–14.08)

AP, accelerated phase; BP, blast phase; CP, chronic phase.

- Eighty-five dose modifications took place in 34 CP CML patients; 26 were due to adverse events (AEs), 50 were due to medical decision, 2 were a dose increase for ineffectiveness, and 7 were due to other reasons (**Table 3**).
- Two dose modifications also occurred in 1 AP CML patient, and 1 dose modification occurred in 1 BP CML patient.

Table 3. Ponatinib dose modifications by starting dose

	45 mg	30 mg	15 mg	Other dose
Dose modifications[a], n	21	34	25	8
Cause of dose modification, n				
AE	7	9	8	2
Medical decision	12	21	15	5
Increase for ineffectiveness	0	2	0	0
Other	2	2	2	1

[a]Some patients had more than one dose modification.
AE, adverse event.

Efficacy

- Of 44 CP CML patients evaluable for cytogenetic response at 6 months, 39 (88.6%) achieved CCyR (primary endpoint).
- Of 40 CP CML patients evaluable for molecular response at 6 months, 37.5% and 15.0% achieved MMR and DMR, respectively (**Table 4**).

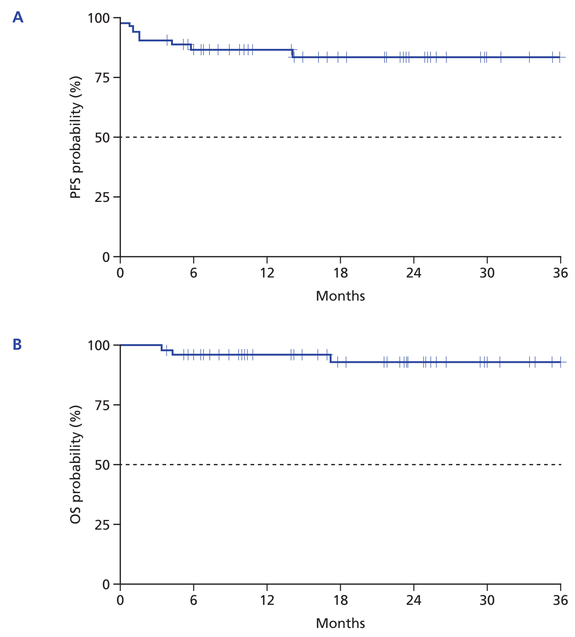
Table 4. Molecular response rates by ponatinib treatment line

	Treatment line			
	2L	3L	≥4L	Overall
Month 3, n (%)				
Evaluable patients, n	22	14	5	41
No molecular response	9 (47.4)	3 (23.1)	4 (80.0)	16 (43.2)
MR2.0	1 (5.3)	2 (15.4)	0	3 (8.1)
MR3.0	5 (26.3)	6 (46.2)	0	11 (29.7)
MR4.0	3 (15.8)	2 (15.4)	1 (20.0)	6 (16.2)
MR4.5	1 (5.3)	0	0	1 (2.7)
Month 6, n (%)				
Evaluable patients, n	18	16	6	40
No molecular response	2 (11.1)	3 (18.8)	0	5 (12.5)
MR2.0	5 (27.8)	2 (12.5)	4 (66.7)	11 (27.5)
MR3.0	8 (44.4)	7 (43.8)	0	15 (37.5)
MR4.0	0	2 (12.5)	1 (16.7)	3 (7.5)
MR4.5	3 (16.7)	2 (12.5)	1 (16.7)	6 (15.0)

2L, second-line; 3L, third-line; 4L, fourth-line; MR, molecular response.

- The estimated progression-free survival (PFS) rates for patients with CP CML at Months 12 and 24 were 86.6% (95% CI, 77.8–96.4%) and 83.7% (95% CI, 73.8–94.9%), respectively (**Figure 1A**).
- Corresponding overall survival (OS) rates were 96.2% (95% CI, 91.1–100.0%) and 93.1% (95% CI, 85.6–100.0%), respectively (**Figure 1B**).
- Four patients died due to progression to AP or BP in 2 patients, cerebral bleed in 1 BP CML patient, and an unknown cause in 1 patient.

Figure 1. PFS (A) and OS (B) for patients treated with ponatinib in the OITI trial



OS, overall survival; PFS, progression-free survival.

Safety

- Fifty-two treatment-related adverse events (TRAEs) occurred in 30 patients (53.6%) (**Table 5**).
- The most frequent TRAEs were skin lesions (n=13) and hypertension (n=8).
- The only hematologic TRAE reported was thrombocytopenia (n=1).
- Five cardiovascular events occurred in 3 patients (1 patient experienced both cerebrovascular accident and pulmonary arterial occlusive disease, 1 patient experienced both cerebrovascular accident and syncope, and 1 patient experienced transient ischemic attack).
- Of the 3 patients who experienced cardiovascular events, 2 received third-line ponatinib, and 1 received second-line ponatinib.
- Dose interruptions occurred in 13 patients due to TRAEs (n=5, 38.5%), medical decision (n=4, 30.8%) or other causes (n=4, 30.8%; comprising death in 3 cases and 1 attempt at treatment-free remission).

Table 5. Incidence of TRAEs across all patients[a]

TRAEs	n	TRAEs	n
Skin lesions	13	Pancreatitis	1
Hypertension	8	Pericardial effusion	1
Lipase increased	2	Erectile dysfunction	1
Pain in extremity	2	Pancreatitis acute	1
Cerebrovascular accident	2	Peripheral arterial occlusive disease	1
Decreased appetite	1	Fatigue	1
Dizziness	1	Photophobia	1
Dry eye	1	Gynecomastia	1
Dry mouth	1	Pyrexia	1
Asthenia	1	Hemorrhoids	1
Dysesthesia	1	Headache	1
Thrombocytopenia	1	Syncope	1
Dyspepsia	1	Transient ischemic attack	1
Metabolic disorder	1	Hypercholesterolemia	1
Hypothyroidism	1	Arthralgia	1

[a]Some patients experienced more than one TRAE.
TRAE, treatment-related adverse event.

Conclusions

- **Data show that ponatinib has a favorable efficacy and safety profile in patients with CML treated in standard clinical practice in Italy.**
- **By Month 6, most patients achieved CCyR; 44% of patients achieved an MMR with second- or third-line ponatinib.**
- **The probability of overall survival at 2 years was greater than 90%.**
- **Only 3 patients experienced cardiovascular events; no new safety signals emerged with ponatinib treatment than those previously reported.**
- **The early use of ponatinib (84% of patients received it as second- or third-line treatment) and careful dose selection appear key to the safety and efficacy outcomes as observed in this preliminary study evaluation.**

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References

1. Cortes JE, et al. *N Engl J Med*. 2013;369:1783–96.
2. Cortes JE, et al. *Blood*. 2018;132:393–404.
3. Ponatinib (ICLUSIG®) Summary of Product Characteristics 2019.