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REVIEW ARTICLE

Asciminib a new player in treatment of TKI-resistant/intolerant chronic phase chronic myelogenous leukemia

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Abstract

The introduction in 1998 of imatinib mesylate (IM), a first-generation BCR-ABL1 tyrosine kinase inhibitor (1G-TKI), to the treatment of chronic myelogenous leukemia patients in the chronic phase (CML-CP), significantly improved the prognosis of a previously incurable disease with a prognosed 5-year-long overall survival and progression-free survival of 91.7% and 94.7%, respectively. Long term follow-up studies of CML-CP patients verified the initial results, showing a 10-year overall response rate of 82–83.2%. In about one quarter of CML-CP patients, IM primary/secondary resistance or intolerance is diagnosed. After switching to a second generation BCR-ABL1 TKI (dasatinib, nilotinib, bosutinib), a complete cytogenetic response is obtained in only c. 50% of CML-CP patients. Also the frequency of deep molecular responses (DMR: $MR^{4.0}$ and $MR^{4.5}$) is relatively low. The results of 2G-TKI treatment are particularly unsatisfactory in patients carrying the TKI resistant BCR::ABL1 kinase domain mutants (BCR::ABL1 KD), especially BCR-ABL1 T315I. For this reason, other orally biocompatible compounds have been developed to target BCR-ABL T315I. One of these is ponatinib, which allows a major molecular response (MMR) and $MR^{4.5}$ to be obtained in 40% and 24% of severely TKIs-pretreated CML-CP patients, respectively. The latter represent a new class of allosteric BCR-ABL1 tyrosine kinase inhibitor [asciminib (ABL001)], specifically targeting the ABL myristoyl pocket of BCR-ABL tyrosine kinase. Its application in CML-CP patients previously treated with at least two TKIs resulted in an MMR rate and a $MR^{4.5}$ rate of 37.6% and 10.8%, respectively, at 96 weeks. The favorable asciminib response and tolerance profile was also confirmed in real-life conditions, even in subjects with previous ponatinib therapy failure ($MR^{4.5}$ in 10.5%). Recent data suggests that asciminib may be used in the first line or in combination with a 1G- or 2G-TKI. This latter strategy may enhance the rate of DMR obtained and increase the number of patients eligible for an attempt at treatment-free remission.

Keywords: chronic myelogenous leukemia, tyrosine kinase inhibitors, cytogenetic response, molecular response, BCR::ABL1 KD mutations, asciminib

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Introduction

The introduction in 1998 of imatinib mesylate (IM), a first-generation BCR-ABL1 tyrosine kinase inhibitor (1G-TKI), to the treatment of chronic myelogenous leukemia patients in the chronic phase (CML-CP), significantly improved the prognosis of a previously incurable disease [1–4]. The results of the International Randomized Study of Interferon and STI571 (IRIS) study confirmed the high therapeutic efficacy of IM in CML-CP patients, with an estimated probability of

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event-free survival (EFS) of 8 years of 81% and an 8-year-long overall survival (OS) of 85% [5].

Long-term treatment results (with a median follow-up of almost 11 years) showed an estimated OS rate of CML-CP patients receiving IM therapy of 83.3% [6]. Also, the results of a German CML IV trial including 1,551 patients with CML-CP treated with imatinib-based regimens showed a 10-year OS rate of 82%. Moreover, the study showed that about one quarter of the studied patients (26.5%) required therapy change to first-generation BCR-ABL1 tyrosine kinase inhibitor (2G-TKI) due to resistant disease (10%) and IM intolerance, as well as for other reasons [7]. This was also confirmed by the EUTOS population-based registry based on a long-term observation of 2,904 CML-CP patients, documenting IM primary/secondary resistance or intolerance in 28% of the patients qualified for the IM 1-line therapy [8].

IM resistance/intolerance is an important clinical problem, especially in the light of data documenting that the administration of the 2G-TKIs (dasatinib, nilotinib or bosutinib) in a 2-line setting in CML-CP patients with IM intolerance/resistance resulted in complete cytogenetic response (CCyR) rates of 49%, 44%, 41%, PFS of 90%, 64%, 81% and OS of 96%, 87%, 91%, respectively [9–11]. In addition, data concerning the frequency of deep molecular response (DMR: $MR^{4.0}$ and $MR^{4.5}$) after a 2-line treatment with 2G-TKI is unsatisfactory. A real-life comparison of nilotinib versus dasatinib as second-line therapy in CML-CP patients with IM therapy failure showed that only 47% and 38% of 108 evaluable patients achieved an major molecular response (MMR) BCR::ABL1 [on the International Scale (IS) <0.1%], and 18.2% and 16.2% a DMR, with dasatinib and nilotinib, respectively, after 12 months of treatment [12].

The implementation of the 2G-TKI to the first line treatment of CML-CP did not significantly improve the therapy results in terms of PFS and OS. During a 10-year follow-up of the ENEST trial, the estimated 10-year OS rates in the nilotinib 300 mg twice-daily, nilotinib 400 mg twice-daily arms were 92.7%, 94.5%, respectively [13]. Analysis of the DASISION trial showed similar rates for PFS and OS at 5 years across both treatment arms (IM 400 mg once daily vs. dasatinib 100 mg once daily) [14]. Also, the results of treatment with another 2G-TKI, bosutinib, in first-line settings showed a 5-year OS rate of 94.5% [15].

It has been documented that compared to imatinib, the administration of 2G-TKIs in the 1-line setting resulted in faster and deeper molecular responses in CML-CP patients. In the ENEST trial, the frequency of $MR^{4.5}$ after 10 years of treatment with nilotinib 300 mg twice daily or nilotinib 400 mg twice daily was established to be 61% and 61.2%, respectively. Meanwhile in the imatinib (400 mg once daily) treated patients, the $MR^{4.5}$ rate was 39.2% only [16]. In the DASISION study, the administration of dasatinib at a dose of 100 mg once a day resulted in $MR^{4.5}$ in 42% of participants after five years of follow-up [14]. Interestingly, despite lower response dynamics in the IM treated patients, compared to 2G-TKIs, the cumulative $MR^{4.5}$ rate in CML-CP patients treated with IM 400 mg/d after nine years of follow-up was established to be 70% in the CML-atudy IV participants [17].

According to the 2020 recommendations of European LeukemiaNet (ELN), the main goal of the CML management is the prolongation of OS with a normal life expectancy, and reducing the risk of the disease progressing to more advanced phases. The introduction of IM into clinical practice reduced the risk of CML progression to 1–1.5% per year from more than 20% per year in the pre-TKI era [4, 18–20]. The maintenance of a normal quality of life and avoiding early and late toxicity of the TKI applied are equally important. Recently, the implementation of the above-mentioned idea has become possible in CML patients achieving and maintaining stable DMR, while avoiding the TKI administration that had resulted in early and long-term organ toxicities [21].

Unfortunately, there is still no precise guideline for patients who fail to qualify for the 2G-TKI treatment according to the ELN 2020 criteria. It has been postulated that the individual decision about the consecutive line of therapy must be based on the patient's age, the TKI toxicity profile with respect to the patient's comorbidities, the disease phase, and the BCR::ABL1 mutation(s) profile at the time of diagnosis of the therapy failure [22, 23]. Nevertheless, the clearly desirable treatment aims [i.e. prolongation of survival, treatment-free remission (TFR) attempt] in individual cases is of similar importance [24, 25].

This paper summarizes data about the therapeutic efficacy and tolerability of subsequent lines treatment in patients with CML-CP, with particular emphasis on new therapeutic options, including therapy with ponatinib [third-generation TKI (3G-TKI)] and the allosteric BCR-ABL kinase inhibitor asciminib. This drug belongs a newly developed class of BCR-ABL kinase inhibitors with a different mechanism of action — it inhibits the kinase activity by blocking the myristoyl pocket of BCR-ABL tyrosine kinase (STAMP).

Impact of IM and 2G-TKI therapy failure/ /intolerance on CML outcome and disease evolution

The main consequence of TKI therapy failure is disease progression to a more advanced stage. It has been shown that in CP-CML patients who are resistant to ≥2 TKIs, the risk of progression to BP is significantly increased [26, 27]. This is the result of selection of CML leukemic stem cells (LSC) and disease clonal evolution [28, 29]. Preliminary reports indicate that TKI-resistant CML cells have high expression levels of DNA damage repair genes, such as RAD51L1, FANCA, and ERCC5, which may reflect CML LSC

genetic instability. This might, at least in part, explain the mechanism of molecular disease evolution and progression to the more advanced phase [30–32].

Another possible mechanism of TKI resistance of leukemic cells includes the activation of alternative signaling pathways (i.e. RAS–MAPK, SRC, JAK–STAT, and PI3K–AKT). Also, abnormal function of transmembrane protein participating in the TKI influx/TKI efflux (i.e. ABCB1, ABCG2, SLCO1B) to/from the leukemic cells may be responsible for the TKI treatment failure. In c. 50% of CML-CP cases, the presence of BCR::ABL1 kinase domain (BCR::ABL1 KD) mutations is responsible for the TKI resistance. BCR::ABL1 KD mutations have emerged during the TKI treatment and they may have single, and combined or compound character (≥2 of BCR::ABL1 mutations in cells from different clones and ≥2 BCR::ABL1 mutations in a single cell, respectively) [33]. The frequency of BCR::ABL1 KD mutations in patients with first-line and second-line TKI treatment failure differs depending on the detection method used. The Sanger sequencing technique and the next generation sequencing method allowed the detection of BCR::ABL1 mutations in 23% and 38% and 47% and 51% of patients, respectively [34]. The negative impact of clonal and/or subclonal BCR::ABL1 KD mutations on the CML evolution and progression is especially evident in the light of data documenting that the sequential use of TKIs is associated with decreased OS and the emergence of new BCR::ABL1 KD mutations, particularly the T315I mutation and compound BCR:ABL1 KD mutations [34, 35]. The above-mentioned data supports the hypothesis that restrained activity of BCR-ABL1 tyrosine kinase and/or increase in the BCR-ABL1 fusion gene amplification status in the CML cells is, at least in part, related to disease molecular evolution and progression [36] (Figure 1).

The results of second-line treatment with 2G-TKI were unsatisfactory in patients carrying the TKI resistant BCR::ABL1 KD mutation(s), especially BCR-ABL1 T315I [14, 38]. For this reason, other orally biocompatible compounds targeting BCR-ABL1 T315I have been developed. This was made possible with the help of computational and molecular structure-based designing. One of the substances identified in this way was ponatinib (3G-TKI), a dual SRC-ABL inhibitor with a documented potential to overcome the T315I and other single BCR::ABL1 KD mutants associated with resistance to IM and 2G-TKIs.

The pivotal phase II ponatinib Philadelphia positive acute lymphoblastic leukemia (Ph+ ALL) and CML evaluation trial (PACE) evaluated the efficacy and safety of ponatinib at a starting dose of 45 mg once a day in 449 patients with CML-CP (n = 270) or Ph+ ALL resistant/intolerant to dasatinib or nilotinib, or with the BCR-ABL1 T315I mutation [38]. The efficacy and safety of the drug was evaluated in severely pretreated CML-CP patients (93% of them received ≥2TKI, 57% ≥3TKI) with a median follow up of 56.8 months. Among the evaluable patients, 40% and 24% achieved MMR and $MR^{4.5}$, respectively. The probability of maintaining major cytogenetic response (MCyR) for five years, which was obtained in 60% of patients, was estimated to be 82% among the responders. During the PACE study, a relatively high frequency of arterial occlusive events (AOEs) was noted, which resulted in the implementation of a drug dose reduction recommendation in October 2013. Despite a drug dose reduction of ≥90% in CML-CP patients with previously documented MCyR or MMR, the response remained after 40 months of follow-up [40]. A post hoc multivariate regression analysis of pooled data from three clinical trials on the use of ponatinib in patients with Ph^+ leukemia showed a 33% potential reduction in the risk of AOEs for each 15-mg/d decrease in the average ponatinib dose intensity [40]. To study this hypothesis, the phase II Optimizing Ponatinib Treatment in CP-CML (OPTIC) trial, exploring a response-based dose-reduction strategy, was designed and performed. The OPTIC trial included 283 CML-CP patients resistant to ≥2 prior TKI or BCR::ABL1 T315I mutation positive, with BCR::ABL1 [IS] transcript level >1%. The study participants were randomly allocated to ponatinib 45 mg/day, or 30 mg/day, or 15 mg/day. The final analysis of the study results confirmed that the absolute gain in efficacy was larger than the increase in AOEs, when therapy was started at a dose of 45 mg and followed by a reduction to 15 mg upon the achievement of a transcript level reduction of ≥1% $BCR\text{-}ABL1^{IS}$ [41].

Recently published data supports the use of ponatinib, rather than alternative 2G-TKIs, in the 3-line of treatment in CML-CP patients with 2G-TKI treatment failure (3-year PFS 83% vs. 59%, OS 87% vs. 83%) [42].

Data is scarce regarding the second-line treatment of CP-CML patients resistant and/or intolerant to prior TKI therapy with the 3G-TKI — ponatinib. Breccia et al. [43] collected the data of 29 patients in whom treatment with ponatinib allowed an improved molecular response in 85% of all patients and an $MR^{4.0}$ and $MR^{4.5}$ reduction of BCR::ABL1 copy numbers in 10 of the studied patients.

New concept of BCR-ABL1 tyrosine kinase inhibition

Despite evident progress in the treatment of CML-CP patients, there has long been a need for improvement in the therapy tolerance and efficacy in patients intolerant or resistant to adenosine triphosphate (ATP) competitive TKI (ATP-competitive inhibitors) BCR-ABL.

For this reason, novel methods of bypassing the ATP-competitive inhibitors resistance have been developed [39]. The first to appear in this new class was allosteric BCR-ABL1 TKI [asciminib (ABL001)] STAMP [44].

Under normal conditions, ABL1 activity is autoregulated by binding myristoylated N-terminus to the myristoyl pocket

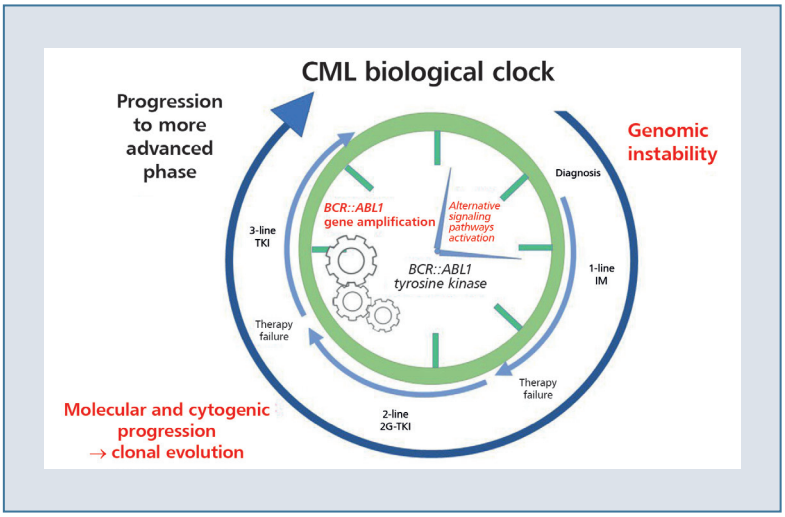


Figure 1. Unfavorable scenario of chronic myelogenous leukemia (CML) outcome due to multi-tyrosine kinase inhibitor (TKI) therapy failure. Imatinib resistance is associated with an increased risk of blastic transformation due to accumulation of genetic abnormalities detectable as additional cytogenetic changes and mutations in individual genes [37]. Another possible mechanism of disease clinical progression is associated with sequential use of TKI which may result in selection of TKI-resistant cells and disease clonal evolution [28]

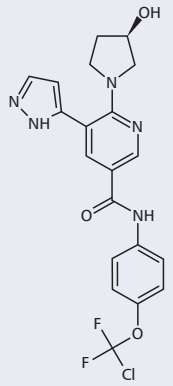
of the KD. In CML, c-ABL1 kinase is constitutively activated due to the loss of regulatory function with BCR::ABL1 fusion oncoprotein formation. The mechanism of action of asciminib includes binding to the myristoyl pocket of the ABL1 KD, induction of inactive conformational change, and inhibition of kinase activity [45, 46].

Asciminib was introduced after approval by the US Food and Drug Administration (FDA) into clinical practice in 2021 in CML patients after resistance and/or intolerance to two previous lines of treatment [47]. The detailed characteristics of asciminib are set out in Table I. Initially, asciminib has been evaluated in a phase I dose escalation study (10 to 200 mg once a day or twice a day) in severely pretreated CML patients (CP = 141, CP, accelerated phase = 9) with resistance to or unacceptable side effects from at least two previous ATP-competitive TKIs therapy, with promising results. Moreover, primary results of the phase I trial in patients with CML-CP or CML-acceleration phase, harboring the T315I BCR::ABL mutation and not in MMR at the screening, confirmed that asciminib administration at a dose of 200 mg twice a day resulted in durable molecular responses in both ponatinib-pre-treated and ponatinib-naïve cases (overall MMR rate by 96 weeks 32.1% and 66.7%, respectively) as well [53].

The pivotal trial evaluating asciminib vs. bosutinib efficacy and tolerability in adult patients with Ph+ CML-CP previously treated with at least two TKIs was the open-label, randomized, phase III ASCEMBL study [54]. The dose of asciminib was 40 mg twice a day. In the control arm, bosutinib daily dose was established at 500 mg once a day. Due to known bosutinib resistance, patients with T315I and/or V299L mutations at any time prior to study entry were excluded from the ASCEMBL trial. The MMR rate at 24 weeks was the primary endpoint of the study. The major secondary endpoints were MMR rate at 96 weeks and CCyR rate at 24 and 96 weeks. The initial evaluation after 24 weeks of follow-up showed a significantly higher MMR rate in asciminib vs. bosutinib arm (25.5% vs. 13.2%). The differences were even more pronounced at 96 weeks (37.6% vs. 15.8%). Also, differences in the CCyR rates obtained at 24 and 96 weeks were evident (40.8% vs. 24.2% and 39.8 vs. 16.1%). Another important study result was a higher probability of the $MR^{4.5}$ response obtained at 24 and 96 weeks in the asciminib compared to the bosutinib group (8.9% vs. 1.3% and 10.8% vs. 5.3%, respectively). The most frequent, at least grade 3, treatment emergent adverse events (TEAE) were thrombocytopenia, neutropenia, anemia, elevated pancreatic enzymes, and hypertension. At 96 weeks (median follow-up of 31.3 months), the treatment discontinuation rates due to drug-related adverse reactions were 7.7% vs. 23.6% in the asciminib and bosutinib arms, respectively [54]. The key results of the clinical trials designed to evaluate the efficacy and tolerability of asciminib in CML patients resistant/intolerant to ATP-competitive BCR-ABL tyrosine kinase inhibitors are set out in Table II.

A favorable asciminib response and tolerance profile was also confirmed in real-life analyses. Luna et al. [58] presented data concerning asciminib treatment efficacy and safety in ponatinib pre-treated (PPT, n = 19) and non-ponatinib pre-treated (non-PPT, n = 31) patients with resistance/intolerance to previous lines of TKI therapy. The

Table I. General characteristics of asciminib, an allosteric BCR-ABL tyrosine kinase inhibitor, specifically targeting ABL1 myristoyl pocket

Chemical structure		
IUAPC name	N-[4-[chloro(difluoro)methoxy]phenyl]-6-[(3R)-3-hydroxypyrrolidin-1-yl]-5-(1H-pyrazol-5-yl) pyridine-3-carboxamide	
Molecular formula	$C_{20}H_{18}ClF_2N_5O_3$	
Spectrum of inhibitory activity [43]	Myristoyl pocket of BCR-ABL1	
BCR-ABL1 tyrosine kinase inhibitory mode of action	On fusion of ABL1 to BCR, myristoylated N-terminal is lost and ABL1 kinase is activated. By allosterical binding of myristoyl site, asciminib mimics myristate and restores inhibition of BCR-ABL1 kinase activity [46, 47]	
	After binding to myristoyl pocket of ABL1 kinase domain, asciminib induces an inactive conformational change and inhibits kinase activity [45]	
Half-life time ($T_{1/2}$) [44, 48]	5.5 h (40 mg/day)	
	9 hours (200 mg twice a day)	
Resistant BCR-ABL1 mutants* [23, 44, 46, 49, 51]	**Detected in in vitro conditions**	**Emergence in clinical trials**
	A337V	G109D
	A344P	Y115N
	P465S	M244V
	F497F	V289I
		A337V/T
		E355G
		F359V
		E462K
		G463D/S
		P465S
		V468F
		S501R
		I502L
Oral dose per day	CP – 80 mg/d or 40 mg twice a day, in a case of T315I BCR::ABL1 mutation dosages up to 200 mg twice a day**	
Off-target inhibition [49]	Reversible inhibitor of CYP3A4/5, CYP2C8, CYP2C9, CYP2B6, inhibitor of BCRP, Pgp and weak inhibitor of OCT1	

**in vitro* and *in vivo*; ***not approved in T315I BCR::ABL1 mutation positive cases in Poland; IUAPC – International Union of Pure and Applied Chemistry; BCRP – breast cancer resistance protein; Pgp – glycoprotein P; OCT1 – organic cation transporter 1

Table II. Clinical trials designed to evaluate efficacy and tolerability of asciminib in chronic myeloid leukemia patients resistant/intolerant to ATP-competitive BCR-ABL1 tyrosine kinase inhibitors [48, 55–57]

Trial title (study identifier)	Study population/design	Main objective	Relevant data
A phase I, multi-center, open-label study of oral ABL001 in patients with chronic myelogenous leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) (NCT02081378)* (a dose-escalation study)	141 pts with CP and 9 pts with accelerated-phase CML who had resistance to or unacceptable side effects from at least two previous ATP-competitive tyrosine kinase inhibitors (TKIs)	The primary objective was to determine the MTD or the recommended dose (or both) of asciminib	Identification of the MTD, as well as assessing the safety, pharmacokinetics and efficacy of asciminib
ASC2ESCALATE: A phase II, multi-center, open-label, single-arm dose escalation study of asciminib monotherapy in 2nd line chronic phase chronic myelogenous leukemia (NCT05384587)* (a dose escalation study)	Adult pts (aged ≥18 years) with CML-CP without the T315I mutation who experienced resistance (*BCR::ABL1*^{IS} >1% with 6–12 months of 1L treatment or >10% with >12 months of 1st-line treatment) or intolerance (*BCR::ABL1*^{IS} >0.1%) with ≥6 months of treatment with 1 prior ATP-competitive TKI are eligible. All pts will initiate treatment with asciminib 80 mg once a day. For pts not achieving *BCR::ABL1*^{IS} <1% at 6 months, dose will be escalated to 200 mg once a day if pts do not have grade ≥3 toxicity or persistent grade 2 toxicity refractory to optimal management. In pts not achieving MMR at 12 months, either dose escalation from 80 to 200 mg once a day or from 200 mg once a day to 200 mg twice a day will occur or the pts will discontinue study treatment. Pts who achieve MMR at 12 months will continue asciminib at their current dose. Pts deriving clinical benefit from asciminib per investigator assessment may receive post-trial access	Percentage of participants who MMR (time frame: baseline up to 12 months) Secondary endpoints include: • MMR rates by 3, 6, 18, and 24 months • MR$^{4.5}$ (BCR::ABL1^{IS} ≤0.0032%) at 24 months • time to and duration of MMR • time to treatment failure; • and safety/tolerability	Ongoing trial (data not published yet)
A phase III, multi-center, open-label, randomized study of oral abl001 versus bosutinib in patients with chronic myelogenous leukemia in chronic phase (CML-CP), Previously treated with two or more tyrosine kinase inhibitors (ASCEMBL, NCT03106779)*	Pts with CML-CP previously treated with ≥2 TKIs randomized (2:1) to receive third-line asciminib 40 mg twice a day vs. bosutinib 500 mg once a day Randomization was stratified by MCyR status at baseline. Pts with documented treatment failure (specifically meeting the lack of efficacy criteria adapted from the 2013 ELN recommendations) while on bosutinib treatment were offered the option to switch to asciminib treatment within 96 weeks after the last pt was randomized to the study	Number of participants with MMR rate at 24 and 96 weeks	MMR rate: • at 24 weeks: 25.5% vs. 13.2% (bosutinib) • at 96 weeks: 37.6% vs. 15.8% (bosutinib)
A phase II, multi-center, open-label, randomized study of oral asciminib added to imatinib versus continued imatinib versus switch to nilotinib in patients with CML-CP who have been previously treated with Imatinib and have not achieved deep molecular response (ASC4MORE, NCT03578367)*	Pts aged ≥18 years, have CML-CP, and have been treated with 1st-line IM for ≥12 months. Study entry requires patients to be receiving IM 400 mg once a day at randomization, have *BCR-ABL1* transcript levels in the range of ≤1% to >0.01% on the IS, no prior achievement of MR^{4} (*BCR-ABL1*^{IS} ≤0.01%) confirmed by two consecutive tests, and no prior treatment failure	Molecular response (MR$^{4.5}$) rate between asciminib + IM and IM alone (time frame: at 48 weeks)	At week 96, 19.0%, 19.0%, 4.8%, and 9.5% of pts in the 40-mg asciminib add-on, 60-mg asciminib add-on n, IM, and NIL arms, respectively, were in MR$^{4.5}$

Table II (cont.). Clinical trials designed to evaluate efficacy and tolerability of asciminib in chronic myeloid leukemia patients resistant/intolerant to ATP-competitive BCR-ABL1 tyrosine kinase inhibitors [48, 55–57]

Trial title (study identifier)	Study population/design	Main objective	Relevant data
	The study evaluates the efficacy of asciminib in two different doses (40 mg or 60 mg) in combination with IM 400 mg vs. continued IM vs. switch to nilotinib, vs. asciminib 80 mg single agent in subjects with CML-CP who have been previously treated with IM 1st-line therapy for at least one year and have not achieved DMR. 84 eligible subjects were randomized 1:1:1:1 to receive asciminib 60 mg once a day as add–on therapy to IM 400 mg once a day, or 40 mg once a day as add–on therapy to IM 400 mg once a day, or to continue IM 400 mg once a day, or to switch to nilotinib 300 mg twice a day		Cumulative $MR^{4.5}$rates at week 96 were 28.6%, 28.6%, 9.5%, and 19.0%, respectively Despite longer median durations of exposure with asciminib add–on, fewer pts experienced adverse evenst leading to discontinuation with asciminib 40 mg (4.8%) and 60 mg (14.3%) add–on vs. switching to NIL (33.3%). Rates of discontinuation with asciminib add–on did not increase with longer follow up compared to the primary analysis

*https://clinicaltrials.gov/; ATP — adenosine triphosphate; ELN — European LeukiemiaNet; IM — imatinib; IS — International Scale; MMR — major molecular response; MTD — maximum tolerated dose; NIL — nilotinib; pts — patients; TKI — tyrosine kinase inhibitors

CCyR were obtained and maintained in 74% and 53% of patients, respectively. $MR^{4.5}$ was confirmed in 16% of the studied patients (10.5% in PPT vs. 19.4% in the non-PPT group). Grade 3–4 TEAE was observed in 22% of the non-PPT and 20% of PPT patients. Asciminib cross-intolerance was diagnosed in 20% of the ponatinib-exposed patients [58]. According to the available data, cross-toxicity does not appear to affect the occurrence of cardiovascular events, edema, abdominal pain, diarrhea or rash [59]. The most frequent adverse events associated with the administration of different TKIs and asciminib are set out in Figure 2.

Third-line CML-CP treatment dilemma

The final role of asciminib in the treatment strategy of CML patients remains to be established. It has been confirmed already that asciminib is an effective treatment option in CML-CP patients intolerant or resistant to ATP-competitive BCR-ABL1 tyrosine kinase inhibitors. This is mainly due to different inhibitory modes of action and good tolerability associated with limited off-target effects (*see* Tables I, II, Figure 2). A direct comparison of clinical asciminib and ponatinib efficacy in third-line settings is difficult. The OPTIC and the ASCEMBL studies differ in many aspects, especially in terms of the percentage of recruited patients with resistance to the prior TKI line therapy (97.3% vs. 61%), and the number of patients with and without T315I BCR::ABL1 mutation (23.7% vs. 0%) at study entry [54, 60]. Initial data suggests that asciminib and dose-modified ponatinib probably represent different therapeutic options which should be recommended in specific clinical situations in CML-CP patients. In a case of TKI 'pan-intolerance', asciminib would probably be the drug of choice, whereas a TKI pan-resistant patient with no evidence of optimal molecular response to previous TKIs might benefit from initial ponatinib therapy [47]. This is mainly due to different inhibitory modes of action and good tolerability associated with limited off-target effects (*see* Tables 1, 2, Figure 2).A still unanswered question is how to manage CML-CP patients non-optimally responding or resistant to the first-line TKI therapy or experiencing TEAE. Recent data suggests that asciminib may be used in the first-line setting or in combination with a 1G- or 2G-TKI. The latter strategy may enhance the rate of DMR obtained and the number of patients eligible for an attempt at TFR. Both ideas are now under vigorous investigation [asciminib in the first-line setting: CML13 study (ASCEND, ACTRN12620000851965) and ASC4 First trial ((NCT04971226); and asciminib to improve the DMR rate: ASC4MORE (NCT03578367) study] [57, 61, 62].

Summary

The introduction into clinical practice of a new category of BCR-ABL1 tyrosine kinase inhibitor specifically targeting

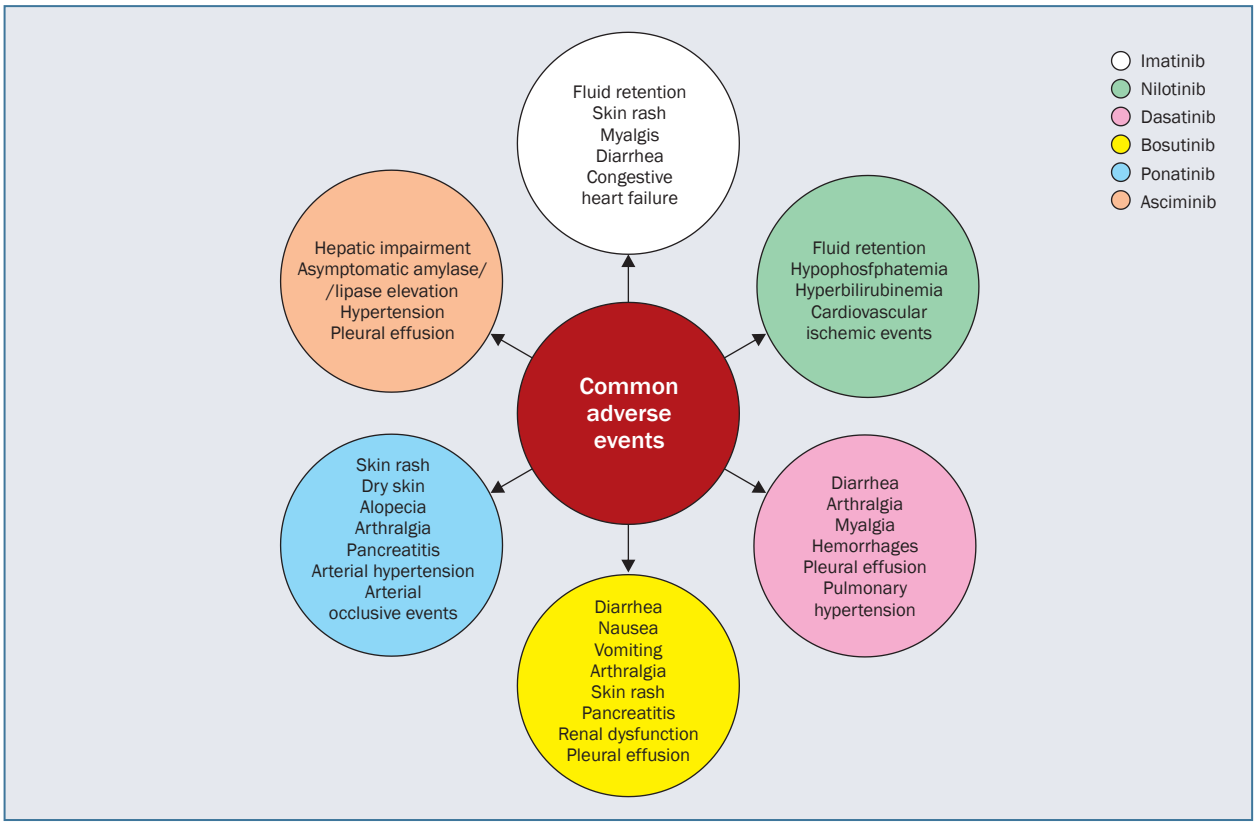


Figure 2. Common adverse events reported in chronic myelogenous leukemia patients treated with individual ATP-competitive BCR-ABL1 tyrosine kinase inhibitors and specifically targeting the ABL1 myristoyl pocket [64–71]. Common symptoms of intolerance: edema, muscle cramps, arthralgias, diarrhea/constipation, cytopenias

the myristoyl pocket of ABL tyrosine kinase changes the therapeutic approach in CML-CP patients not eligible to receive ATP-competitive inhibitors due to therapy failure or intolerance. Other possible applications of asciminib in CML patients include combined drug administration with ATP-binding TKIs. The applicability, tolerability and efficacy of such a therapeutic strategy is currently under investigation in clinical trials. Another potential practical benefit of using STAMP is the possibility of avoiding distant cardiovascular toxicity, increasingly reported in cases of long-term therapy with TKIs [63].

Article information and declarations

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Author contributions

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Conflict of interest

The author declare no conflict of interest.

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