EFFICACY AND SAFETY OF PONATINIB IN CML AND PH+ ALL PATIENTS IN REAL-WORLD CLINICAL PRACTICE: DATA FROM A BELGIAN REGISTRY

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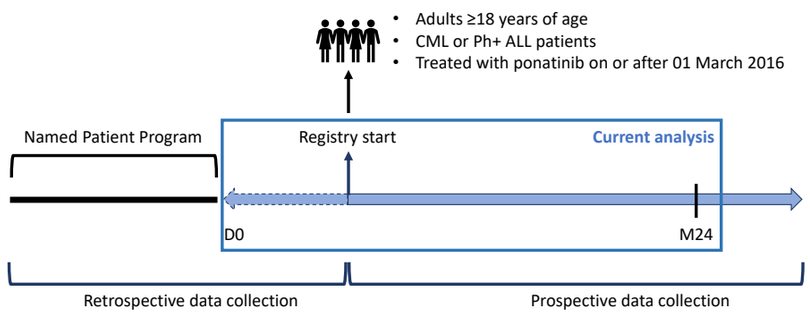
INTRODUCTION

- Ponatinib is a third-generation tyrosine kinase inhibitor (TKI), with activity against native and mutated BCR-ABL1.[1]
- In the European Union, ponatinib is indicated for adult patients with:
  - chronic myeloid leukemia (CML) in chronic phase (CP), accelerated phase, or blast phase, who are resistant or intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.
  - Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL), who are resistant or intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.[1]
- Long-term efficacy and safety of ponatinib have been demonstrated in the PACE clinical trial in heavily pre-treated CML or Ph+ ALL patients, with five years of follow-up.[2]
- In Belgium, ponatinib became available in 2012 via a Named Patient Program and has been commercially available since March 2016.
- This registry study aimed to collect real-world efficacy and safety data in CML and Ph+ ALL patients and evaluated ponatinib in routine clinical practice in Belgium.

METHODS

- This ongoing registry study is currently conducted in 19 centers across Belgium (**Figure 1, Figure 2**).

Figure 1. Study design



D, day; **M**, month. **D0**, the start of reimbursement of ponatinib in Belgium, i.e. 01 March 2016.

Figure 2. Overview of participating study centers

1. Algemeen Ziekenhuis Sint-Jan Brugge
2. Universitair Ziekenhuis Antwerpen
3. Ziekenhuis Netwerk Antwerpen Stuivenberg
4. Algemeen Ziekenhuis Klina
5. Algemeen Ziekenhuis Sint-Elisabeth
6. Algemeen Ziekenhuis Groeninge
7. Hôpital Erasme
8. Institut Jules Bordet
9. Centre Hospitalier Universitaire Brugmann
10. Universitair Ziekenhuis Brussel
11. Université catholique de Louvain Saint-Luc
12. Universitair Ziekenhuis Leuven
13. Jessa Ziekenhuis
14. Ziekenhuis Oost-Limburg
15. Centre Hospitalier Universitaire de Liège
16. Centre Hospitalier Régional Verviers
17. Hôpital de Jolimont
18. Centre Hospitalier Universitaire Charleroi Vésale
19. Centre Hospitalier Universitaire Université catholique de Louvain Namur, Site Godinne

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- The collected demographic, efficacy and safety data were analyzed by descriptive statistics.
- Ethics Committee approval was obtained, as well as patient informed consent.

RESULTS

Patients' characteristics

- At time of data analysis, 34 patients (21 diagnosed with CP-CML and 13 with Ph+ ALL) were enrolled.

Table 1. Previous treatment, ponatinib starting doses and baseline characteristics of study participants

	All (N=34)	CML patients (N=21)	Ph+ ALL patients (N=13)
Age in years, median (range)	57 (19–80)	57 (19–78)	55 (28–80)
Age in years, mean (SD)	54.6 (14.83)	55.9 (13.90)	52.5 (16.59)
Gender, n (%)			
Male	22 (65)	14 (67)	8 (62)
Female	12 (35)	7 (33)	5 (38)
Previous TKI lines, n (%)			
1 TKI	3 (9)	2 (10)	1 (8)
2 TKI	16 (47)	6 (29)	10 (77)
3 TKI	12 (35)	10 (48)	2 (15)
4 TKI	3 (9)	3 (14)	-
Ponatinib starting dose, n (%)			
45 mg/day	27 (79)	16 (76)	11 (85)
30 mg/day	3 (9)	2 (10)	1 (8)
15 mg/day	4 (12)	3 (14)	1 (8)
Medical history, n (%)			
Liver disorder	1 (3)	-	1 (8)
Pancreas disorder	2 (6)	2 (10)	-
Reduced kidney function	6 (18)	2 (10)	4 (31)
Hypertension	10 (29)	7 (33)	3 (23)
History of cardiovascular disease	11 (32)	7 (33)	4 (31)
Smoking	10 (29)	7 (33)	3 (23)
Diabetes	4 (12)	1 (5)	3 (23)
Hyperlipidemia	3 (9)	2 (10)	1 (8)
Hypercholesterolemia	5 (15)	1 (5)	4 (31)
History of significant alcohol abuse	3 (9)	3 (14)	-
Other	25 (74)	14 (67)	11 (85)

SD, standard deviation; **N**, total number of patients; **n (%)**, number (percentage) of patients in respective category

- The main reason for starting ponatinib treatment was refractoriness (36%) or intolerance (29%) to previous TKIs (**Figure 3**). Eighty percent (8/10) of the patients who started ponatinib due to intolerance to previous TKIs had received 3 or more prior TKIs.
- At entry, 16 patients had a confirmed BCR-ABL mutation. Of these, 63% (5 CML and 5 Ph+ ALL patients) had the T315I mutation (**Figure 4**).

Figure 3. Reasons for starting ponatinib treatment

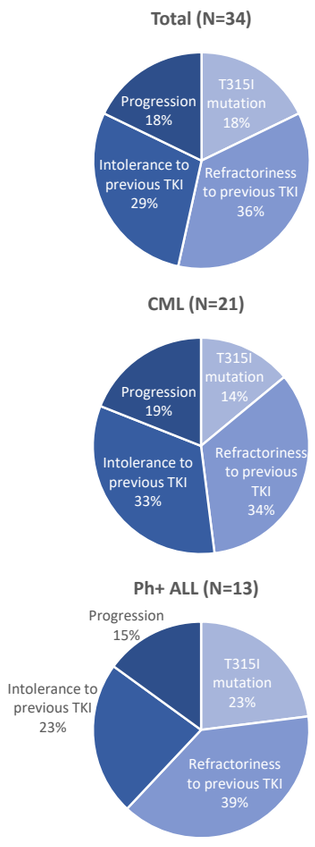
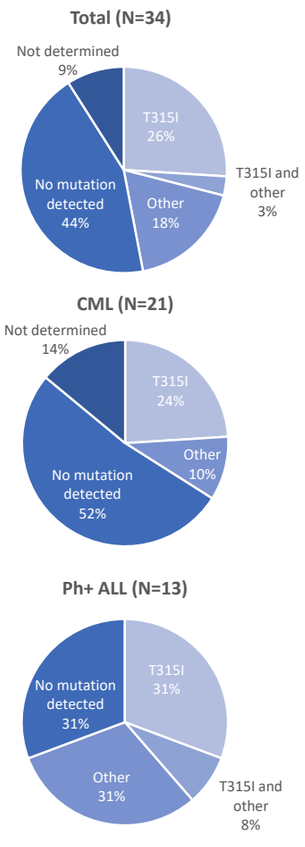


Figure 4. Patients with mutations



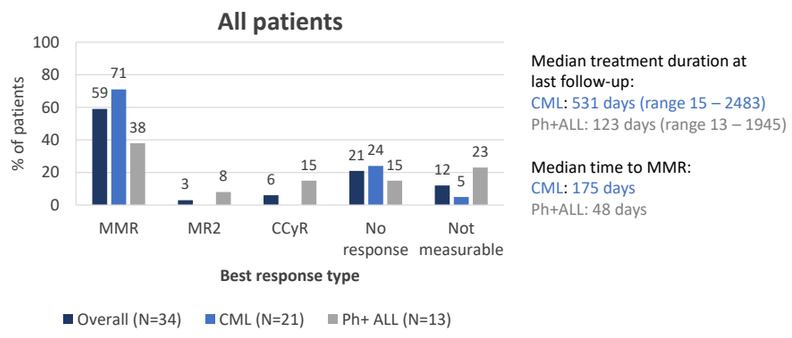
Percentages may not total 100 due to rounding

Treatment duration and responses

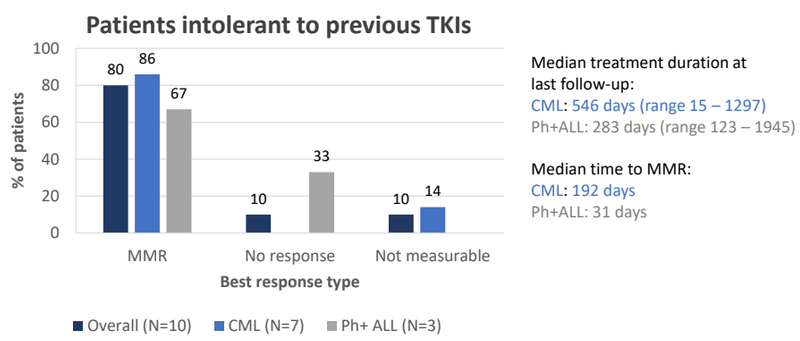
- The median follow-up of patients in the registry was 539 days for CML and 135 days for Ph+ ALL patients.
- Of patients with CML, 71% achieved a major molecular response (MMR); the median time to MMR was 175 days. In Ph+ ALL patients, 38% achieved MMR; the median time to MMR was 48 days (**Figure 5**).

Figure 5. Treatment duration and best responses by diagnosis for all patients (A) and for those who started ponatinib due to intolerance to previous TKIs (B)

A.



B.

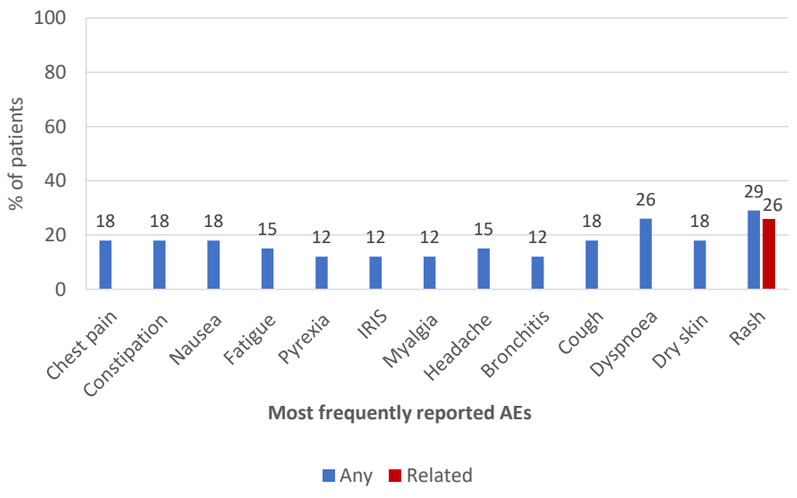


MMR, major molecular response; **MR2**, 2-log molecular response; **CCyR**, complete cytogenic response

Adverse events

- At least one adverse event (AE) was reported by 31 (91%) patients. Treatment-related AEs were reported in 20 (59%) patients. The most commonly reported AEs (by ≥10% of patients) are presented in **Figure 6**.
- Three patients reported at least one treatment-related serious AE (SAE): thrombocytopenia (n=1), cholecystitis (n=1) and hepatocellular injury (n=1).
- Three serious cardiovascular events were observed in 1 patient, who had a history of congenital cardiomyopathy and aortic prosthesis. These AEs were considered by the investigator as not related to ponatinib.

Figure 6. Most frequently reported adverse events (≥10% of patients), any and treatment-related



IRIS, immune reconstitution inflammatory syndrome

Treatment modifications

Table 2. Overview of and reasons for treatment modifications

	All	CML patients	Ph+ ALL patients
Treatment modification, n (%)	**N=34**	**N=21**	**N=13**
Dose reduction	16 (47)	11 (52)	5 (38)
Dose increase	10 (29)	8 (38)	2 (15)
Treatment interruption	10 (29)	6 (29)	4 (31)
Treatment termination	19 (56)	9 (43)	10 (77)
No change	3 (9)	2 (10)	1 (8)
Reasons for dose reduction/interruption, n' (%)	**N'=33**	**N'=20**	**N'=13**
AE	25 (76)	16 (80)	9 (69)
Prevention	6 (18)	4 (20)	2 (15)
Other	2 (6)	-	2 (15)
Reasons for dose increase, n' (%)	**N'=12**	**N'=10**	**N'=2**
No or low response	4 (33)	3 (30)	1 (50)
Good tolerance of treatment	7 (58)	6 (60)	1 (50)
Other	1 (8)	1 (13)	-
Reasons for treatment termination, n' (%)	**N'=19**	**N'=9**	**N'=10**
AE	6 (32)	5 (56)	1 (10)
SAE	1 (5)	-	1 (10)
Disease progression	3 (16)	1 (11)	2 (20)
Primary resistance	-	-	-
Relapse	-	-	-
Intolerance	-	-	-
Planned allogenic transplantation	4 (21)	-	4 (40)
Other	5 (26)	3 (33)	2 (20)

AE, adverse event; **SAE**, serious AE; **N**, total number of patients; **N'**, total number of treatment modifications (dose increase, dose decrease/interruption or treatment termination); **n (%)**, number (percentage) of patients in respective category; **n' (%)**, number (percentage) of treatment modifications in respective category.

CONCLUSIONS

- Real-world evidence from this Belgian registry confirms the PACE results in real life, and supports the use of ponatinib in CML and Ph+ ALL patients who are resistant or intolerant to second generation TKIs and in patients with the T315I mutation.
- Deep molecular responses were obtained in the majority of patients.
- The side effect profile was manageable and no new safety signals emerged with ponatinib treatment than those previously reported.

References

1. Iclusig (ponatinib) Summary of Product Characteristics. September 2018.
2. Cortes JE et al. Blood. 2018;132(4):393–404.

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