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Expert Review of Hematology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierr20

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To cite this article: Françoise Huguet, Delphine Réa, Emilie Cayssials, Gabriel Etienne & Franck-Emmanuel Nicolini (2023) Dose optimisation of ponatinib in chronic phase chronic myeloid leukemia, Expert Review of Hematology, 16:9, 633-639, DOI: 10.1080/17474086.2023.2234084

To link to this article: https://doi.org/10.1080/17474086.2023.2234084

Published online: 27 Jul 2023.

EXPERT REVIEW OF HEMATOLOGY
2023, VOL. 16, NO. 9, 633–639
https://doi.org/10.1080/17474086.2023.2234084

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PERSPECTIVE

Dose optimisation of ponatinib in chronic phase chronic myeloid leukemia

Françoise Huguet[a,b], Delphine Réa[b,c], Emilie Cayssials[b,d], Gabriel Etienne[b,e] and Franck-Emmanuel Nicolini[b,f]

[a]Hematology Department, Institut Universitaire du Cancer, Centre Hospitalier Universitaire, Toulouse, France; [b]Fi-LMC Group, Lyon, France; [c]Hematology Department, Hôpital Saint-Louis, Assistance Publique, Hôpitaux de Paris, France; [d]Hematology Department, Centre Hospitalier Universitaire, Poitiers, France; [e]Hematology Department, Institut Bergonié, Bordeaux, France; [f]Hematology Department, Centre Léon Bérard, Lyon, France

ABSTRACT

Introduction: Ponatinib exhibits a high inhibition potency on wild-type and most mutated forms of the *BCR:ABL1* kinase, but also a significant cardiovascular toxicity. Improving the efficacy/safety ratio should allow patients to safely draw benefit from the drug.

Areas covered: Based on pharmacological findings and international guidelines on chronic myeloid leukemia and cardiovascular risk management, as well as on the most recent data collected in real-life studies and in a randomized phase II trial, we propose a decision-tree of dose selection of the drug.

Expert opinion: We distinguish (1) highly resistant patients according to poor previous response to second generation tyrosine kinase inhibitors (complete hematologic response or less) or to mutational status (T315I, E255V, alone or within compound mutations), requiring a starting daily dose of 45 mg, reduced to 15 or 30 mg according to the patient's profile, preferentially upon major molecular achievement (3-log reduction or MR3, *BCR:ABL1* ≤ 0.1%^{IS}); (2) less-resistant patients justifying an initial dose of 30 mg, reduced to 15 mg upon MR2 *(BCR:ABL1* ≤ 1%^{IS}) or preferentially MR3 in patients with a favorable safety profile; (3) intolerant patients to be treated by 15 mg.

ARTICLE HISTORY
Received 15 May 2023
Accepted 4 July 2023

KEYWORDS
Ponatinib; chronic myeloid leukemia; dose; response; safety

1. Introduction

Dramatic improvements in the outcome of chronic myeloid leukemia (CML) have occurred more than 20 years ago. However, despite their efficacy, imatinib and second-generation tyrosine kinase inhibitors (2 G-TKIs) can face resistance due to various mechanisms, among which *BCR:ABL1* mutations, or intolerance, leading to switch toward another drug in 25–50% of patients in each consecutive line [1]. Patients in chronic phase (CP) with resistance mutations to 2 G-TKIs, especially T315I, and/or failing optimal response and reaching third line or beyond, are at risk of progression to accelerated and blastic phases, underlining the need for a more effective drug. Ponatinib (PON), registered in 2012 in the U.S.A. and 2013 in Europe, has confirmed an important role in this setting. In parallel, there is a growing trend toward dose optimization of all TKIs in order to improve tolerance. Adverse events of PON susceptible to drive morbidity and mortality are mostly arterial occlusive events (AOEs). In 2019 and 2021, extensive reviews of available trials and real-life protracted experience of PON stressed the need for titration options tailored to the characteristics of both patient and CML [2–5]. Here, we discuss the dose optimization issue of PON in light of recent data that contribute to further clarification.

2. Pharmacological background

PON, a 3 G-TKI tightly linked to the kinase by five hydrogen bonds [6,7], is the most potent TKI on wild-type BCR:ABL1 [8], with a lower half maximal inhibitory concentration (IC_{50}) than that of any other TKI [9]. This in vitro potency translates into high rates of early, deep and durable responses in patients treated in phase I, II and III trials [10–12]. The gap with imatinib, dasatinib, bosutinib, and to a lesser extent nilotinib, appears particularly marked in patients with high risk scores [13–15]. PON, originally designed to overcome the T315I mutation that confers resistance to imatinib and all 2 G-TKIs, is a pan-inhibitor, active on almost all single mutations of *BCR:ABL1* with a few exceptions [16,17] and a mitigated action against E255V [7,18]. Compound mutations remain an important issue [19]. Those without T315I exhibit various levels of sensitivity to PON, thus requiring different dosages for their inhibition. Those including T315I are resistant to PON, as to all TKIs given as single agents [18]. Their emergence is favored by low-level mutations detectable by next generation sequencing [20]. These data establish the rationale to favor PON after resistance to a 2 G-TKI rather than to sequence several 2 G-TKIs, in order to prevent selection of mutated clones, as recommended by the last European Leukemia Net guidelines (ELN 2020) [8] and supported by a propensity score matching analysis [21]. In pre-clinical studies [7], a concentration of 20 nM allows eradication of all mutated clones, with the exception of T315I and E255V, which require 40 nM. Sustained concentrations beyond this value were only achieved by doses of 30–45 mg/day in the phase I trial of PON [10].

CONTACT Françoise Huguet huguet.francoise@iuct-oncopole.fr Hematology Department, Institut Universitaire du Cancer, Centre Hospitalier Universitaire, Toulouse, France

Article highlights

- Ponatinib is a third generation (3 G) tyrosine kinase inhibitor (TKI), indicated in patients failing 2 G-TKIs, either for intolerance, or for resistance where it should be preferred to another 2 G-TKI.
- Because its potent efficacy is counterbalanced by cardiovascular tolerance issues, safety must be insured by dose optimization and prevention/management of adverse events.
- Summary of product characteristics, ELN 2020 recommendations and OPTIC trial contribute to dose options but present some imprecisions and discrepancies, reflected in the heterogeneity of real-life data.
- In order to adapt more accurately to various clinical situations and design a response-based strategy, we propose a new decision tree.
- In patients having only reached complete hematologic response or less, or harboring highly resistant mutations (T315I, E255V, compound mutations), we favor a starting dose of 45 mg/day, reduced in a stepwise way to 30 mg when major molecular response is achieved, then 15 mg if sustained or deepened.
- In patients in other situations of failure/warning, unmutated or harboring less resistant mutations, a dose of 30 mg/day is warranted before reduction to 15 mg upon response, preferentially major molecular response.
- The initial dose of 15 mg is sufficient for patients intolerant to previous TKIs, and also to further deepen an optimal response with the goal of treatment-free remission.

3. Clinical background

Since clinical results corroborate the superiority of PON over alternative 2 G-TKI in third line [21], the dose issue of the drug is critical. The pivotal phase II trial PACE (Ponatinib Ph+ ALL and CML Evaluation) was led in patients resistant or intolerant to nilotinib or dasatinib, or harboring the T315I mutation [11]. The initial daily dose was 45 mg, the maximum tolerated dosage defined because of pancreatic toxicity at 60 mg/day in phase I [10]. At 24 months, in October 2013, dose reductions were recommended after identification of an excess risk of AOEs [22]. With a median follow-up of 15 months, the incidence of cardio-, cerebro-, and peripheral vascular events was 7.1%, 3.6%, and 4.9%, respectively, of which 2.2%, 0.7%, and 1.6% possibly related to PON. Later, an independent cardiovascular adjudication committee analyzing the final data of PACE with a median follow-up of 37.3 months concluded in an overestimation of the risk, with adjudicated *vs* non-adjudicated AOE rates of 17% *vs* 25% [23]. Nevertheless, the recommended dosages were 15 mg or 30 mg for CP-CML patients with or without major cytogenetic response (MCyR), respectively. Median dose was 27.2 mg/day in the five-year final report PACE [24]. However, PON was registered at 45 mg/day, still the recommended starting dose in the Summary of Product Characteristics, even if prescribers are advised to lower this dosage in responding patients at risk of AOEs. A dose of 15 mg daily is advised upon MCyR achievement, taking into account individual factors such as CV risk, side effects of PON, time to response, and transcript levels. It is also advised to resume the previous tolerated dose if loss of response, and to consider discontinuing PON in non-responders after three months of administration [25]. The clinical experience of PON over 10 years now allows to challenge the approved initial dose of 45 mg in all patients, as well as the policy of dose-adaptation. Real-world data, conclusions of the Optimizing Ponatinib Treatment in CP-CML (OPTIC) trial [26]and ELN 2020 guidelines [8] constitute the basis of this discussion.

3.1. Real-life data

Their heterogeneity is illustrated by two large surveys (U.S. A., 578 patients and Italy, 515 patients) in which 50% and 100% of patients, respectively, started PON at 45 mg/day, 42% and 70% later experiencing dose reduction or discontinuation [27,28]. The French TOPASE observatory (Therapeutic Observatory of Ponatinib About Safety and Efficacy) [29] and the Italian OITI trial (Observational study of Iclusig® (ponatinib) Treatment in patients with CML in Italy) [30] are large real-life studies conducted in an ambispective way. In TOPASE, patients in any phase of CML (87% CP-CML) were included if treated by PON for less than 6 months, or prospectively. Two thirds of 120 patients had received only 1 or 2 previous TKIs, one third were not resistant (intolerant or in search of a deeper response), nearly half had a CV history. In CP-CML patients, the initiating daily doses were 15 mg in 35.6%, 30 mg in 44.2% and 45 mg in 20.2%. At 3 months, the mean doses were 16.8 mg, 26.9 mg and 35.8 mg, respectively, showing that the dosage in the 45 mg subgroup was reduced early. It remained stable thereafter. Major molecular response (MMR or MR3, *i.e. BCR:ABL1* $\leq$ 0.1%^{IS}, a 3-log reduction), was achieved in 60% of CP-CML patients lacking this response at enrollment, in a median time of 4.8 months. PON was discontinued for adverse events in 27% of patients (CV events in four patients). This real-world study thus showed a high rate of response and an acceptable tolerance. The OITI trial, which also included 120 patients (92.5% CP-CML), reaches the same conclusions despite some discrepancies in inclusion criteria and recruitment : half on the patients received PON in second line only, 58% for another reason than resistance. The proportion of 50% of patients with a prior CV disease was similar. More patients received a higher starting dose than in TOPASE (15 mg in 21.6%, 30 mg in 41.4%, 45 mg in 36.9%). Dose modifications occurred in 62% of patients, of which 41% for adverse events occuring in the 45 and 30 mg cohorts (including hypertensive crisis in two patients, AOE in 4). At 6 months, the rates of overall and newly achieved CCyR were 75.2% and 53.7%, respectively. At 12 months, the rate of MMR was 43.5%. Estimated rates of progression-free survival (PFS) and overall survival (OS) at 36 months were 83% and 86.7%, respectively.

Real-world studies have also been conducted during the SARS-CoV-2 outbreak. Most data suggest that the outcome of both COVID-19 and CML, as well as the efficacy and safety of vaccination, are not worse than expected [31]. Due to the low number of patients on PON, the risk of specific complications, such as thrombosis during the first COVID-19 wave, is not specifically assessed. However, suboptimal response to CML treatment is an adverse factor for COVID-19, and multi-TKI-resistant patients receiving a 3 G-TKI could suffer more severe infection by the Omicron variant [32]. A possible protective effect of TKIs, including PON [33], on the outcome of COVID-19 is not demonstrated. Continuing CML treatment during the course of infection is advocated [34].

3.2. ELN 2020 recommendations [8]

In third line or beyond, the panel of ELN experts considers that a *BCR:ABL1* transcript level > 1%, or less than complete cytogenetic response (CCyR), is insufficient for optimal survival. The initial recommended daily dose is 45 mg in patients with T315I or compound mutations. Once CCyR or MMR is achieved, the daily dose should be decreased to 15 mg. The formulation of these recommendations let 'gray zones' persist : the initial dosage (45 or 30 mg) as well as the level of response authorizing to later lower it (CCyR or MMR) are not distinctly selected; the criteria justifying to return to a higher dose 'only if needed' are not specified. ELN guidelines also apply to CP-CML patients progressing toward accelerated phase who need a starting dose of 45 mg/day. Since the availability of PON, indications for stem cell transplantation have stepped back, considered only if failure of PON at 3 months.

3.3. OPTIC trial [26]

The phase II OPTIC trial, conducted from 2015 to 2019 in 283 patients resistant/intolerant to ≥ 2 TKIs or harboring the T315I mutation, addressed the question of the optimal dose of PON in a prospective and comparative manner. At randomization, patients were assigned to three starting doses of 45, 30, and 15 mg, then a response-based dose-reduction strategy was applied. The doses of 45 and 30 mg were reduced to 15 mg upon MR2 (*BCR:ABL1* ≤ 1%, 2-log reduction), roughly equivalent to CCyR. Noteworthy, the population included in 19 countries did not reflect the characteristics of patients coming only from countries with an earlier experience of PON [35–37]. In OPTIC, patients were more often highly resistant or T315I mutated, had received more lines of previous TKIs. Median daily dose intensity (median time to dose reduction) was 27.7 mg (3.4 months), 23.0 mg (7.1 months), 14.7 mg (11.4 months) in the 45, 30, and 15 mg cohorts, respectively. Although starting therapy at the daily dose of 45 mg did not translate into major overexposure as compared with lower doses, response rate at 12 months was superior in this subgroup (44.1% *vs* 29.0% *vs* 23.1%, $p < .017$), and increased with time despite scheduled dose reduction. In parallel, the exposure-adjusted AOE rates were 5.6%, 3.6%, and 2.1%, respectively. The benefit in terms of efficacy was superior to the unfavorable effects. With a median follow-up of 32 months, PFS was not reached in the 45 and 30 mg cohorts and was 45.6 months in the 15 mg cohort. Median overall survival was not reached in all three cohorts. Interestingly, the OPTIC trial identified various situations in which the three doses yielded clear-cut different response rates (Table 1).

4. Algorithm proposal for PON therapy in CP-CML (Table 2)

In an attempt to integrate the findings of the above studies, we propose to adapt PON dosage to different situations.

4.1. Highly resistant patients

In OPTIC, they belong to two subsets of patients, in whom the starting dose of 45 mg is warranted. First, patients having achieved only CHR or worse on previous lines of therapy. The starting dose of 45 mg, reduced to 15 mg upon achievement of MR2, offered 50% responses, clearly above the rates of roughly 20% with 30 and 15 mg. In this dose-

Table 1. Responses in the OPTIC trial according to various clinical situations and to the starting dose of PON.

	Starting dose		
Response	45 mg	30 mg	15 mg
Overall response (≤1% *BCR:ABL1*^{IS} at 12 months)*	44.1%	29%	23.1%
Overall response (≤1% BCR:ABL1^{IS} by 12 months)	51.6%	33.5%	25.3%
Response by previous response status			
CHR or worse	50%	20.8%	15.4%
Better than CHR	50%	58.6%	39.1%
Response by mutational status			
T315I mutation	60%	25%	10.5%
Mutation other than T315I	56.3%	40%	33.3%
No mutation	46%	37.9%	28.3%

**primary end-point*.

Table 2. Algorithm for dose optimization of PON.

	DAILY DOSE
HIGHLY RESISTANT PATIENTS	
Achievement of CHR or less	45 mg reduced to 15 mg upon MR2 achievement. If favorable safety profile, wait for MMR and decrease dose in a stepwise fashion to 30 mg first.
T315I, by extension E255V, compound mutations and progression to advanced phases	45 mg reduced to 30 mg or 15 mg, only when MMR is achieved
LESS RESISTANT/SUBOPTIMAL PATIENTS	
No mutation or mutation other than above	30 mg reduced to 15 mg upon MR2 achievement. If favorable safety profile, wait for MMR before decreasing the dose.
Patients in MR2	30 mg reduced to 15 mg upon MMR achievement
Patients in MMR in search of DMR *(no approval in this indication)*	15 mg
INTOLERANT PATIENTS	15 mg

finding trial, such highly resistant patients represent as many as 61% of the patients, unlike the French TOPASE observatory in which this subset gathers only 20% of the patients [38]. The second setting is that of patients with T315I mutation, in whom the gap in the response rates between the three doses of 45, 30, and 15 mg/day is more important than for the other mutational contexts in OPTIC (Table 1). While a starting dose of 45 mg thus appears optimal for these patients, the pattern of dose reduction warrants discussion, based on several considerations. First, the comparison between PACE and OPTIC showed a lower dose-intensity in the 45 mg arm of OPTIC than in PACE, and a more rapid dose reduction, resulting in fewer reductions for adverse events [39,40]. Noteworthy, exclusion criteria were also more stringent in OPTIC than in PACE. Second, in PACE, the median time of onset of ischemic heart events, earlier than cerebrovascular and peripheral AOEs, was 11.5 months. Non-CV adverse events occur earlier, within the first 3 months for the most frequent of them, thrombopenia and pancreatitis, as well described in PACE, and their frequency is not clearly influenced by the starting dose. For example, in OPTIC, grade ≥ 3 AEs occur in 68.1% of patients at 45 mg, 61.7% at 30 mg, 63.8% at 15 mg. Thus, these non-CV events do not appear as barriers to a rather long exposure to high doses of PON when initially well-tolerated. Finally, among the 283 patients of OPTIC, 18 lost response upon dose reduction, of whom 11 (61%) had T315I at baseline. Loss of response occurred early after dose reduction, within 6 months in most cases (70%). Even if the majority of patients regained response after dose re-escalation, a sudden reduction to 15 mg at the mere level of MR2 might be hazardous. Altogether, these data suggest that a deeper threshold of response could be more cautious, with dose reduction upon MMR only. A tapering dose is also an option, at 30 mg first in selected patients without major CV risk factors, and later at 15 mg when MMR is confirmed overtime. Finally, discontinuing PON in the absence of CHR should also be delayed after 3 months, especially if there is no therapeutic alternative, since some patients can respond later. Because of their reduced sensitivity to PON, these dosage adaptations can be extrapolated to E255V and composite mutations. Patients progressing to accelerated phase obviously are also highly resistant. Finally, though sharing the general philosophy of a response-adapted dosage, our proposal does not strictly stick to the OPTIC design. Indeed, higher requirements in terms of dosage and response appear legitimate in the most resistant patients when allowed by the patient's profile and the potential to evaluate and control CV risk factors and other toxicities.

4.2. Patients with a lower level of resistance or deemed suboptimal responders

The stratification of CML patients according to their level of resistance to PON is not shared by all learned societies. The 2.2021 NCCN (National Comprehensive Cancer Network) guidelines do not discuss a lower dosage than 45 mg according to the CML profile, but only in case of CV risk, though considering that 15 or 30 mg can be 'an effective dose' [41]. In the ESMO (European Society for Medical Oncology) 2017 guidelines, the dose of 45 mg could be reserved to patients 'in advanced disease or in the case of problematic mutations', dose optimization being 'still under investigation'[42]. Finally, in the ELN 2020 recommendations, a starting dose of 45 mg should be given only to patients with T315I, or compound mutations, or progression to an advanced phase. A lower dose, increased 'only if needed' is advocated for patients 'with lesser degrees of resistance.' In our opinion, such patients are those harboring other mutations than the most resistant ones (T315I, E255V, compound mutations), and also unmutated patients in failure, for whom the dose of 30 mg seems appropriate. Even if dose reduction to 15 mg was scheduled as soon as MR2 was reached in OPTIC, continuing the dosage of 30 mg should be an option for patients in MR2 but not in MMR, with dose reduction upon MMR achievement only. The dose of 45 mg, although yielding 34% of responses as compared to 24% at 30 mg is not proper since the risk of toxicity could offset the benefit. The question is more difficult for patients in warning, such as those lacking MMR after 12 months of exposure to first and second line TKIs according to the ELN guidelines. Although PON, as all other TKIs, is not stricto sensu registered for the warning population, these patients represent a significant proportion of patients receiving PON in the real-world setting [29]. Finally, patients already in MMR are not resistant, but deepening the response with the aim of treatment-free remission has become a reasonable goal in CP-CML, as illustrated in the TOPASE observatory with 10% of patients receiving PON in this approach [29]. PON is not approved in this context, and the dose of 15 mg/day should not be exceeded if the drug is nevertheless chosen.

5. Prevention and management of cardiovascular events

The European Society of Cardiology (ESC) has updated in 2021 the guidelines on cardiovascular disease (CVD) prevention [43]. A new Systemic Coronary Risk Estimation (SCORE) algorithm, which estimates the 10-year risk of CVD death, takes into account both the fatal and non-fatal risk, in apparently healthy patients aged 40–69 years (SCORE2) and in older persons (SCORE2-OP). This algorithm includes age, gender, smoking habits, systolic blood pressure and non-HDL cholesterol. The ESC has also established other guidelines in the field on onco-cardiology, with a chapter detailing the various BCR: ABL1 TKIs and stressing the importance of QTc measurement, echocardiography and ankle-brachial index [44]. Several guidelines specifically concern the CV effects of PON [45,46]. The most recent ones, coming from the French group Fi-LMC [47], take into account the results of the OPTIC trial and the last version of the ESC Guidelines of 2021. They underscore the need for multi-disciplinary management by hematologists, cardiologists and pharmacologists. They rely on four principles : (1) evaluation of the CV risk before and during treatment, with a focus on blood pressure; (2) primary or secondary prevention adapted to the CV risk before and during treatment; (3) avoidance of PON in high CV risk patients whenever

Table 3. Fi-LMC recommendations for prevention of CV risk factors.

	Target	Treatment*
Blood pressure	*>65 yrs* : < 140/80 mmHg *≤65 yrs* : < 130/80 mmHg (favor self-measurement/home blood pressure monitoring)	Step 1 : ACEi or ARB + CCB or diuretic Step 2 : ACEi or ARB + CCB + diuretic Step 3 : add spironolactone or another diuretic or an alpha- or beta-blocker
Dyslipidaemia	*Low/intermediate CV risk*: LDL-C < 2,60 mmol/L (1,00 g/L)	Lifestyle optimization
	High CV risk: < 1,8 mmol/L (0,7 g/L)	Statin (favor atorvastatin)
	Very high CV risk: < 0.55 g/l	Statin (favor atorvastatin)
Diabetes	HbA1C ≤ 7%	Diet, anti-diabetic drugs + annual follow-up of organ impact (heart, kidneys, eyes, feet, teeth)

**Treatment of overt CV risk factors is preferred to primary prevention by aspirin and statin in all patients..*

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CV = cardiovascular; LDL-C : low-density lipoprotein-cholesterol.

possible; (4) cessation of PON after any AOE, at least until specialized CV checkup before resumption at the lowest possible dose if the benefit/risk balance is in favor of this drug. Here, we point out the main therapeutic rules to control CV risk factors, along with dose adaptation of PON and counseling on lifestyle optimization (Table 3).

6. Expert Opinion

The strong efficacy of PON has been counterbalanced by a high rate of AOEs. A rational selection of patients needing either the approved initial dose of 45 mg/jday or a lower dose, a response-based dose reduction strategy, and a stringent management of CV risk factors have recently been studied in search of a more favorable efficacy/safety ratio. We propose a new decision tree integrating these improvements, stressing the point that, for patients with T315I, E255V and compound mutations, the starting dose of 45 mg should be reduced less early and less deeply than previously suggested, namely to 30 mg first, before 15 mg, upon MMR rather than MR2. A starting dose of 30 mg is adapted to less resistant patients, the goal of major molecular response achievement being also favored, at least in patients free from CV risk factors. With a dose of 15 mg/day, patients having experienced intolerance to previous TKIs can also safely be treated by PON. In parallel, CV management, with a focus on the control of blood pressure, must be optimized with the support of published recommendations and the intervention of a specialist when needed. While the development of PON has been impaired by the discovery of arterial toxicity, a more mature experience and a rationale use of the drug now offer the opportunity to patients in complex situations to draw the best benefit from this drug. In the future, deciphering the mechanisms by which PON promotes arterial thrombosis might bring further improvements in the prevention of CV events. For example, it has been suggested that pioglitazone, an anti-diabetic drug with a potential action on CML residual disease [48], might reverse the deleterious effects of PON on the vessel wall and reduce platelet reactivity [49]. From a clinical point of view, an important question is now to define the respective indications of PON and asciminib. This TKI is a STAMP inhibitor (Specifically Targeting the ABL1 Myristoyl Pocket), active on most mutations [50], except M244V, L248V, Y253F, F359C/I/V, when used at low dose [51]. It has been approved by the Federal Drug Administration in October 2021 for patients with CP-CML after at least two TKIs or T315I mutated, at the dose of 40 mg and 200 mg twice daily, respectively; and by the European Medicines Agency in September 2022 for the first indication only, in patients ineligible to PON. In a phase III trial, asciminib has been compared to bosutinib, chosen because of its wide use in this setting around the world at the time of the trial design [52]. As third-line therapy or beyond, asciminib proved superior to bosutinib in terms of tolerance and response. However, comparative data with PON are lacking. Experience and follow-up with asciminib are still limited, and the ability of the drug to control genetic instability and mutational evolution is uncertain. This drug combined to PON might contribute to eradicate the clones exhibiting compound mutations with T315I/E255V, whereas PON alone does not reach the serum concentration of 640 nM needed to do so [53]. However, asciminib is approved as single agent only, and its further development in combination is uncertain. Several other TKIs are being evaluated, such as vodobatinib, structurally similar to PON, with less VEGFR inhibition and thus a better CV tolerance, but inactive on the T315I mutation [54], and olverembatinib [55], active on the T315I mutation. Beside TKIs, agents acting by different mechanisms, aiming at targeting leukemic stem cells and/or other mechanisms of leukemogenesis, are still experimental [56]. The future place of PON in the moving landscape of CML therapy will be challenged by these innovations if they keep their promises. The availability of more and more drugs is indeed a progress in the management of situations of unmet medical needs in CML, in which response achievement is the condition of favorable long-term outcome. For the time being, PON remains a major tool to face these alarming situations, and optimal handling of the drug is a prerequisite to take advantage of its unique properties.

Funding

This paper was not funded.

Declaration of interest

F Huguet is a consultant and speaker for Incyte Biosciences, Novartis, Pfizer. D Rea is a steering committee member for Novartis; a consultant and speaker for Incyte Biosciences, Novartis, and Pfizer. E Cayssials is a consultant for Incyte Biosciences, Novartis, and Pfizer. G Étienne is a consultant and speaker for Incyte Biosciences, Novartis, and Pfizer. FE Nicolini is a consultant for Novartis and Sun Pharma; speaker for Incyte Biosciences and Novartis; board member of Incyte Biosciences, Novartis, and Pfizer; and has received institutional grants from Incyte Biosciences and Novartis.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer Disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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