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Asciminib: the first-in-class allosteric inhibitor of BCR::ABL1 kinase

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Abstract

The prognosis of patients with chronic phase (CP) chronic myeloid leukemia (CML) has significantly improved due to the development of potent BCR::ABL1 tyrosine kinase inhibitors (TKIs). However, approximately 15–20% of patients ultimately experience treatment failure due to resistance or intolerance to TKI therapy. As the prognosis of patients in whom multiple TKIs fail remains poor, an optimal therapeutic approach is required to treat the condition. Asciminib, an allosteric inhibitor that targets ABL1 myristoyl pocket, has been approved by the Food and Drug Administration for use in patients with CP-CML resistant or intolerant to ≥2 prior TKIs or those with T315I mutation. In a phase 1 trial, asciminib monotherapy showed a relatively favorable safety profile and potent efficacy in patients with and without the T315I mutation. In a subsequent phase 3 trial, asciminib treatment was associated with a significantly higher major molecular response rate and lower discontinuation rate than bosutinib in patients with CP-CML for whom two previous TKIs failed. Several clinical trials are being performed in various clinical settings to evaluate the role of asciminib as a frontline treatment for newly diagnosed CP-CML, either as a single agent or in combination with other TKIs as a second-line or additive treatment to improve treatment-free or deep remission. This review summarizes the incidence, available therapies, and outcomes of patients with CP-CML who experienced treatment failure, the mechanism of action, preclinical and clinical data, and ongoing trials for asciminib.

Key Words Asciminib, Allosteric inhibitor, Chronic myeloid leukemia

INTRODUCTION

The treatment outcomes of patients with chronic myeloid leukemia (CML) have markedly improved over the past two decades owing to the introduction of several tyrosine kinase inhibitors (TKIs) targeting the ATP-binding site of the constitutively activated tyrosine kinase in the fusion BCR::ABL1 protein. In the imatinib era, the life expectancy of patients with chronic phase (CP)-CML approached that of the general population, with a 10-year overall survival exceeding 80% [1, 2]. However, many patients eventually discontinue the treatment due to resistance or intolerance to the first or subsequent lines of TKI treatment. Treatment failure may result from various toxicities associated with TKIs, inadequate reduction of *BCR::ABL1* transcript levels, or disease progression to the accelerated phase or blastic phase (AP/BP), although the rate is low. Furthermore, response rates are expected to worsen as treatment lines increase. As a result, there remains an unmet clinical need for more effective therapeutic options for patients with CP-CML who fail to respond to two or more TKIs and those with advanced-phase CML.

Asciminib, a first-in-class STAMP (Specifically Targeting the ABL Myristoyl Pocket) inhibitor of BCR::ABL1, was approved by the Food and Drug Administration in October 2021 to treat patients with CP-CML-resistant or-intolerant to two prior TKI therapies and for those with the T315I mutation. The efficacy of asciminib in CML was evaluated in a phase 1 trial as a third or beyond line of treatment for patients with CML-CP or CML-AP, or a second or beyond line for those with the T315I mutation [3]. A subsequent phase 3 trial showed that asciminib was more potent than bosutinib in patients with CP-CML who failed two or more prior TKIs, irrespective of the number of previous TKI therapies [4]. Ongoing studies are evaluating the potential applications of asciminib in various contexts, including newly diagnosed CML, CML with suboptimal response or resistance to prior TKIs targeting deep molecular response (DMR), achieving first or second treatment-free remission (TFR), and

in Philadelphia chromosome-positive acute lymphoblastic leukemia.

This study reviews the definition and incidence of treatment failure in CML treated with imatinib or 2G-TKIs, preclinical and clinical data on asciminib, and the potential role of asciminib in overcoming TKI resistance, minimizing toxicities, and achieving a deeper response leading to successful TFR.

TREATMENT FAILURE IN CHRONIC PHASE CML

Treatment milestones and definition of treatment failure

As early molecular response to TKI therapy has been associated with an increased chance of achieving DMR and improved overall and progression-free survival for patients with CML [5-8], a standardized detection method of leukemic burden and specific target of molecular response based on which therapeutic decisions are made is required. Cytogenetic and molecular milestones for patients with CP-CML treated with TKIs have been recommended by several guidelines (Table 1) [9-11]. Although definitions of optimal response and treatment failure are inconsistent among recommendations, a *BCR::ABL1* transcript level of over 1% at 12 months of treatment is generally considered a TKI-resistant disease [9-11]. If treatment failure is identified, mutational analysis of the *BCR::ABL1* kinase domain and a treatment switch to alternative TKI or allogeneic hematopoietic cell transplantation (HCT) should be considered. According to the European Leukemia Net (ELN) recommendations, a treatment change may be considered if a major molecular response (MMR), which is defined as *BCR::ABL1* transcript (International Scale) ≤0.1%, is not achieved by 36–48 months of treatment.

TKI treatment failure in CP-CML

In the 10-year follow-up of the IRIS study, 183 of 553 (33.1%) patients in the imatinib arm discontinued therapy owing to adverse events (AE, N=37, 6.7%), unsatisfactory therapeutic effects (N=29, 5.2%), HCT (N=8, 1.4%), death (N=2, 0.4%), and other causes (N=107, 19.3%) [12]. Progression to AP/BP was observed in 38 (6.9%) patients in the imatinib arm, showing the estimated annual rate of treatment failure of 3.3% in the first year, 7.5% in the second year, 4.8% in the third year, 1.5% in the fourth year, and 0.9% in the fifth year [12, 13]. In a phase 3 trial of dasatinib, DASISION, 100 of 258 patients (38.8%) in the dasatinib arm discontinued treatment. Reasons for discontinuation included treatment-related or unrelated toxicities (N=64, 21%), progression or treatment failure (N=28, 11%), and other causes (N=18, 7%). At the 5-year follow-up, 5% of patients receiving dasatinib transformed AP/BP [7]. In a 10-year follow-up of the ENESTnd trial comparing nilotinib to imatinib, of 282 patients of nilotinib 300 mg twice daily arm, 175 patients (62.1%) discontinued the treatment because of AE (N=53, 18.8%), suboptimal response or treatment failure (N=37, 13.1%), disease progression to AP/BP (N=2, 0.7%), death (N=9, 3.2%), and other causes (N=72, 26.2%), respectively [14]. Progression to AP/BP was observed in 11 (3.9%) patients during the study period. In the BFORE trial, which compared

Table 1. Milestones for patients with CP-CML treated with tyrosine kinase inhibitors.

European Leukemia Net (2020)			
	Optimal	Warning	Failure
3 months	*BCR::ABL1* ≤10%	*BCR::ABL1* >10%	*BCR::ABL1* >10% if confirmed within 1–3 months
6 months	*BCR::ABL1* ≤1%	*BCR::ABL1* >1–10%	*BCR::ABL1* >10%
12 months	*BCR::ABL1* ≤0.1%	*BCR::ABL1* >0.1–1%	*BCR::ABL1* >1%
Any time	*BCR::ABL1* ≤0.1%	*BCR::ABL1* >0.1–1%, loss of MMR	*BCR::ABL1* >1%, resistance mutations, high-risk ACA
National Comprehensive Cancer Network (2023)			
	TKI-sensitive	Possible TKI-resistant	TKI-resistant
3 months	*BCR::ABL1* ≤10%	*BCR::ABL1* >10%	
6 months	*BCR::ABL1* ≤10%		*BCR::ABL1* >10%
12 months	*BCR::ABL1* ≤1%	*BCR::ABL1* 1–10%	*BCR::ABL1* >1%
European Society for Medical Oncology (2017)			
	Optimal	Warning	Failure
3 months	Ph ≤35%, *BCR::ABL1* <10%	Ph 36–95%, *BCR::ABL1* >10%	No CHR, Ph >95%
6 months	Ph 0%, *BCR::ABL1* <1%	Ph 1–65%, *BCR::ABL1* 1–10%	Ph >35%, *BCR::ABL1* >10%
12 months	*BCR::ABL1* <0.1%	*BCR::ABL1* 0.1–1%	Ph ≥1%, *BCR::ABL1* >1%
>18 months	*BCR::ABL1* <0.01%	*BCR::ABL1* 0.1–1%	
Any time			Relapse, loss of MMR

Abbreviations: ACA, additional chromosomal abnormality; CHR, complete hematological response; MMR, major molecular response; Ph, Philadelphia chromosome-positive; TKI, tyrosine kinase inhibitor.

the efficacy and safety of bosutinib and imatinib, 268 patients were assigned to the bosutinib arm. The discontinuation rate of the bosutinib arm was 40.3% (N=108), and the causes of treatment discontinuation included AE (N=67, 25%), suboptimal response or treatment failure (N=13, 4.8%), disease progression to AP/BP (N=2, 0.7%), death (N=3, 1.1%), and others (N=23, 8.6%) [15]. In summary, the treatment discontinuation rate of first-line (1 L)-TKI therapy in patients with CP-CML was estimated to be between 28–40%, of which approximately 10% is associated with a suboptimal response or treatment failure. The treatment discontinuation rate due to AEs was reported to be higher with 2G-TKIs (20–25%) than with imatinib (less than 10%).

Beyond the second-line (2 L) setting, the discontinuation rates of TKI therapy were reported to be much higher than those of 1 L-treatment, most of which were due to disease progression or lack of efficacy. In a phase 3 CA180-034 study that evaluated the efficacy of dasatinib in patients with imatinib-resistant or-intolerant CP-CML, 110 of 166 patients (66.3%) discontinued treatment due to protocol-defined progression (N=35, 21.1%), drug-related or unrelated AE (N=49, 29.3%), and investigator or patient request (N=26, 15.6%), except for other reasons, including study termination [16]. In a phase II study of 321 CP-CML patients with imatinib resistance or intolerance who were treated with nilotinib, the discontinuation rate was 69.8% at the 2-year follow-up. The reasons for treatment discontinuation included disease progression (N=96, 29.9%), drug-related or unrelated AE (N=66, 20.6%), death (N=4, 1.2%), and others (N=58, 18.1%), respectively [17]. Bosutinib was studied in patients with CP-CML in whom imatinib failed, followed by dasatinib or nilotinib as third- or fourth-line therapy. Of the 119 patients, 90 (75.6%) discontinued treatment for 4-year because of disease progression (N=24, 20.1%), lack of efficacy (N=22, 18.5%), or AE (N=28, 23.5%) [18]. In the PACE trial evaluating the efficacy of ponatinib in CP-CML with 2G-TKI failure or T315I mutation, treatment discontinuation was observed in 63.3% of the patients, with the most common reason being the discontinuation of AE (N=57, 21.1%), followed by disease progression (N=29, 10.7%), lack of efficacy (N=15, 5.6%), and others (N=70, 25.9%), except for study closure [19].

Patients in whom multiple lines of TKI treatment fail tend to show worse outcomes [20, 21]. In a retrospective study from a single institute that included 206 patients with CML, only 37% maintained their initial TKI therapy, whereas 35% and 28% were treated with two and >two TKIs, respectively [22]. In this study, the number of TKIs administered significantly predicted progression-free and overall survival. Patients treated with fifth-line TKI showed worse survival outcomes, with an estimated 10-year overall survival of 55%, significantly lower than those treated with between two and four TKIs. In this regard, there is a need for more effective therapeutic options with acceptable toxicity profiles for CML patients who exhibit resistance or intolerance to 1 L- or, particularly, beyond 2 L-TKI treatment.

Current recommendations of treatment for CML with TKI failure

Treatment changes are imperative in patients when 1 L-therapy fails due to TKI resistance [23]. In case of treatment failure, physicians should evaluate the presence of *BCR::ABL1* kinase domain mutations, as well as patient compliance and drug interactions, followed by switching TKI. If a known *BCR::ABL1* kinase domain mutation exists, treatment decisions should be made based on the mutation profiles (Table

Table 2. Treatment recommendations based on *BCR::ABL1* kinase domain mutation and responses to TKI therapy.

Treatment	Contraindicated mutations
Dasatinib	T315I/A, F317L/V/I/C, or V299L
Nilotinib	T315I, Y253H, E255K/V, or F359V/C/I
Bosutinib	T315I, V299L, G250E, or F317L
Asciminib	A337T or P465S
Ponatinib	None

Contraindicated treatment	*BCR::ABL1* mutations	Bosutinib [18]	Dasatinib [33]		Nilotinib [34]		Ponatinib [35]
		MCyR	CCyR	MCyR	CCyR	MCyR	MCyR
Contraindication for bosutinib	G250E	0/5 (0%)	20/60 (33%)	29/60 (48%)	3/5 (60%)	3/5 (60%)	8/12 (67%)
Contraindication for bosutinib and dasatinib	F317L	1/7 (14%)	1/14 (7%)	2/14 (14%)	-	-	13/29 (45%)
	V299L	0/2 (0%)	-	-	-	-	3/8 (38%)
Contraindication for nilotinib	E255K	-	6/16 (38%)	9/16 (56%)	0/7 (0%)	3/7 (43%)	8/13 (62%)
	E255V	-	4/11 (36%)	4/11 (36%)			1/4 (25%)
	F359C	1/2 (50%)	3/5 (60%)	3/5 (60%)	0/11 (0%)	1/11 (9%)	1/7 (14%)
	F359V	2/3 (67%)	14/27 (52%)	17/27 (63%)			11/20 (55%)
	F359I	2/2 (100%)	7/12 (58%)	10/12 (83%)	-	-	3/4 (75%)
	Y253H	5/6 (83%)	14/23 (61%)	15/23 (65%)	0/8 (0%)	1/8 (13%)	1/2 (50%)

Abbreviations: CCyR, complete cytogenetic response; MCyR, major cytogenetic response.

2) [9]. The 2G-TKIs are preferred for patients treated with imatinib as 1 L-treatment. In case of resistance to 2G-TKI without specific kinase domain mutations, the ELN recommendation states that ponatinib is the preferred option rather than an alternative 2G-TKI [11]. The ELN statements also recommend the same definitions for monitoring milestones in patients receiving 2 L-treatment.

Although there is no standardized treatment recommendation or definition of acceptable response for beyond 2 L-treatment, a *BCR::ABL1* transcript level ≤1% or complete cytogenetic response is generally considered a minimum requirement. The choice of TKI should be based on the mutational profile or *BCR::ABL1* kinase domain mutations, and allogeneic HCT should be considered if the second- or third-line treatment shows a suboptimal response. To date, ponatinib, a third-generation TKI, is considered a potent therapeutic option as a third-line treatment for patients with resistance to 2G-TKIs, including those with T315I mutations.

PRECLINICAL DATA OF ASCIMINIB

Mechanism of action of Asciminib

In CML, constitutive activation of tyrosine kinase is caused by BCR::ABL1 oncoprotein formation, with loss of the regulatory N-terminal cap of ABL1. Conventional TKIs compete with ATP (adenosine 5′ -triphosphate) for binding to the catalytically active or inactive conformations of the kinase domain of ABL1. Kinase activity can also be suppressed by inhibitors that bind in an allosteric manner to ABL1 in addition to the ATP-binding site. Asciminib is a first-in-class specific allosteric inhibitor of BCR::ABL1 that selectively binds to a myristoyl pocket, leading to conformational changes induced by myristate-binding to the N-terminus of ABL1 under normal conditions (Fig. 1) [24].

Conventional TKIs frequently show off-target effects because they are not specific for targeting BCR::ABL1 but bind to other tyrosine kinases, including PDGFR, c-KIT, CSF1R, and the Src family [25]. As against conventional TKIs, asiminib has fewer off-target effects because of the limited number of tyrosine kinases containing myristate-binding sites. When viability was assessed in a diverse panel of human cancer cell lines, it selectively inhibited the proliferation of *BCR::ABL1* expressing leukemic cell lines but showed minimal or no effect on cells not expressing *BCR::ABL1* [26, 27].

In vitro and in vivo activity of asciminib

Asciminib displayed anti-proliferative activity against cell lines with several ABL1 kinase domain mutations, including T315I, a gatekeeper mutation that leads to resistance to most conventional TKIs, except ponatinib [24, 27, 28]. It also demonstrated tumor regression of xenografts implanted with T315I harboring KCL-22 cell, a CML blast-phase cell line, when treated with 30 mg/kg twice daily [27]. However, cell lines with compound mutations (two mutations within the same allele of *BCR::ABL1*) with or without the T315I mutation exhibited resistance to asciminib, unlike most kinase domain mutations, which were effectively suppressed by single-agent asciminib at nanomolar concentrations [28].

Resistance to asciminib has been observed in several preclinical studies. Point mutations in *BCR::ABL1* within or near the myristoyl pocket, including A337V, P465S, V468F, F359C/I/V, and C464W, have been reported to confer asciminib resistance [27-29]. In addition to the *BCR::ABL1* mutation, in asciminib-resistant K562, LAMA84, and KYO1 cell lines, which were generated by treatment with increasing concentrations of asciminb, ABCG-2 mediated drug efflux was found to be a major driving mechanism of resistance [29]. Combined treatment with asciminib and conventional TKIs has shown preclinical evidence for overcoming asciminib resistance. When asciminib was co-administered with nilotinib, durable and complete tumor regression was observed in KCL-22 xenograft mice, as against sequential or single-agent treatment, which showed emerging resistance due to T315I, A337V, or P223S mutations [27]. Notably, ponatinib and asciminib combination treatment at therapeutically relevant concentrations showed synergistic anti-leukemic effects in cell lines harboring *BCR::ABL1* compound mutations and in the primary cells of patients with

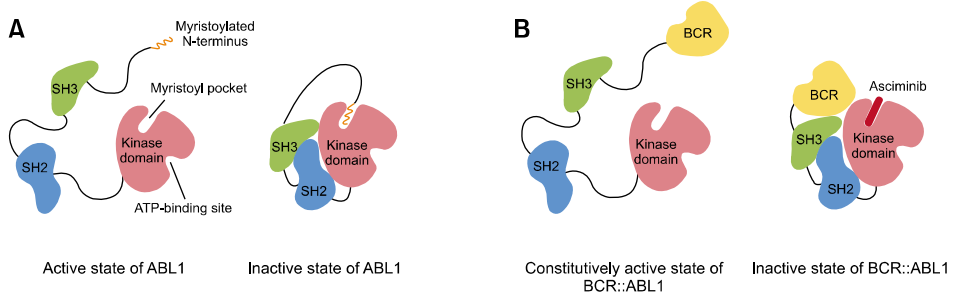

Fig. 1. Mechanism of action of asciminib. **(A)** Under normal conditions, ABL1 activity is autoregulated by binding of myristoylated N-terminus to the myristoyl pocket of the kinase domain. **(B)** In CML, ABL1 kinase is constitutively activated due to loss of regulatory function with BCR::ABL1 fusion oncoprotein formation (left side). Asciminib binds to the myristoyl pocket of the ABL1 kinase domain, inducing an inactive conformational change and inhibiting kinase activity.

T315I mutated CML [28, 30].

CLINICAL DATA OF ASCIMINIB

Phase I study (CABL001X2101)

First, the safety and efficacy of asciminib monotherapy were evaluated in a phase I, open-label study (NCT02081378) in patients with Philadelphia chromosome-positive adult CML who relapsed or were refractory to two or more previous TKIs and those with T315I mutation treated with one or more TKI and having no other effective treatment [3]. In this phase I study, 141 patients with CP-CML and nine patients with AP-CML were enrolled and treated with asciminib at doses between 10 and 200 mg twice daily or between 80 and 200 mg once daily in the dose escalation and dose expansion phases. Of the 150 enrolled patients, 105 (70%) had been previously treated with at least 3 previous TKIs, and 49 (32.7%) had been exposed to ponatinib. The maximum tolerated dose was not reached, and a dose of 40 mg twice daily was recommended for patients with CP-CML without the T315I mutation based on a pharmacokinetic-pharmacodynamic model. At the time of analysis, 110 patients (73.3%) continued with the study treatment, with a median follow-up duration of 59 weeks. The commonly observed non-hematologic AEs during treatment were asymptomatic elevation of lipase or amylase levels (26.7% and 12.7%, respectively), rash (23.3%), and constitutional symptoms, including fatigue (29.3%), headache (28%), and arthralgia (24%). Hypertension (19.3%) was the most common cardiovascular AE, and thrombocytopenia, anemia, and neutropenia were observed in 22%, 11.3%, and 10.7% of the patients, respectively. Most AEs were of grade 1 or 2 and were reversible. Among the 113 evaluable patients with CP-CML without the T315I mutation, 91.9%, 54.4%, and 36.1% of patients without complete hematologic response (CHR), complete cytogenetic response (CCyR), and MMR at enrollment, respectively, achieved CHR, CCyR, and MMR during treatment. The response was rapid and durable, with a median time to MMR of 20 weeks (range, 2–120 wk), and the median response duration was >61 weeks (range, 4–154 wk). Among the 28 CP-CML patients with the T315I mutation, 87.5%, 40.9%, and 23.5% of patients without CHR, CCyR, and MMR at enrollment achieved CHR, CCyR, and MMR, respectively. Myristoyl-pocket point mutations, including V468F, G463S, P465S, and F359I, developed in four patients, two of whom experienced disease progression, while two showed no evidence of progressive disease at the time of analysis.

The safety and efficacy of asciminib combination therapy with imatinib, nilotinib, or dasatinib has also been evaluated in separate cohorts within the same study based on the additive effects of asciminib on conventional TKIs in preclinical studies. In the imatinib cohort, asciminib with doses of 40 mg, 60 mg, 80 mg once daily, or 40 mg twice daily was administered with imatinib 100 mg to 25 patients with CP-CML. Among these patients, any-grade drug-related AEs were observed in 22 patients (88%) and grades 3 to 4 in 11 patients (44%). Of 19 patients without MMR at baseline, 8 patients (42.1%) achieved MMR and 3 patients (15.8%) achieved $MR^{4.5}$, which is defined as a *BCR::ABL1* transcript level of ≤0.0032%, by 48 weeks of treatment [31]. In the dasatinib and nilotinib cohorts, 17 patients were enrolled in each treatment arm. The rates of any-grade and grade 3/4 drug-related AEs were reported to be 82.4% (14 of 17) and 52.9% (9 of 17) in nilotinib cohort, and 88.2% (15 of 17) and 29.4% (5 of 17) in dasatinib cohort, respectively. Of the 13 and 14 patients without MMR at baseline, 4 patients (30.8%) and 5 patients (35.7%) achieved MMR by 48 weeks of treatment, respectively [32].

Phase 3 study (ASCEMBLE)

A subsequent phase 3, open-label, randomized trial compared asciminib 40 mg twice daily with bosutinib 500 mg once daily in patients with CP-CML previously treated with two or more prior TKIs without the T315I or V229L mutation [4]. Patients who were intolerant to the most recent TKI must have *BCR::ABL1* transcript over 0.1% at screening which was amended from initial criteria requiring ≥1% of *BCR::ABL1* transcript. The patients were randomly assigned in a 2:1 ratio to either the asciminib arm (N=157) or the bosutinib arm (N=76). Of the total patients, 121 (51.9%) had received 3 or more previous TKIs, and the reasons for discontinuation of the last TKI included lack of efficacy (63.9%) and intolerance (34.8%). After a median follow-up duration of 14.9 months from randomization, treatment was ongoing in 97 (61.8%), and 22 (28.9%) patients in the asciminib and bosutinib arms, respectively, and the most common cause of discontinuation was lack of efficacy (33 of 59 for asciminib and 22 of 54 for bosutinib). The primary endpoint of the study was the MMR rate at week 24, which was observed in 25.5% and 13.2% of patients receiving asciminib and bosutinib, respectively (P=0.029). The rate of $MR^{4.0}$, defined as a *BCR::ABL1* transcript level of ≤0.01%, and $MR^{4.5}$ at 24 weeks was 10.8% and 8.9% in the asciminib arm and 5.3% and 1.3% in the bosutinib arm, respectively. In a subgroup analysis, asciminib was superior in terms of achieving MMR, irrespective of the number of prior TKI treatments and in patients who discontinued the last session of the prior TKI due to treatment failure. Asciminib was well tolerated in terms of fewer AEs and a lower discontinuation rate due to AEs of 5.8% compared with 21.1% in the bosutinib arm. Grade ≥3 AEs were observed in 50.6% of patients receiving asciminib, which included thrombocytopenia (21.8%), neutropenia (17.9%), hypertension (5.8%), and amylase elevation (3.8%). Overall, asciminib showed improved efficacy with favorable toxicity profiles compared with bosutinib as a later-line treatment for CP-CML who failed 2 or more previous TKIs.

Ongoing clinical trials for asciminib and future perspectives

Since asciminib showed significant efficacy with an acceptable safety profile as a later-line treatment for CP-CML with or without the T315I mutation, and preclinical data support the potential of asciminib with synergistic effects when com-

Table 3. Ongoing clinical trials for asciminib.

Phase	Study title	Treatment	Target population	Primary endpoint
3 First-line (NCT05456191)	A phase IIIb, open-label, randomized study of tolerability and efficacy of asciminib versus nilotinib in patients with newly diagnosed philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase (ASC4START)	Asciminib 80 mg qd vs. nilotinib 300 mg bid	Newly diagnosed CP-CML	Time to discontinuation of study treatment due to an adverse event (TTDAE)
3 First-line (NCT04971226)	A phase III, multicenter, open-label, randomized study of oral asciminib versus investigator selected TKI in patients with newly diagnosed philadelphia chromosome positive chronic myelogenous leukemia in chronic phase	Asciminib 80 mg qd vs. investigator-selected TKIs (imatinib, nilotinib, dasatinib, or bosutinib)	Newly diagnosed CP-CML	MMR at week 48
3b Third-line (NCT04948333)	A phase 3b, multicenter, open-label, treatment optimization study of oral asciminib in patients with chronic myelogenous leukemia in chronic phase (CML-CP) previously treated with 2 or more tyrosine kinase inhibitors	Asciminib 40 mg bid or 80 mg qd, with possible dose escalation upto 200 mg qd	CP-CML with warning or resistance criteria based on ELN 2020 recommendations	MMR rate at week 48
3b Third-line (NCT04666259)	An open label, multicenter phase IIIb study of asciminib (ABL001) monotherapy in previously treated patients with chronic myeloid leukemia in chronic phase (CML-CP) with and without T315I mutation	Asciminib 40 mg bid, 80 mg qd, or 200 mg bid	CP-CML failed ≥2 prior TKIs (no T315I) or 1 prior TKI (T315I)	Number of AE and SAE up to 24 weeks
3 TFR (NCT05413915)	A phase 3, multicenter, randomized, open-label, trial evaluating the efficacy and safety of asciminib used in consolidation with imatinib vs. imatinib to achieve treatment-free remission in chronic phase-chronic myelogenous leukemia patients	Consolidation with asciminib 60 mg qd for 52 weeks added to imatinib vs. imatinib for 52 weeks followed by TFR	CP-CML in DMR (≥MR^4) for at least 12 months with imatinib	EFS at 12 months
2 First-line (NCT05143840)	Asciminib as initial therapy for patients with chronic myeloid leukemia in chronic phase	Asciminib 40 mg bid (nilotinib added for patients not achieving a response after 24 months of treatment)	Newly diagnosed CP-CML	MMR at week 24
2 Second-line (NCT05384587)	A phase II multicenter, open-label, single-arm dose escalation study of asciminib monotherapy in 2nd line chronic phase - chronic myelogenous leukemia (ASC2ESCALATE)	Asciminib 80 mg qd with possible dose escalation upto 200 mg bid	CP-CML failed 1L-TKI without T315I mutation	MMR at 12 months
2 DMR (NCT03578367)	A phase 2, multicenter, open-label, randomized study of oral asciminib added to imatinib vs. 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	Asciminib 60 mg qd+imatinib 400 mg qd vs. asciminib 40 mg qd+imatinib 400 mg qd vs. imatinib 400 mg qd vs. nilotinib 300 mg bid vs. asciminib 80 mg qd	CP-CML with *BCR::ABL1* >0.01% and ≤0.1% receiving 1L-imatinib >12 months	MR$^{4.5}$ at week 48
2 DMR (NCT04216563)	Phase II study of dual targeting of *BCR::ABL1* by adding the allosteric inhibitor ABL001 in patients with chronic myeloid leukemia (CML) and minimal residual disease (MRD) while on therapy with tyrosine kinase inhibitors	Asciminib bid for up to 36 months while receiving standard-of-care dasatinib or nilotinib	CP-CML in CCyR but detectable *BCR::ABL1* transcript on TKIs ≥24 months	Molecular response rate at 12 months
2 TFR (NCT03874858)	A phase II, single-arm study of de-escalation and treatment-free remission in patients with chronic myeloid leukemia treated with nilotinib in first-line therapy followed by a second attempt after nilotinib and asciminib combination: DANTE Study	(Second stage) Asciminib 40 mg bid and nilotinib 300 mg bid for patients failed a first TFR attempt with nilotinib consolidation	CP-CML, failed the first TFR attempt, followed by nilotinib retreatment ≥1 yr and MR4 or better	TFR rate 48 weeks after the second TFR attempt

bined with conventional TKIs in resistant CML, several trials are currently evaluating this treatment, as listed in Table 3. Asciminib monotherapy as a first-line treatment for newly diagnosed CP-CML is being compared with other conventional TKIs in two phase 3 trials (NCT05456191, NCT04971226). Other ongoing studies are evaluating asciminib as a second-line treatment with possible dose escalation (NCT04948333, NCT05384587), as consolidation therapy to increase the possibility of successful TFR (NCT05413915, NCT03874858), and to achieve DMR in patients with an insufficient response (NCT03578367, NCT04216563).

In Korea, the Ministry of Food and Drug Safety approved the use of asciminib in July 2022 as a third-line treatment for patients with CP-CML, irrespective of T315I mutation status. Although patients with the T315I mutation have limited access to asciminib as an early treatment option in Korea, those who have failed two or more prior TKIs, particularly those with a high cardiovascular risk or medical frailty, may benefit from asciminib, given its relatively favorable safety profile and efficacy in heavily treated CML-CP. Furthermore, current studies are evaluating various approaches to using asciminib in multiple clinical settings, including 1 L- or 2 L-treatment, adjunctive treatment to achieve DMR, and prior to attempting TFR. These investigations suggest that asciminib has potential applications in multiple therapeutic contexts in the near future.

CONCLUSION

Over the past 20 years, the development of TKIs has changed the treatment paradigm for patients with CML; accordingly, the survival outcomes of patients with CML have also improved dramatically. However, a substantial proportion of patients still experience resistance or intolerance to TKI treatment, leading to a discontinuation rate of approximately 30% for 1 L-TKI, which gradually increases with the treatment lines. As patients who fail to respond to multiple lines of TKIs show worse outcomes, a more efficacious therapy is required for CML patients with treatment failure. Asciminib is a first-in-class allosteric inhibitor that binds to the myristoyl pocket of ABL1. Preclinical data support the specificity and potent efficacy of asciminib in CML cells with or without *BCR::ABL1* mutations as well as the synergistic effects of asciminib and conventional TKIs, especially in terms of overcoming resistance. In phase 1 and phase 3 clinical trials, asciminib showed a significantly improved and durable response with a favorable safety profile, even when the enrolled patients were heavily pretreated with multiple TKIs. Asciminib was also effective in patients with the T315I mutation. Current research efforts aim to determine if using asciminib as a 1 L-treatment in comparison to conventional TKIs, as an adjunct therapy to achieve DMR, or as consolidation therapy for successful TFR can enhance patient outcomes in diverse clinical scenarios involving CML.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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