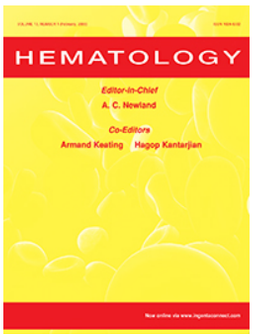

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Real-world outcomes in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia or chronic myeloid leukemia treated with ponatinib – final 6-year results from a Belgian registry

Timothy Devos [a], Dries Deeren [b], Koen Theunissen[c], Dominik Selleslag[d], Benjamin Bailly[e], Violaine Havelange [f], Philippe Lewalle [g], Stef Meers [h], Fleur Samantha Benghiat [i†], Alain Gadisseur [j], Nikki Granacher[k], Gaëtan Vanstraelen[l], Hélène Vellemans[m], Ann De Becker [n], Mia Janssen[o], Inge Vrelust[p], Marie Lejeune[q], Ann Van de Velde [j,r], Agnès Triffet[s‡], Michael Beck[t], Hinde Sebti[t] and Dominiek Mazure[u]

[a]Department of Hematology, University Hospitals Leuven and Laboratory of Molecular Immunology (Rega Institute), KU Leuven, Leuven, Belgium; [b]Algemeen Ziekenhuis Delta, Roeselare, Belgium; [c]Jessa Ziekenhuis, Hasselt, Belgium; [d]Algemeen Ziekenhuis Sint-Jan Brugge, Brugge, Belgium; [e]Hôpital de Jolimont, Haine-Saint-Paul, Belgium; [f]UCL Saint-Luc, Woluwe-Saint-Lambert, Belgium; [g]Institut Jules Bordet, Université Libre de Bruxelles, Bruxelles, Belgium; [h]Algemeen Ziekenhuis Klina, Brasschaat, Belgium; [i]HUB Hôpital Erasme, ULB, Brussels, Belgium; [j]Universitair Ziekenhuis Antwerpen, Edegem, Belgium; [k]Ziekenhuis Netwerk Antwerpen Stuivenberg, Antwerpen, Belgium; [l]CHR Verviers, Verviers, Belgium; [m]CHU UCL Namur, Site Godinne, Yvoir, Belgium; [n]Department of Hematology, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium; [o]Ziekenhuis Oost-Limburg, Genk, Belgium; [p]Algemeen Ziekenhuis Turnhout, Turnhout, Belgium; [q]Centre Hospitalier Universitaire de Liège (Sart Tilman), Liège, Belgium; [r]Heilig Hart Ziekenhuis Lier, Lier, Belgium; [s]Centre Hospitalier Universitaire Charleroi Vésale, Charleroi, Belgium; [t]Incyte Biosciences Benelux BV, Amsterdam, The Netherlands; [u]Universitair Ziekenhuis Gent, Gent, Belgium

ABSTRACT

Background: Ponatinib is a third-generation tyrosine kinase inhibitor (TKI) for treatment of chronic myeloid leukemia (CML) and Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) in patients who fail or are intolerant to a second generation TKI or who carry the *T315I* mutation.

Method: This is the final analysis of the Belgian ponatinib registry evaluating use of ponatinib in clinical practice, with data available for up to 6 years after reimbursement.

Result: Forty-eight percent of 54 CML and 28% of 29 Ph+ ALL patients had received ≥3 previous TKIs. Before ponatinib, most patients had already achieved a response, including at least a major molecular response (MMR), in 19% of CML and 17% of Ph+ ALL patients. Ponatinib was initiated due to intolerance to previous TKIs in 50% of CML and 41% of Ph+ ALL patients. Median follow-up was 545 and 258 days for CML and Ph+ ALL patients, respectively. Best response to ponatinib was at least an MMR in 65% of CML and 55% of Ph+ ALL patients. Overall and progression-free survival were 85.8% and 83.8% in CML patients after 48 months of treatment, and 82.5% and 54.2% in Ph+ ALL patients after 30 months of treatment. Adverse reactions were reported by 85% of CML and 76% of Ph+ ALL patients, with 33% of CML and 24% of Ph+ ALL patients experiencing cardiovascular events.

Conclusion: In line with previously published trials, these real-world data support use of ponatinib in CML and Ph+ ALL patients with resistance or intolerance to previous TKIs or carrying the *T315I* mutation.

Trial registration: ClinicalTrials.gov identifier: NCT03678454; September 19, 2018.

Plain language summary

What is this study about?

- Chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) are types of blood cancer.
- Ponatinib belongs to a group of medicines called tyrosine kinase inhibitors (TKIs).

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Ponatinib; real-world evidence; registry; Philadelphia chromosome-positive acute lymphoblastic leukemia; chronic myeloid leukemia

CONTACT Timothy Devos timothy.devos@uzleuven.be Department of Hematology, University Hospitals Leuven and Laboratory of Molecular Immunology (Rega Institute), KU Leuven, Leuven, Belgium
†At the time of the study. Prof. Benghiat's current affiliation is CHU Tivoli, Tivoli, Belgium
‡At the time of the study. Dr Triffet's current affiliation is Clinique Saint Pierre, Ottignies, Belgium.
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People with CML or Ph+ ALL can use ponatinib if they no longer benefit from or cannot tolerate treatment with at least two previous TKIs, or if their cancer cells have a gene change (or mutation) called *T315I*.
- This study looked at people with CML and Ph+ ALL being given ponatinib at Belgian hospitals over 6 years and how they responded to ponatinib treatment.

What were the results?
- Almost 50% of people with CML and 30% of people with Ph+ ALL received treatment with three or more TKIs before ponatinib.
- Many people started taking ponatinib because they could not tolerate their previous TKI.
- 86% of people with CML were alive after 48 months of ponatinib treatment. The cancer did not get any worse in 84% of people during this time.
- 83% of people with Ph+ ALL were alive after 30 months of ponatinib treatment. The cancer did not get any worse in 54% of people during this time.
- 33% of people with CML and 24% of people with Ph+ ALL experienced cardiovascular side effects

What do the results mean?
- This real-world study shows that people with CML and Ph+ ALL who do not respond to or cannot tolerate another TKI, or who carry the *T315I* mutation, may benefit from ponatinib treatment and toxicity is generally acceptable.

1. Introduction

Patients with chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) benefit from tyrosine kinase inhibitor (TKI) treatment because they suppress malignant cell growth by targeting the constitutively active *BCR-ABL1* tyrosine kinase [1–3]. The development of resistance, notably through the acquisition of mutations in the *ABL1* kinase domain, is one of the challenges of TKI therapy [3]. Using a second-generation TKI in CML patients resistant to another second-generation TKI is of limited value because the responses are usually not durable [4,5]. Some patients also develop adverse events (AEs) and become intolerant to TKIs if the AEs cannot be managed [6].

First-generation (imatinib), second-generation (nilotinib, dasatinib, and bosutinib) and third-generation (ponatinib) TKIs are currently reimbursed in Belgium for the treatment of CML [7]. Asciminib, an allosteric BCR-ABL1 inhibitor, is reimbursed for the treatment of chronic-phase CML (CP-CML) [7,8]. Imatinib, dasatinib, and ponatinib are also reimbursed for Ph+ ALL [7]. In Belgium, ponatinib is reimbursed for patients aged $\geq$ 18 years diagnosed with CML (chronic, accelerated, or blast phase) who have received $\geq$ 2 previous TKIs, or at any time if they harbor a *T315I* mutation. In Ph+ ALL patients, ponatinib is reimbursed in case of resistance or intolerance to dasatinib and when treatment with imatinib is not appropriate, or for any line of treatment if they harbor a *T315I* mutation [7].

Ponatinib is active against the *BCR-ABL1* oncoprotein and all its common mutated forms, including the *T315I* mutation [9]. A high proportion of CML and Ph+ ALL patients with resistance to previous TKI therapies were shown to respond to ponatinib treatment [2,9]. The recommended starting dose for ponatinib is 45 mg/day [10]. For patients with resistance to a second-generation TKI without a specific mutation, the European LeukemiaNet guidelines recommend ponatinib over another second-generation TKI, unless unacceptable cardiovascular risk factors are present [11,12].

Ponatinib received market approval in Europe on July 1, 2013, based on the Ponatinib Ph+ ALL and CML Evaluation (PACE) trial results [10]. This trial showed the efficacy and safety of ponatinib in CML and Ph+ ALL patients resistant or intolerant to dasatinib or nilotinib, and in patients with the *T315I* mutation [9,13]. The 5-year follow-up data from PACE demonstrated deep and durable responses to ponatinib in CP-CML patients [9]. A prolonged efficacy and safety evaluation of ponatinib was carried out during the POST-PACE study [14]. Twenty-one CP-CML patients agreed to participate, and all but two patients maintained their response, indicating a long-term clinical benefit of ponatinib [14].

In the 5-year follow-up of the PACE trial, the cumulative incidence of arterial occlusive events (AOEs) was 25% [9]. An independent cardiovascular adjudication committee performed a retrospective analysis of the AOEs in the PACE trial and reported an adjudicated AOE rate of 17% [15]. As AOEs were shown to be dose-dependent in the PACE trial [9], the benefit/risk ratio of the different starting doses (45, 30, and 15 mg/day) was assessed in the Optimizing Ponatinib Treatment in CP-CML (OPTIC) trial [16]. This trial

showed a better benefit/risk ratio in CP-CML patients treated with ponatinib at a starting dose of 45 mg/day, and showed that responses were maintained in most of the patients after a response-based dose reduction to 15 mg/day [16]. The efficacy in the OPTIC trial was in the same range as in the PACE trial for CP-CML patients [13,16]. The rates of AOEs and exposure-adjusted AOEs in the OPTIC trial (9.6% and 5.6%, respectively, in the 45 mg/day cohort) were lower than those reported for the PACE trial [9,16].

The previously reported 3-year results of the present registry showed that 58% of CML patients ($n = 33$) and 41% of Ph+ ALL patients ($n = 17$) achieved at least a major molecular response (MMR) as best response, and adverse reactions were reported in 34 patients (68%) [17]. Here, we report the final data, based on up to 6 years of follow-up, on the routine use of ponatinib and its outcomes in CML and Ph+ ALL patients in Belgium.

2. Methods

2.1. Study objectives

The primary objective was to gather data on ponatinib dosage and treatment duration in routine practice in Belgium, up to 6 years after reimbursement. The secondary objectives were to describe the demographic and disease characteristics of CML and Ph+ ALL patients treated with ponatinib, and the treatment outcomes.

2.2. Registry design and patients

This was a multi-center, prospective registry (clinicaltrials.gov identifier: NCT03678454) conducted in 21 hospitals in Belgium. The registry was initiated on January 5, 2017; the study was completed on March 31, 2022; and the database lock was on September 1, 2022. The inclusion and exclusion criteria were previously described [17].

The registry was conducted in accordance with the Declaration of Helsinki; the International Conference on Harmonisation Good Clinical Practice guidelines; the International Ethical Guidelines for Epidemiological Research; all applicable legal, regulatory and patient privacy requirements; Good Pharmacoepidemiology Practices; and Good Epidemiological Practice guidelines. All patients provided written informed consent before data collection. A waiver was granted by the ethics committee (EC) for Named Patient Program (NPP) patients who were still on ponatinib treatment on March 1, 2016, but deceased before registry initiation. The registry protocol, any subsequent amendments and the informed consent form were approved by the central EC and/or local ECs at each participating center (i.e. UZ Leuven EC onderzoek, Commission éthique Saint-Luc, Commissie voor Medische Ethiek ZNA, Comité d'éthique CHU UCL Namur, Ethisch Comité UZA, Ethisch Comité Instituut Jules Bordet, Ethische zorg AZ Turnhout, Comité d'Éthique Hospitalo-Facultaire Universitaire de Liège, Ethisch comité AZ Klina, Ethische Toetsingscommissie Jessa, Comité éthique CHPLT, Comité d'Ethique Hôpital Erasme, Commissie Medische Ethiek UZ Brussel, Commissie Medische Ethiek AZ Groeninge, Comité voor ziekenhuisethiek CHU Brugmann, Commissie voor Medische ethiek UZ Gent, Commissie medische ethiek AZ Delta, Commissie voor Ethiek AZ Sint-Jan Brugge, Comité d'éthique de Jolimont, Comité medische ethiek Ziekenhuis Oost-Limburg, Ethische commissie Heilig Hart ziekenhuis Lier and Comité d'éthique CHU Charleroi Vésale).

All procedures related to registry conduct, data management, statistical analysis and scientific writing were performed by Akkodis, Wavre, Belgium.

2.3. Data collection

Data were collected during routine care visits or every 6 months and were encoded in electronic case report forms. Information was captured from the start of ponatinib treatment, meaning some data were collected retrospectively. Since the objective of the trial was the collection of efficacy and safety data on the use of ponatinib in real-world setting, per protocol, no information was collected on the use of TKIs following ponatinib.

Concomitant use of additional active antileukemic agents such as chemotherapy was allowed during the study. However, the type, dose and duration of concomitant treatment was not captured in the study. Also to note, for patients with Ph+ ALL no use of ponatinib with blinatumomab was expected considering that blinatumomab was not approved in Belgium at the time of the study. For patients in the NPP, data were collected retrospectively. The data collected included documentation and date of informed consent, participation in NPP, patient demographics, disease characteristics, medical history, treatment patterns, treatment outcomes, and safety. Safety data were collected as of March 1, 2016. All AEs were reported based on a pre-defined list (Supplementary Table S1). The treating health care professional could select the option 'other' to describe an AE not included in the list. All AEs assessed as potentially related to ponatinib treatment were described as adverse reactions. The treating health care professional and the Incyte pharmacovigilance and risk manager performed causality assessments. Adverse reactions of interest (notably including cardiovascular events and AOEs) were assessed based on the Summary of Product Characteristics and the expertise of two investigators (Timothy Devos and Philippe Lewalle). The decision on the choice of treatments prior to the use of ponatinib was at the discretion of the treating physician and was not collected in the study.

2.4. Data analysis

Descriptive analyses per indication were conducted, including counts and percentages for categorical endpoints and number, mean, standard deviation, median, minimum and maximum for continuous endpoints. Overall survival (OS) and progression-free survival (PFS) were generated using the Kaplan-Meier method. The sample size was not determined before the start of the registry. Subgroup analyses were performed per indication for patients who started ponatinib due to TKI intolerance (further referred to as patients with TKI intolerance) or for other reasons (i.e. progression, *T315I* mutation and refractoriness, including primary refractoriness, no response and hematologic, cytogenetic, or molecular relapse; further referred to as patients without previous TKI intolerance), for patients who had an allogeneic stem cell transplantation (SCT) before initiation of ponatinib and for patients with at least an MMR as best response during ponatinib treatment.

Table 1. Patient baseline characteristics.

	CML patients ($N = 54$)	Ph+ ALL patients ($N = 29$)
Age in years, median (range)	60 (19–83)	56 (19–89)
Age in years, mean (SD)	57.2 (16.68)	54.8 (17.32)
Male, *n* (%)	35 (65)	15 (52)
Previous TKI lines, *n* (%)		
1 TKI	6 (11)	1 (3)
2 TKIs	22 (41)	20 (69)
≥ 3 TKIs	26 (48)	8 (28)
Presence of mutations, *n* (%)		
No mutation	34 (63)	13 (45)
T315I	8 (15)	9 (31)
Other	6 (11)	5 (17)
T315I and other mutation	1 (2)	1 (3)
Not determined	5 (9)	1 (3)
Medical history, *n* (%)		
Liver disorder	1 (2)	3 (10)
Pancreas disorder	2 (4)	1 (3)
Reduced kidney function	4 (7)	5 (17)
Hypertension	15 (28)	9 (31)
Cardiovascular disease	18 (33)	9 (31)
Smoking	12 (22)	4 (14)
Diabetes	7 (13)	6 (21)
Hyperlipidemia	4 (7)	2 (7)
Hypercholesterolemia	4 (7)	4 (14)
Significant alcohol abuse	4 (7)	–
Other	41 (76)	25 (86)

CML, chronic myeloid leukemia; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukemia; SD, standard deviation; TKI, tyrosine kinase inhibitor.

3. Results

3.1. Patient characteristics

During the study period, 54 patients with CML (65%) and 29 with Ph+ ALL (35%) were included in the registry (Table 1). The median age was 60 (19–83) years for CML patients and 56 (19–89) years for Ph+ ALL patients, and more patients were male (65% for CML and 52% for Ph+ ALL) (Table 1). Some CML and Ph+ ALL patients reported a history of cardiovascular disease (33% and 31%), hypertension (28% and 31%), smoking (22% and 14%), and diabetes (13% and 21%) (Table 1). Among the CML patients, 47 were diagnosed with CP-CML, 5 with accelerated-phase CML (AP-CML), 1 with CML in myeloid blast phase and 1 with CML in lymphoid blast phase. Five CML patients and 6 Ph+ ALL patients received ponatinib through the NPP; the other patients started treatment after March 1, 2016.

Among CML patients, 15 had a mutation in the *BCR-ABL1* kinase domain, with 8 patients (15%) having a *T315I* mutation, 6 (11%) having another mutation and 1 (2%) having both a *T315I* mutation and another mutation. No mutations were detected in 34 patients (63%) and mutation status was not determined for 5 patients (9%) (Table 1). Among Ph+ ALL patients, 15 had a mutation in the *BCR-ABL1* kinase domain, with 9 patients (31%) having a *T315I* mutation, 5 (17%) having another mutation and 1 (3%) having the *T315I* mutation and another mutation, and no mutation could be identified for 13 patients (45%). Mutation status was not determined in 1 patient (3%) (Table 1).

3.2. Previous treatment

Almost half of CML patients (48%) had received $\geq$ 3 previous lines of TKI treatment before ponatinib initiation. Six CML patients (11%) received 1 previous line of TKI treatment, of whom 3 had the *T315I* mutation, 2 had no mutation and 1 had an undetermined mutation status. Twenty-two CML patients (41%) had received 2 previous lines of TKI treatment (Table 1). For Ph+ ALL, 69% ($n = 20$) of the patients had received 2 previous TKIs, 28% ($n = 8$) had received 3 previous TKIs, and 3% ($n = 1$) have received 1 previous TKI (Table 1). None of the Ph+ ALL patients had received > 3 previous treatment lines. The most commonly used first-line TKI was imatinib (65% for CML and 97% for Ph+ ALL), dasatinib was the first choice as second-line TKI (57% and 83%) and nilotinib was mostly used as third-line TKI (17% for both diagnoses). Three CML patients (6%) and 6 Ph+ ALL patients (21%) had an allogeneic SCT before ponatinib treatment initiation.

3.3. Response at baseline (before ponatinib treatment)

Before starting ponatinib treatment, 10 CML patients (19%) had achieved at least an MMR (*BCR-ABL1*$^{International\ Scale\ [IS]} \leq 0.1\%$), 16 (30%) a molecular response 2 (MR2; *BCR-ABL1*$^{IS} \leq 1\%$), 7 (13%) a complete cytogenetic response (CCyR), 9 (17%) a partial cytogenetic response (PcyR), 6 (11%) had an unknown response, and 6 (11%) did not have a hematologic response (Figure 1). For the 29 Ph+ ALL patients, the responses at baseline were as follows: 5 (17%) had achieved at least an MMR, 4 (14%) an MR2, 5 (17%) a CcyR, 5 (17%) a PcyR, 1 (3%) a complete hematologic response, 5 (17%) an unknown response, and 4 (14%) did not have any response (Figure 1).

3.4. Ponatinib treatment

In CML patients, treatment with ponatinib was initiated due to intolerance to previous TKIs in 27 patients (50%), due to refractoriness in 13 patients (24%), due to progression in 8 patients (15%) and due to the presence of the *T315I* mutation in 6 patients (11%) (Figure 2). Among Ph+ ALL patients, treatment with ponatinib was initiated due to intolerance to previous TKIs in 12 patients (41%), due to refractoriness in 9 patients (31%), due to progression in 2 patients (7%), and due to the presence of the *T315I* mutation in 6 patients (21%) (Figure 2).

The median time from diagnosis to start of ponatinib treatment was 1065 (44–8139) days in CML patients and 418 (80–5851) days in Ph+ ALL patients. Most patients (69% for CML and Ph+ ALL) received ponatinib 45 mg/day at initiation. The 30 mg/day starting dose was administered to 9% of

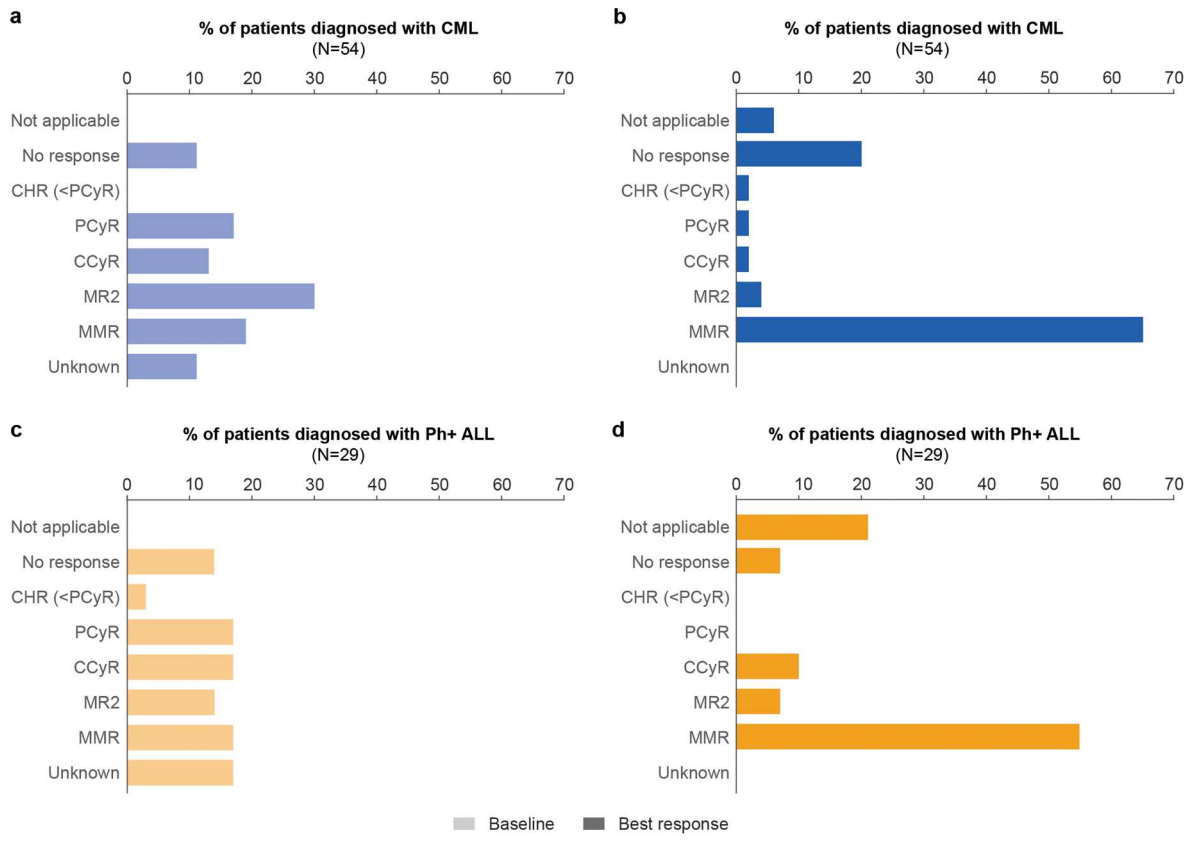

Figure 1. (a) Baseline response before starting ponatinib and (b) best response to ponatinib in patients with CML, and (c) baseline response before starting ponatinib and (d) best response to ponatinib in patients with Ph+ ALL. *CCyR* complete cytogenetic response, *CHR* complete hematologic response, *CML* chronic myeloid leukemia, *MMR* major molecular response, *MR2* molecular response 2, *PCyR* partial cytogenetic response, *Ph+ ALL* Philadelphia chromosome-positive acute lymphoblastic leukemia.

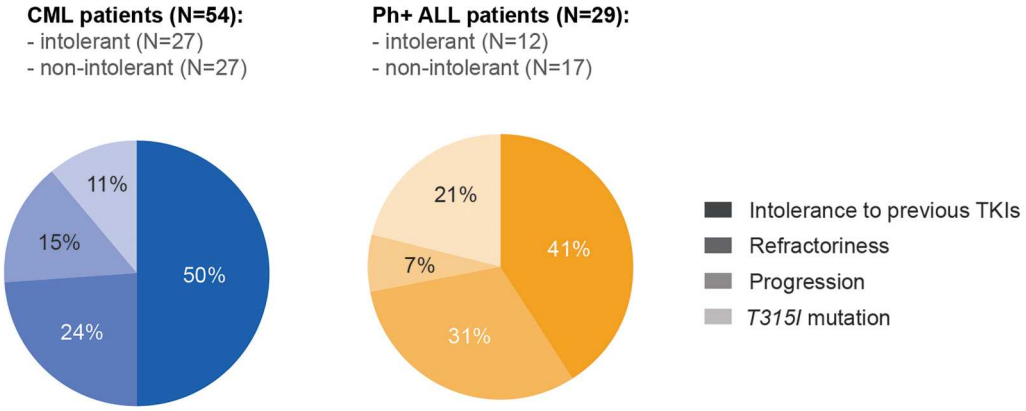

Figure 2. Reasons for starting ponatinib treatment. *CML* chronic myeloid leukemia, *intolerant* patients who started ponatinib due to intolerance to previous TKIs; *non-intolerant* patients who started ponatinib due to progression, *T315I* mutation and refractoriness (including primary refractoriness, no response and hematologic, cytogenetic or molecular relapse), *Ph+ ALL* Philadelphia chromosome-positive acute lymphoblastic leukemia, *TKI* tyrosine kinase inhibitor.

CML patients and 17% of Ph+ ALL patients, the 15-mg/day dose to 20% of CML patients and no Ph+ ALL patients, and 1 CML patient (2%) and 4 Ph+ ALL patients (14%) received 15 mg every 2 days as a starting dose. More than half of the Ph+ ALL patients (52%) did not receive concomitant chemotherapy.

3.5. Treatment outcomes

The median follow-up duration was 545 (14–3890) days for CML patients and 258 (26–3289) days for Ph+ ALL patients. The median treatment duration was 540 (14–3890) days in CML patients and 210 (13–3289) days in Ph+ ALL patients. For CML and Ph+ ALL patients with a previous allogeneic SCT, the median treatment duration was 547 (412–1778) days and 699 (88–3289) days, respectively. Treatment duration and outcome per patient is presented in Figure 3.

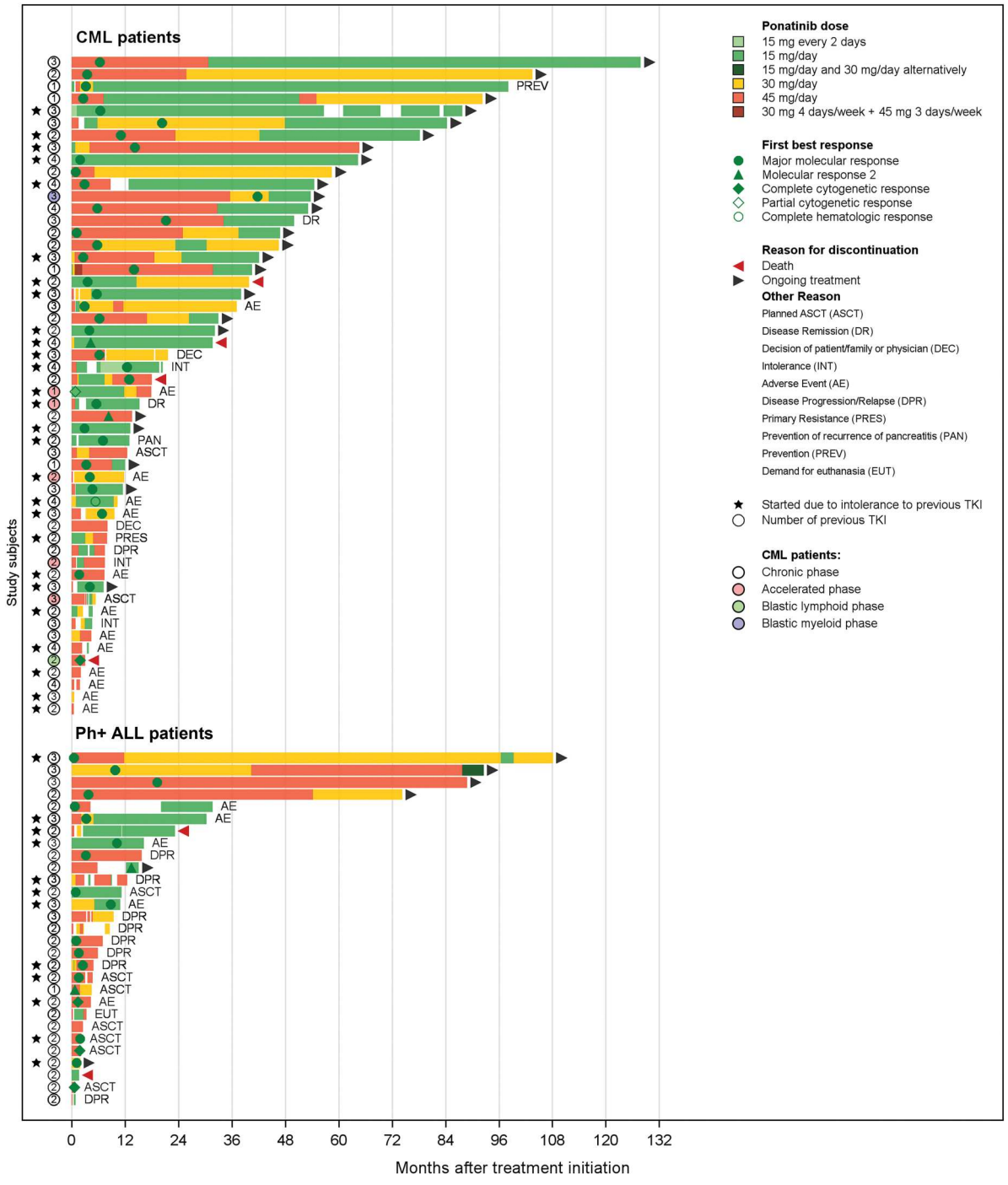

Figure 3. Swimmer plot with the reason for starting ponatinib treatment, the number of previous TKIs, the treatment duration, the treatment modification, the best response per patient and the reason for treatment termination. Each bar represents a single patient. *CML* chronic myeloid leukemia, *Ph+ ALL* Philadelphia chromosome-positive acute lymphoblastic leukemia, *TKI*, tyrosine kinase inhibitor.

The best response to treatment in CML patients was at least an MMR in 35 patients (65%) (Figure 1). Of the CML patients achieving at least an MMR, 71% initiated ponatinib at 45 mg/day, 3% at 30 mg/day, 23% at 15 mg/day and 3% at 15 mg every 2 days. Of the remaining CML patients, 2 (4%) achieved an MR2, 1 (2%) achieved a CcyR, 1 (2%) achieved a PcyR, 1 (2%) achieved a complete hematologic response, and 11 (20%) did not achieve any response (Figure 1). There was no effect of the number of previous TKI lines or the reason for initiating ponatinib treatment on the best response. All CML patients who had received an allogeneic SCT before the start of ponatinib achieved at least an MMR. The best response to treatment in Ph+ ALL patients was at least an MMR in 16 patients (55%) (Figure 1), of whom 57% initiated ponatinib at 45 mg/day, 21% at 30 mg/day and 21% at 15 mg/day. An MR2 was achieved as best response in 7% of Ph+ ALL patients, a CcyR by 10% of patients, and no response in 7% of patients (Figure 1). There was no effect of the number of previous TKI lines on the best response. Ph+ ALL patients with previous TKI intolerance achieved at least an MMR in 75% of cases compared with 41% of patients without previous TKI intolerance. Ph+ ALL patients with an allogeneic SCT prior to ponatinib treatment achieved at least an MMR in 83% of cases.

The median time to best response in CML and Ph+ ALL patients was 151 (24–1271) days and 55 (14–583) days after ponatinib initiation, respectively. For CML patients who achieved at least an MMR as best response, the median time was 168 (26–1271) days. For Ph+ ALL patients, the median time to best response in patients who achieved at least an MMR was 66 (14–583) days. The median time to best response in CML patients with and without TKI intolerance was 130 (24–431) days and 175 (26–1271) days, respectively. For Ph+ ALL patients, this was 52 (14–308) days and 55 (19–583) days, respectively. Within 5 months after first response, > 90% of patients with CML continued to respond to treatment. More patients with previous TKI intolerance continued to respond to treatment compared with patients without previous TKI intolerance (100% vs 90%). Of Ph+ ALL patients, 70% continued to respond to treatment after 1 year. Ten months after first response, more Ph+ ALL patients with previous TKI intolerance continued to respond to treatment compared with patients without previous TKI intolerance (80% vs 60%).

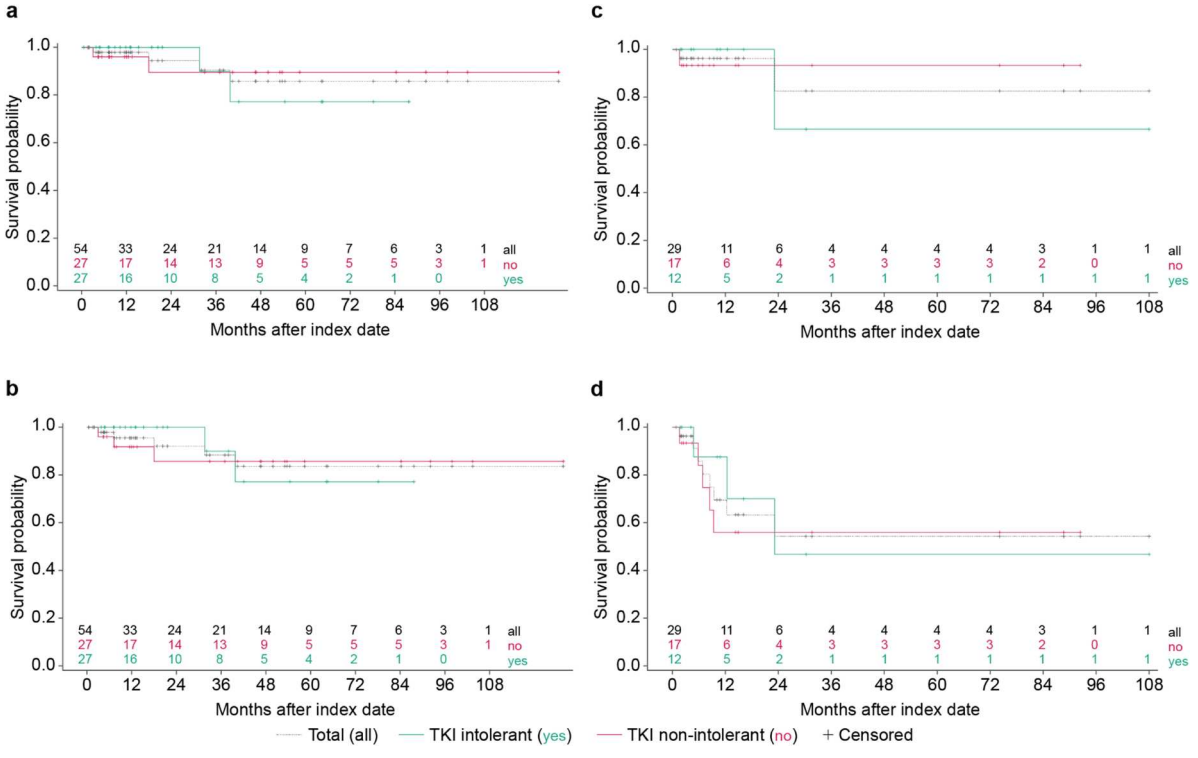

Figure 4. Kaplan–Meier estimates of (a) overall survival and (b) progression-free survival in patients with CML, and (c) overall survival and (d) progression-free survival in patients with Ph+ ALL. *CML* chronic myeloid leukemia, *Ph+ ALL* Philadelphia chromosome-positive acute lymphoblastic leukemia, *TKI* tyrosine kinase inhibitor.

Table 2. Overview and reasons for treatment modifications.

Treatment modification, *n* (%)	CML patients *N* = 54	Ph+ ALL patients *N* = 29
Dose reduction	36 (67)	15 (52)
Dose increase	21 (39)	7 (24)
Treatment interruption	22 (41)	10 (34)
Treatment termination	30 (56)	23 (79)
No change	3 (6)	2 (7)
Reasons for dose reduction/interruption, *n'* (%)	*N'* = 82	*N'* = 37
AE	57 (70)	21 (57)
Prevention	24 (29)	14 (38)
No response	–	1 (3)
Missing	1 (1)	1 (3)
Reasons for dose increase, *n'* (%)	*N'* = 28	*N'* = 10
No or low response	13 (46)	2 (20)
Good tolerance of treatment	14 (50)	8 (80)
Other	1 (4)	–
Reasons for treatment termination, *n'* (%)	*N'* = 30	*N'* = 23
AE	11 (37)	5 (22)
SAE	2 (7)	–
Disease progression	1 (3)	6 (26)
Disease remission	1 (3)	–
Primary resistance	1 (3)	–
Relapse	–	1 (4)
Intolerance	3 (10)	–
Planned allogeneic SCT	2 (7)	7 (30)
Other	9 (30)	4 (17)

AE, adverse event; CML, chronic myeloid leukemia; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukemia; SAE, serious adverse event; SCT, stem cell transplantation.

The probability of OS for CML patients was 85.8% after 48 months of treatment, with 89.7% for patients without TKI intolerance and 77.1% for patients with TKI intolerance (Figure 4(a)). The probability of PFS for CML patients was 83.8% after 48 months of treatment, with 85.7% for patients without TKI intolerance and 77.1% for patients with TKI intolerance (Figure 4(b)). For Ph+ ALL patients, the probability of OS was 82.5% after 30 months of treatment, with 93.3% for patients without TKI intolerance and 66.7% for patients with TKI intolerance (Figure 4(c)). The probability of PFS for Ph+ ALL patients was 54.2% after 30 months of treatment, with 56.0% for patients without TKI intolerance and 46.7% for patients with TKI intolerance (Figure 4(d)).

In CML patients, dose reduction (67%), treatment termination (56%), treatment interruption (41%), and dose increase compared with the starting dose (39%) were observed (Table 2). Dose reduction or treatment interruption was mostly carried out due to an AE (70%), and a dose increase when the treatment was well tolerated (50%) or when there was no or insufficient response (46%) (Table 2). The main reasons for treatment termination were AEs (37%), 'other' (30%), intolerance (10%), serious AEs (7%), and a planned allogeneic SCT (7%) (Table 2). The reasons combined under 'other' are death ($n = 4$), prevention of AEs ($n = 1$), prevention of recurrence of pancreatitis ($n = 1$), complete remission ($n = 1$), at the discretion of the physician ($n = 1$), and patient decision ($n = 1$). In Ph+ ALL patients, the most common treatment modifications were treatment termination (79%), dose reduction (52%), treatment interruption (34%), and dose increase (24%) (Table 2). The main reasons for treatment termination were a planned allogeneic SCT (30%), disease progression (26%), and an AE (22%) (Table 2). Dose reduction or treatment interruption was mostly carried out due to an AE (57%), and a dose increase when the treatment was well tolerated (80%) (Table 2).

3.6. Safety

Adverse reactions were reported by 85% of CML and 76% of Ph+ ALL patients. The most frequently observed adverse reactions for CML patients (reported by ≥ 10% of patients) were cardiovascular events (33%, including 17% AOEs), rash (24%), gastrointestinal disorders (20%), dry skin (15%), abdominal pain (13%), and fatigue (11%) (Figure 5). For Ph+ ALL patients, these were cardiovascular events (24%, including 7% AOEs), rash (24%), gastrointestinal disorders (14%), dry skin (14%), fatigue (10%), headache (10%), and

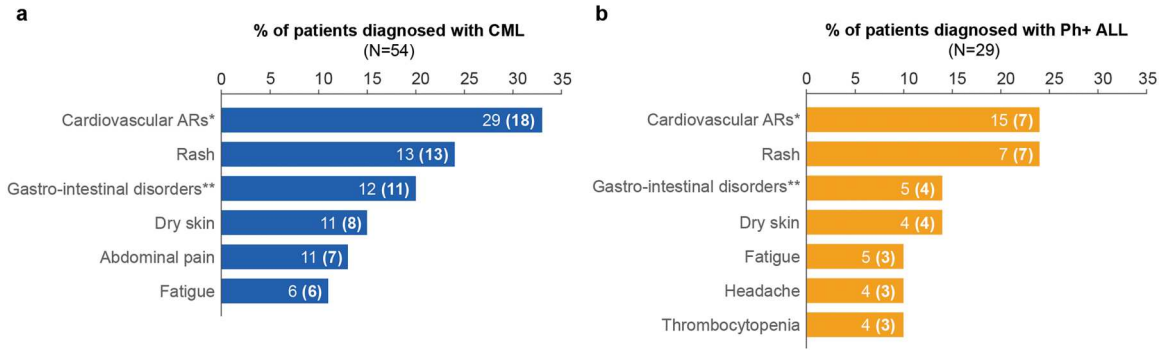

Figure 5. ARs reported in ≥ 10% of patients with (a) CML and (b) Ph+ ALL. Values in each bar represent the number of adverse reactions (the number of patients). *Including angina, arteritis, atrial fibrillation, cardiac failure and arrythmia, chest pain, hypertension, ischemic colitis, palpitations and thrombosis. **Including constipation, diarrhea, and nausea. *AR* adverse reaction, *CML*, chronic myeloid leukemia, *Ph+ ALL* Philadelphia chromosome-positive acute lymphoblastic leukemia.

thrombocytopenia (10%) (Figure 5). These adverse reactions were all considered of interest. Other reported adverse reactions of interest for CML patients were pancreatitis (9%), hepatocellular injury (7%), anorexia (6%), headache (6%), and thrombocytopenia (6%). For Ph+ ALL patients, these were hepatocellular injury (7%) and myalgia (7%) (see Supplementary Table S2 for the full list of adverse reactions).

Deaths were reported for 5 CML and 5 Ph+ ALL patients; none were considered by the investigator to be causally related to ponatinib. The causes of death were pneumonia ($n = 1$), general deterioration ($n = 1$), a combination of general deterioration and drop attacks ($n = 1$), and undetermined ($n = 2$) for CML patients, and disease progression ($n = 1$), general deterioration ($n = 1$), cardiorespiratory arrest induced by euthanasia ($n = 2$; reason for euthanasia unknown), and undetermined ($n = 1$) for Ph+ ALL patients.

4. Discussion

Data on the routine use of ponatinib in CML and Ph+ ALL patients in 21 hospitals in Belgium were collected in this registry. Compared with the previously published, interim data, this analysis included 33 additional patients (a total of 83 patients, including 54 patients with CML and 29 patients with Ph+ ALL), with an extended follow-up period of 6 years [17]. We noted during this analysis that the proportion of patients who were sensitive to previous TKI treatment before initiating ponatinib was substantial. This can probably be explained, at least in part, by the number of patients switching to ponatinib due to intolerance (50% CML and 41% Ph+ ALL patients). Interestingly, this is an increase in the number of patients switching to ponatinib due to intolerance compared with the previous 3-year analysis of this registry (42% CML and 35% Ph+ ALL patients) [17]. This final 6-year analysis shows an MMR rate with ponatinib treatment versus baseline (from 19% at baseline to 65% in CML patients and from 17% at baseline to 55% in Ph+ ALL patients). Unfortunately, it was not possible to analyze the quality of the response in patients receiving ponatinib compared with prior response due to the low number of patients in each group. To note, a sensitivity analysis completed using the 3-year data [17] failed to show a difference between patients who started ponatinib for reasons other than intolerance or for intolerance to a previous TKI. Compared with the 3-year results of the present registry, the overall percentage of CML patients achieving at least an MMR increased from 58 to 65% after up to 6 years of follow-up [17]. For Ph+ ALL patients, there was an increase from 41 to 55% [17]. We believe this difference is likely due to the longer follow-up period. The slightly higher proportion of patients who started ponatinib due to intolerance included in the final analysis versus the 3-year analysis may also have influenced this result, but we were unable to show this due to the limited sample size.

Although a direct comparison is not possible due to differences in the patient population (such as, sensitivity to prior TKIs), sample size, study design and follow-up, the results of this real-world registry analysis are in line with the phase II PACE trial that demonstrated efficacy and safety of ponatinib 45 mg/day in 449 patients with CML or Ph+ ALL who were TKI intolerant or resistant to dasatinib or nilotinib, or who carried the

T315I mutation [9,13]. Among the 267 evaluable CP-CML patients in the PACE trial, 159 (60%) achieved a major cytogenetic response at any time, of whom 144 (54%) achieved a CCyR and 108 (40%) achieved an MMR [9]. Among the 32 Ph+ ALL patients, 13 (41%) had a major hematologic response, 15 (47%) achieved a major cytogenetic response, and 12 (38%) achieved a CCyR [9].

Not all patients in this Belgian registry received the ponatinib starting dose of 45 mg/day. However, this did not prevent some patients from achieving at least an MMR as best response when receiving ponatinib 30 mg/day (3% of CML and 21% of Ph+ ALL) or 15 mg/day (23% of CML and 21% of Ph+ ALL). These results are in line with the OPTIC trial, which showed the highest benefit/risk ratio for patients receiving a starting dose of 45 mg/day, but also reported benefits for patients starting at 30 and 15 mg/day [16].

In this 6-year analysis of the registry, the OS and PFS were 85.8% and 83.8% after 48 months of treatment for CML patients and 82.5% and 54.2% after 30 months of treatment for Ph+ ALL patients. In the PACE trial, the OS rate among CP-CML patients was estimated at 73% and the PFS rate at 53% at 5 years. The estimated 5-year OS in AP-CML and the estimated 3-year OS in blast-phase CML patients were 49% and 9%, respectively. The estimated 3-year OS in Ph+ ALL patients was 12% [9].

No new safety signals were observed compared with the previous analysis of this registry, and safety outcomes were in line with the PACE and OPTIC trials [9,16]. In the current study, the most common adverse reactions (all of interest) were cardiovascular events, rash, gastrointestinal disorders, dry skin, abdominal pain, and fatigue for CML patients, and cardiovascular events, rash, gastrointestinal disorders, dry skin, fatigue, headache, and thrombocytopenia for Ph+ ALL patients. In the PACE trial, the most common treatment-emergent AEs in CP-CML patients were rash (47%), abdominal pain (46%), thrombocytopenia (46%), headache (43%), dry skin (42%), and constipation (41%) [9]. In the OPTIC trial, treatment-emergent AEs in CP-CML patients were thrombocytopenia (40%), arterial hypertension (28%), neutropenia (26%), anemia (19%), headache (18%), and lipase increase (17%) [16]. The lower percentages of AEs observed in the present registry could be due to several factors, including the implementation of risk-minimization activities, a good patient selection and monitoring, as well as a potential lower reporting of AEs in a real-world setting compared with a clinical trial. During the 5-year follow-up of the PACE trial, the cumulative incidence of AOEs was 25% in CP-CML patients [9], compared with 17% for CML patients included in this registry. In the OPTIC trial, treatment-emergent AOEs were reported for 6% of patients [16]. The lower percentage of AOEs in the OPTIC trial could be due to the lower dose of ponatinib administered to CML patients, as 66.6% of patients received ponatinib 15 mg or 30 mg in the OPTIC trial versus 31% of patients in the present registry [16,18,19].

This registry was the first to evaluate the effectiveness and safety of ponatinib in a real-world setting by collecting data from leading hospitals treating CML and Ph+ ALL patients in Belgium. Longitudinal data were collected for an extended period (6 years), allowing assessment of effectiveness and safety in routine clinical practice. The main limitation of the study is its local character, as data were collected solely in Belgium, a country with reimbursement criteria that differ from the inclusion criteria used in clinical trials and from the reimbursement criteria in other countries. Due to inconsistencies in the way response was measured pre- and post-treatment with ponatinib, detailed analysis of the response rates to ponatinib in relation to the response present at ponatinib initiation was not possible. Additionally, clinical interpretation of the AEs in terms of severity was limited because Common Terminology Criteria for AEs grading was not collected. Other limitations of the present registry are inherent to real-world evidence studies, such as the lack of uniform treatment decision criteria, data verification, complete data or follow-up, and the underestimation of some events. The descriptive nature of the study is an additional limitation, as no causal associations could be made.

In conclusion, the results of the final 6-year analysis of this Belgian registry including 83 patients with CML or Ph+ ALL treated with ponatinib are in line with those of previously published studies and support the use of ponatinib in CML and Ph+ ALL patients with resistance or intolerance to previous TKIs or who carry the *T315I* mutation. Compared to the 3-year analysis, the main findings of this publication are that the efficiency of ponatinib in the real-world setting is confirmed with a higher MMR rate than observed in the previous analysis, and with more mature OS and PFS Kaplan–Meier curves. Moreover, no new safety signals were discovered during this registry when including an additional 3 years of data after the first analysis, confirming the acceptable real-world toxicity of ponatinib in view of the beneficial disease outcomes provided in these patient populations.

Research involving human participants and/or animals

This registry was conducted in accordance with the ethical standards of the institutional and/or national ECs and with the Declaration of Helsinki and the International Council for Harmonisation guidelines for Good Clinical Practice.

Consent to participate

Informed consent was obtained from all individual participants included in the registry, but a waiver was granted by the EC for patients in the NPP who were still on ponatinib treatment on March 1, 2016, but were deceased before the registry start.

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Authors' contributions

Timothy Devos, Dries Deeren, Koen Theunissen, Dominik Selleslag, Benjamin Bailly, Violaine Havelange, Philippe Lewalle, Stef Meers, Fleur Samantha Benghiat, Alain Gadisseur, Nikki Granacher, Gaëtan Vanstraelen, Hélène Vellemans, Ann De Becker, Mia Janssen, Inge Vrelust, Marie Lejeune, Ann Van de Velde, Agnès Triffet and Dominiek Mazure participated to the study as principal investigators. Michael Beck and Hinde Sebti contributed to the interpretation of the results. All authors discussed the results, provided feedback, and contributed to the final manuscript.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

ORCID

Timothy Devos http://orcid.org/0000-0002-6881-417X
Dries Deeren http://orcid.org/0000-0001-9599-2142
Violaine Havelange http://orcid.org/0000-0001-6061-6315
Philippe Lewalle http://orcid.org/0009-0005-6483-9782

Stef Meers http://orcid.org/0000-0003-1754-2175
Fleur Samantha Benghiat http://orcid.org/0000-0002-2521-238X
Alain Gadisseur http://orcid.org/0000-0001-9419-8772
Ann De Becker http://orcid.org/0000-0003-4892-9727
Ann Van de Velde http://orcid.org/0000-0002-4579-2916

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