

Prolonged Follow-Up of ASC4MORE Demonstrates Sustained Efficacy and Tolerability of Asciminib Plus Imatinib in Patients with Chronic Myeloid Leukemia

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Abstract

As many as 65% of individuals with chronic myeloid leukemia (CML) who receive imatinib therapy do not attain a sustained deep molecular response, a critical requirement for attempting treatment-free remission. Asciminib represents the sole approved BCR::ABL1 inhibitor that selectively binds to the ABL myristoyl pocket. This novel mode of action facilitates its use in combination with ATP-competitive tyrosine kinase inhibitors, thereby helping to overcome resistance mechanisms and augment therapeutic effectiveness. The phase II ASC4MORE trial examined the addition of asciminib to imatinib in patients who had not reached deep molecular response while on imatinib. The ASC4MORE study enrolled 84 patients with CML in the chronic phase who had failed to achieve a deep molecular response after at least 1 year of imatinib treatment. Participants were randomized to one of four arms: asciminib 40 mg or 60 mg once daily (QD) added to imatinib 400 mg QD, continuation of imatinib 400 mg QD alone, or a switch to nilotinib 300 mg twice daily. At week 48 (the primary endpoint), achievement of MR^{4.5} (BCR::ABL1 $\leq$ 0.0032% on the International Scale) was substantially more frequent in the asciminib 40-mg QD add-on group (19.0%) and the 60-mg QD add-on group (28.6%) than in the continued imatinib arm (0.0%) or the nilotinib switch arm (4.8%). Treatment discontinuation occurred less often with asciminib add-on at 40 mg (14.3%) and 60 mg (23.8%) compared with continued imatinib (76.2%, including patients who crossed over) and nilotinib (47.6%). The asciminib add-on approach demonstrated acceptable tolerability, with lower rates of adverse events and treatment discontinuations due to adverse events than with nilotinib. However, rates remained higher than with continued imatinib (as would be anticipated in patients already stable on imatinib for at least 1 year). The safety profile of asciminib when added to imatinib did not reveal any novel or intensified signals beyond those previously documented with asciminib monotherapy. In summary, these outcomes indicate that adding asciminib to imatinib offers a viable strategy for helping patients with CML in chronic phase continue treatment and achieve rapid, profound molecular responses safely. However, further research is warranted before routine adoption of this approach in clinical settings.

Keywords: ASC4MORE, CML, Asciminib, Tyrosine kinase inhibitors, Deep molecular response, Imatinib

Introduction

The introduction of ATP-competitive tyrosine kinase inhibitors (TKIs) for the management of chronic myeloid leukemia in chronic phase (CML-CP) has extended patient survival to an approximate level with that of the general population [1]. This advancement has prompted a shift in therapeutic priorities toward optimizing quality of life, securing durable deep molecular response (DMR), and enabling treatment-free remission (TFR). Present clinical guidelines specify that sustained DMR—either MR^{4.5} (BCR::ABL1 $\leq$ 0.0032% on the

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International Scale [IS]) maintained for at least two years or MR⁴ (BCR::ABL1IS $\leq$ 0.01%) for at least three years—is necessary before patients may discontinue therapy in pursuit of TFR [2, 3].

Achieving broader, faster access to DMR is therefore essential to increasing the number of patients who qualify for TFR. Durable DMR correlates with minimal risk of disease recurrence while continuing TKI treatment [4, 5] and constitutes a prerequisite for TFR attempts [2, 3]. Nevertheless, many patients remain ineligible for TFR under current standards [2, 3, 6]. Data from key studies show that by five years, 52% to 67% of newly diagnosed patients on imatinib and 35% to 58% on second-generation TKIs do not reach DMR (MR⁴ or MR^{4.5}) [7-9]. In the ENESTnd trial, cumulative TFR eligibility at 10 years was 47.3% to 48.6% in patients treated with nilotinib and 29.7% in those treated with imatinib [10].

Asciminib is an approved BCR::ABL1 inhibitor indicated for adults with Philadelphia chromosome-positive CML-CP after failure of at least two prior TKIs, and in specific regions, for those carrying the T315I mutation [11-13]. Distinct from conventional TKIs that target the ATP-binding domain, asciminib is unique in its ability to inhibit ABL tyrosine kinase through specific engagement of the ABL myristoyl pocket (STAMP) [11, 12, 14]. This precision is believed to limit unintended off-target activity [15-17].

Owing to its differentiated mechanism, asciminib can be effectively paired with ATP-competitive TKIs such as imatinib. Such combinations may counteract existing resistance and hinder its development, thereby expanding options to help more patients meet key therapeutic aims—including sustained quality of life, avoidance of treatment changes, or qualification for TFR. Preclinical investigations have demonstrated that dual inhibition with asciminib and ATP-competitive TKIs effectively restrains the proliferation of resistant BCR::ABL1-mutated cell populations [15, 16], supporting the potential benefit of add-on strategies for more complete target suppression. Clinical evidence from two phase III studies has confirmed asciminib's superior efficacy in various treatment settings. The ASCSEMBL trial (NCT03106779) demonstrated greater efficacy of asciminib compared with bosutinib in heavily pretreated CML-CP patients who had received at least 2 prior TKIs [16, 18]. MMR rates (BCR::ABL1IS $\leq$ 0.1%) were markedly higher with asciminib at weeks 24 and 96 (25.5% and 37.6%) compared with bosutinib (13.2% and 15.8%) [16, 18]. Longer-term analyses at week 96 further

revealed improved attainment of DMR (MR⁴) and MR^{4.5} with asciminib, even among extensively pretreated individuals [18].

In the more recent phase III ASC4FIRST trial (NCT04971226) involving newly diagnosed CML-CP, asciminib produced a statistically superior MMR rate at week 48 relative to investigator-selected standard TKIs (67.5% vs 49.0%) and versus imatinib monotherapy (69.3% vs 40.2%). It also trended toward better MMR outcomes against second-generation TKIs and delivered higher rates of DMR and early molecular responses across comparisons [19].

Long-term data from the phase I X2101 study (NCT02081378) confirmed sustained efficacy at 4 years, along with a manageable, stable tolerability profile for asciminib in CML patients, irrespective of T315I mutation status [14, 20]. The trial additionally explored asciminib combined with imatinib, identifying 40 mg and 60 mg QD as appropriate doses for further study when paired with imatinib 400 mg daily [21].

This article presents findings from the ASC4MORE trial (NCT03578367), which assessed the efficacy and safety of adding asciminib 40 mg or 60 mg QD to ongoing imatinib therapy, in comparison with continued imatinib or a switch to nilotinib, among patients with CML-CP who had received at least one year of imatinib without achieving DMR.

Materials and Methods

This investigation primarily sought to determine whether adding asciminib (40 mg or 60 mg once daily) to ongoing imatinib would result in higher rates of MR^{4.5} achievement by week 48—the primary endpoint—compared with imatinib monotherapy. The study population consisted of individuals with chronic-phase chronic myeloid leukemia (CML-CP) who had received imatinib for a minimum of one year yet had not attained deep molecular response (DMR). A secondary objective compared the effectiveness (MR^{4.5} at week 48) of the two asciminib add-on regimens with that of a switch to nilotinib therapy. Broader aims across the four treatment groups encompassed additional measures of response (MR^{4.5} status at and by week 96, time until MR^{4.5}, and response duration), together with evaluations of safety, tolerability, and pharmacokinetic characteristics (particularly for the asciminib add-on combinations).

Study oversight

The trial's development involved close cooperation between the sponsor, Novartis Pharmaceuticals Corporation, and the participating researchers. Each participating institution's ethics committee reviewed and approved the protocol, with all procedures aligned to the principles of the Declaration of Helsinki. Before participation, every patient provided documented informed consent. The sponsor managed data acquisition and performed the analyses in partnership with the investigators. All authors contributed actively to manuscript preparation and revision. The complete author group and sponsor representatives critically reviewed the final text and assume full responsibility for the integrity, completeness, and protocol fidelity of the reported findings.

Study design

The trial was designed as a phase II, open-label, multicenter, randomized study evaluating the addition of

asciminib to imatinib, continued imatinib alone, or a change to nilotinib in patients with CML-CP. All participants had been treated with imatinib 400 mg once daily as initial tyrosine kinase inhibitor therapy for at least one year without reaching DMR. Eligibility criteria were broadened on August 24, 2023, through a protocol amendment that allowed enrollment of patients whose imatinib dose had been reduced to ≥ 300 mg once daily during ≥ 1 year of first-line treatment without achieving DMR. All patients featured in this report had been recruited before the amendment.

In total, 84 patients meeting the selection criteria underwent randomization in equal proportions (1:1:1:1) to receive asciminib 40 mg once daily plus imatinib 400 mg once daily, asciminib 60 mg once daily plus imatinib 400 mg once daily, continued imatinib 400 mg once daily, or nilotinib 300 mg twice daily (**Figure 1**).

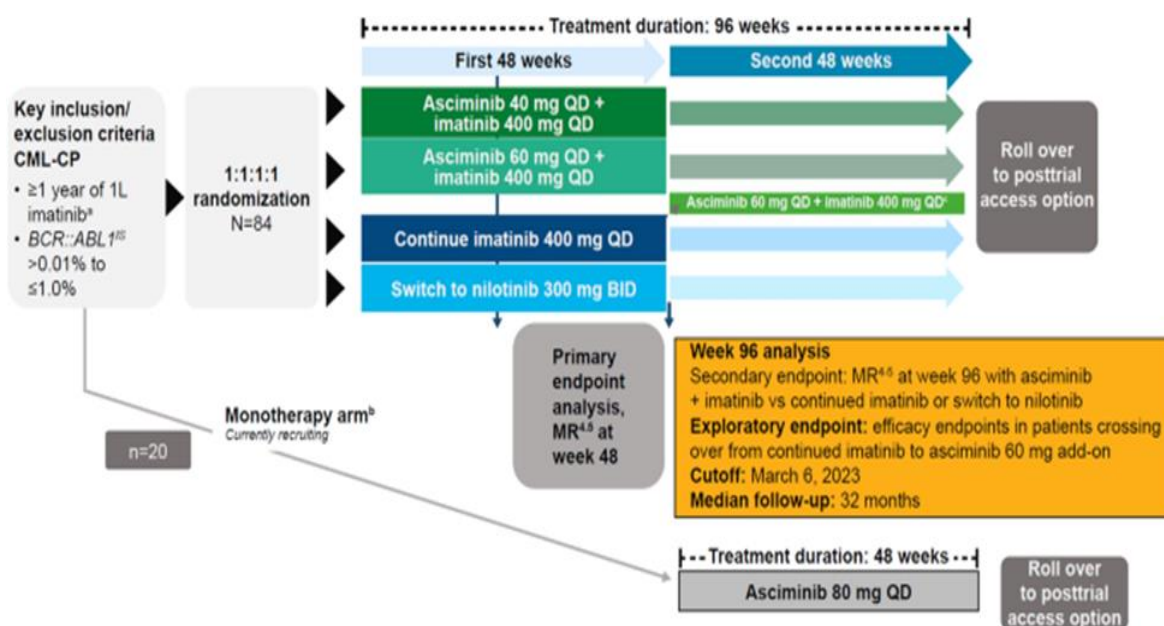


Figure 1. Overall schema of the ASC4MORE trial.

1L, first line; ABL1, ABL proto-oncogene 1; BCR, breakpoint cluster region; BID, twice daily; CML, chronic myeloid leukemia; CP, chronic phase; DMR, deep molecular response; IS, International Scale; MR^{4.5}, BCR::ABL1IS $\leq 0.0032\%$; QD, once daily. a Following investigator recommendations, eligibility criteria were revised in a protocol amendment dated August 24, 2023, to include patients treated with ≥ 300 mg imatinib once daily for at least one year who had not achieved DMR. b

A single-agent asciminib arm was introduced via protocol amendment on July 12, 2022, to gather preliminary safety and efficacy data and is actively recruiting. c Participants continuing on the imatinib-only arm were permitted to transition to the asciminib 60 mg plus imatinib regimen if MR^{4.5} had not been reached by week 48.

Therapy continued until evidence of treatment failure, development of unacceptable side effects, or the

conclusion of 96 weeks from the enrollment of the final patient. All patients still receiving study medication at that point underwent a 30-day follow-up assessment. Those randomized to imatinib monotherapy who failed to achieve MR^{4.5} at the week 48 evaluation could transition to asciminib 60 mg once daily added to imatinib within four weeks. Data from crossover participants were examined separately from those assigned to asciminib add-on therapy from the outset. A 2022 protocol amendment also added an open-label monotherapy cohort of 20 patients receiving asciminib 80 mg once daily. Treatment in this group will proceed until treatment failure, intolerance, or 48 weeks after the final patient's first dose, followed by a 30-day observation period. Recruitment for this cohort remains underway, and outcome data are pending.

An interim analysis was pre-specified to occur after ≥ 40 patients (50% of the planned sample) had either completed the week 24 visit or withdrawn from the study.

Patients

Inclusion required individuals aged 18 years or older with a documented diagnosis of chronic-phase chronic myeloid leukemia (CML-CP). At the point of randomization, BCR::ABL1IS transcript levels ranged from above 0.01% to 1% or lower, as confirmed through central laboratory review during the screening phase. All participants had undergone at least 1 year of initial imatinib therapy at 400 mg once daily without ever achieving deep molecular response (DMR), as evidenced by 2 successive assessments conducted at any stage of imatinib treatment. In addition, their imatinib dose remained unchanged over the three months immediately preceding enrollment. The study excluded those who met criteria for imatinib failure according to the European LeukemiaNet guidelines [2], individuals with a prior second chronic phase after advancing to accelerated or blast phase, and anyone with exposure to tyrosine kinase inhibitors other than imatinib.

Study assessments

Assessment of molecular status involved real-time quantitative polymerase chain reaction performed on

peripheral blood specimens, with processing handled exclusively by a central facility. An unconfirmed loss of major molecular response (MMR) occurred when BCR::ABL1IS exceeded 0.1% and represented at least a 5-fold increase from the patient's lowest recorded value on protocol therapy. Confirmation necessitated a repeat test 4–6 weeks later showing persistent elevation above 0.1%, unless this increase was accompanied by verified loss of complete hematologic response, complete cytogenetic response, disease progression to accelerated phase or blast crisis, or death due to CML.

Statistical analysis

The main analysis was conducted after every randomized participant had either reached week 48 in the study or terminated participation earlier. A subsequent analysis at week 96 was executed once all randomized subjects had completed that visit or withdrawn from the trial.

Rates of MR^{4.5} attainment at weeks 48 and 96 were computed for the full analysis set, encompassing the entire randomized population. MR^{4.5} frequency at week 48 for each arm was accompanied by two-sided 90% confidence intervals generated through the Clopper-Pearson procedure. Between-arm differences in MR^{4.5} rates, along with their two-sided 90% confidence intervals, were derived via the Wald approach. Descriptive summary statistics were applied to characterize time to MR^{4.5} among responders.

Results and Discussion

Patients

Demographic and disease-related features at baseline showed reasonable balance throughout the four treatment arms. Nevertheless, the continued imatinib and nilotinib switch groups included a larger fraction of patients already in major molecular response (MMR) at study start. At the same time, the asciminib add-on arms had a greater representation of patients in MR2 status (BCR::ABL1IS $\leq 1\%$) (**Table 1**). Overall, the study population had been exposed to imatinib for a median period of 2.4 years (range 1.1–18.2 years), and none had previously achieved DMR.

Table 1. Baseline patient characteristics.

Baseline characteristic	Nilotinib n = 21	Imatinib n = 21	Asciminib 60 mg once daily + imatinib n = 21	Asciminib 40 mg once daily + imatinib n = 21
Age, median (range), years	40 (20–68)	51 (28–76)	37 (19–72)	48 (20–72)

Age group, n (%)				
18 to < 65 years	19 (90.5)	16 (76.2)	19 (90.5)	18 (85.7)
65 to < 85 years	2 (9.5)	5 (23.8)	2 (9.5)	3 (14.3)
Male participants, n (%)				
15 (71.4)	16 (76.2)	16 (76.2)	13 (61.9)	
Previous imatinib treatment duration, median (range), years				
2.2 (1.2–18.2)	2.8 (1.1–15.6)	2.3 (1.1–14.4)	2.4 (1.1–12.1)	
Baseline BCR::ABL1IS transcript levels, n (%)				
> 0.1% to ≤ 1% (MR2)	7 (33.3)	6 (28.6)	13 (61.9)	11 (52.4)
> 0.01% to ≤ 0.1% (MMR)	14 (66.7)	15 (71.4)	8 (38.1)	10 (47.6)

Abbreviations: ABL1, ABL proto-oncogene 1; BCR, breakpoint cluster region; IS, International Scale; MMR, major molecular response (BCR::ABL1IS ≤ 0.1%); MR2, BCR::ABL1IS ≤ 1%; QD, once daily.

Analysis was performed with a data cutoff of March 6, 2023, at which stage all randomized participants had either reached their week 96 assessment or exited the study prematurely. The median follow-up period was 32 months. Median treatment duration (with ranges) amounted to 141.7 weeks (27–203) for patients on asciminib 40 mg QD add-on, 124.3 weeks (1–192) for asciminib 60 mg QD add-on, 53.4 weeks (50–186) for continued imatinib, and 110.1 weeks (1–189) for those switched to nilotinib.

By the cutoff date, protocol-defined completion of randomized therapy was achieved by 85.7% of

participants in the asciminib 40 mg QD add-on group, 76.2% in the asciminib 60 mg QD add-on group, 19.0% in the continued imatinib group, and 52.4% in the nilotinib switch group (**Table 2**). Discontinuation patterns differed notably: the leading cause was patient choice (9.5%) in the asciminib 40 mg QD add-on arm, adverse events (14.3%) in the asciminib 60 mg QD add-on arm, physician recommendation (66.7%) in the continued imatinib arm, and adverse events (33.3%) in the nilotinib switch arm (**Table 2**).

Table 2. Summary of patient disposition.

Variable	Nilotinib n = 21	Imatinib n = 21	Asciminib 60 mg QD + imatinib n = 21	Asciminib 40 mg QD + imatinib n = 21
Randomized patients, n (%)				
Received treatment	21 (100)	20 (95.2) ^a	21 (100)	21 (100)
Completed the assigned randomized treatment period	11 (52.4)	4 (19.0)	16 (76.2)	18 (85.7)
Discontinued the randomized treatment period, n (%)	10 (47.6)	16 (76.2)	5 (23.8)	3 (14.3)
Reasons for treatment discontinuation				
Adverse events	7 (33.3)	0	3 (14.3)	0
Patient choice	3 (14.3)	1 (4.8)	2 (9.5)	2 (9.5)
Physician decision	0	14 (66.7) ^b	0	0
Disease progression	0	1 (4.8)	0	0
Death	0	0	0	1 (4.8)
Treatment exposure duration, median (range), weeks	110.1 (1–189)	53.4 (50–186) ^a	124.3 (1–192)	141.7 (27–203)
Patients who switched from continued imatinib to the asciminib 60-mg QD add-on group, n (%) ^b				
Completed the crossover treatment phase				14 (66.7)
Discontinued the crossover treatment phase				1 (4.8) ^c

1. ABL1, ABL proto-oncogene 1; BCR, breakpoint cluster region; IS, International Scale; MR^{4.5}, BCR::ABL1IS ≤ 0.0032%; QD, once daily

2. ^aOne patient was not treated due to patient decision. ^bPatients in the imatinib arm were allowed to switch to the asciminib 60 mg + imatinib arm if they had not achieved MR^{4.5} at week 48. ^cOne patient discontinued crossover due to patient decision

Participants in the continued imatinib arm who stopped treatment on physician advice had not attained MR^{4.5} by week 48 and therefore met requirements for transitioning to asciminib 60 mg QD add-on therapy (**Table 2**). These

crossover cases were examined independently of the group originally assigned to asciminib 60 mg QD add-on at randomization. At crossover entry, 12 patients (85.7%) exhibited major molecular response, while 2

patients (14.3%) remained at MR2. Protocol completion of crossover therapy occurred in 13 patients (61.9%), with 1 patient (4.8%) withdrawing early.

Efficacy

Treatment with asciminib added to imatinib produced markedly higher attainment of the primary endpoint—MR^{4.5} at week 48—than either continued imatinib

monotherapy or a change to nilotinib (**Figure 2**). The corresponding rates were 19.0% (90% CI, 6.8–38.4) in the 40 mg QD add-on arm and 28.6% (90% CI, 13.2–48.7) in the 60 mg QD add-on arm. These figures compared with 0.0% (90% CI, 0–13.3%) for continued imatinib and 4.8% (90% CI, 0.2–20.7) for nilotinib (**Figure 2**).

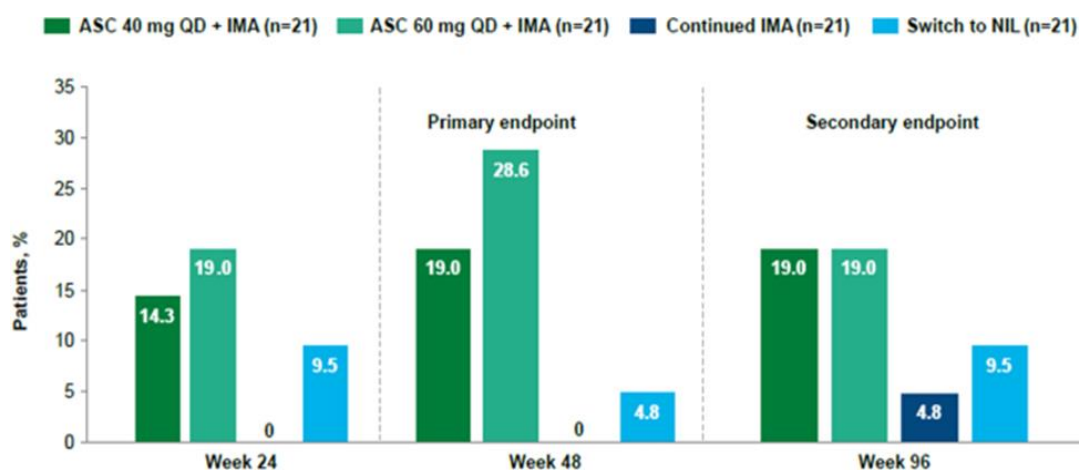


Figure 2. MR^{4.5} response rates observed at weeks 24, 48, and 96. ABL1, ABL proto-oncogene 1; ASC, asciminib; BCR, breakpoint cluster region; IMA, imatinib; IS, International Scale; MR^{4.5}, BCR::ABL1IS $\leq$ 0.0032%; NIL, nilotinib; QD, once daily.

At the week 96 timepoint, 19.0% (90% CI, 6.8–38.4) of patients in each asciminib add-on arm maintained MR^{4.5} status, versus 4.8% (90% CI, 0.2–20.7) on continued imatinib and 9.5% (90% CI, 1.7–27.1) after switching to nilotinib (**Figure 2**). MR⁴ responses at week 48 stood at 42.9% (90% CI, 24.5–62.8) and 28.6% (90% CI, 13.2–48.7) in the asciminib 40 mg and 60 mg QD add-on arms, respectively, against 0.0% (90% CI, 0.0–13.3) and 23.8% (90% CI, 9.9–43.7) in the continued imatinib and nilotinib groups.

Deep molecular responses developed on a faster timeline with asciminib add-on regimens than with the comparator approaches. Earliest DMR milestones appeared at week 4 in the 40 mg QD add-on arm and week 8 in the 60 mg QD add-on arm. By week 24, MR^{4.5} had been reached by 14.3% (90% CI, 4.0–32.9) and 19.0% (90% CI, 6.8–38.4) of patients in the respective

asciminib 40 mg and 60 mg QD add-on groups, compared with 0.0% (90% CI, 0.0–13.3%) on continued imatinib and 9.5% (90% CI, 1.7–27.1%) on nilotinib. Median intervals to MR^{4.5} among responders were 24.6 weeks, 12.4 weeks, 66.4 weeks, and 36.3 weeks in the asciminib 40 mg QD add-on, asciminib 60 mg QD add-on, continued imatinib, and nilotinib switch arms, respectively.

Taken together, the asciminib 40 mg and 60 mg QD add-on strategies enabled more patients to reach MR^{4.5} than either continued imatinib or a nilotinib switch. By week 96, cumulative MR^{4.5} rates stood at 28.6% (90% CI, 13.2–48.7; $n = 6$) in both asciminib add-on arms, compared with 9.5% ($n = 2$; 90% CI, 1.7–27.1) for continued imatinib and 19.0% ($n = 4$; 90% CI, 6.8–38.4) for nilotinib (**Figure 3**).

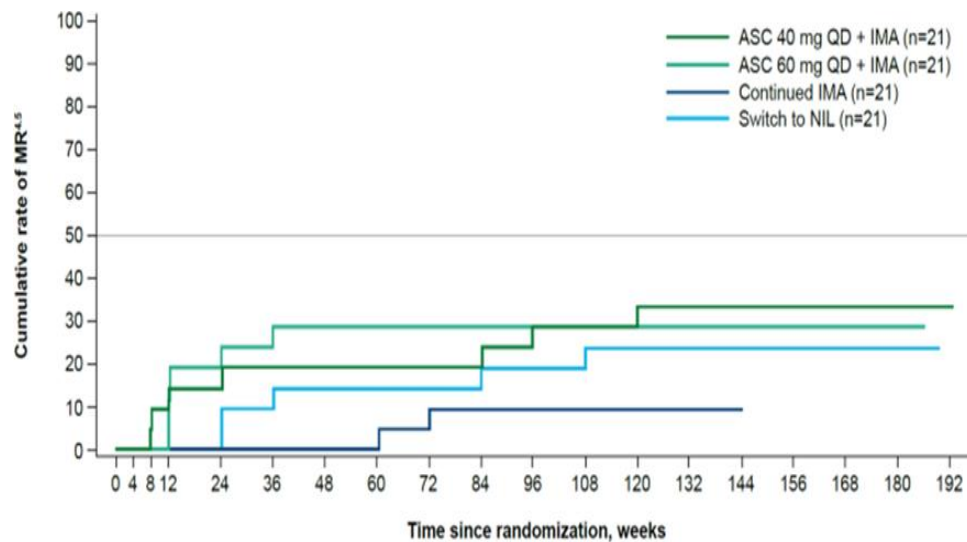


Figure 3. Time-dependent cumulative MR^{4.5} attainment. ABL1, ABL proto-oncogene 1; ASC, asciminib; BCR, breakpoint cluster region; IMA, imatinib; IS, International Scale; MR^{4.5}, BCR::ABL1^{IS} ≤ 0.0032%; NIL, nilotinib; QD, once daily

Confirmed loss of MR^{4.5} was documented in 3 out of 7 responders in the asciminib 40 mg QD add-on arm, none of the 6 responders in the asciminib 60 mg QD add-on arm, none of the 2 responders in the continued imatinib arm, and 1 out of 5 responders in the nilotinib arm among all patients who had ever achieved MR^{4.5} by the data cutoff. At the week 96 evaluation, rates of MR⁴ response were

38.1% (90% CI, 20.6–58.3) for the 40 mg QD add-on arm and 23.8% (90% CI, 9.9–43.7) for the 60 mg QD add-on arm. In comparison, these rates were 9.5% (90% CI, 1.7–27.1) in the continued imatinib arm and 28.6% (90% CI, 13.2–48.7) in the nilotinib switch arm (**Figure 4**).

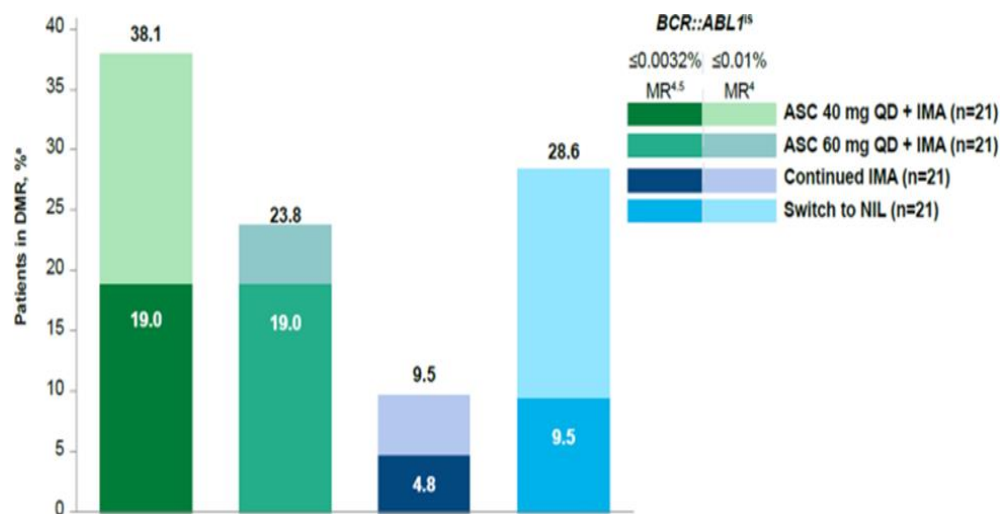


Figure 4. Achievement of deep molecular response or better (MR⁴ and deeper) at the week 96 landmark. ABL1, ABL proto-oncogene 1; ASC, asciminib; BCR, breakpoint cluster region; DMR, deep molecular response; IMA, imatinib; IS, International Scale; NIL, nilotinib; QD, once daily. a DMR is defined as a response level of at least MR⁴ (BCR::ABL1^{IS} ≤ 0.01%)

By week 96, the cumulative incidence of MR⁴ reached 52.4% (90% CI, 32.8–71.4) in patients receiving

asciminib 40 mg QD add-on and 33.3% (90% CI, 16.8–53.6) in those on asciminib 60 mg QD add-on. The

corresponding cumulative rates were 14.3% (90% CI, 4.0–32.9) with continued imatinib and 47.6% (90% CI, 28.6–67.2) after switching to nilotinib.

Among the 14 patients who transitioned from the continued imatinib arm to asciminib 60 mg QD add-on therapy, 4 individuals attained MR^{4.5}, with crossover intervals ranging from 4 to 73 weeks. Three of these four patients maintained MR^{4.5} status through their latest

assessment, sustaining the response for 12, 52, and 134 weeks, respectively. The remaining patient first reached MR^{4.5} at week 72 and continued in MR⁴ through study completion (**Figure 5**). In this crossover cohort, the MR^{4.5} rate observed at week 96 was 14.3% (90% CI, 2.6–38.5), and the cumulative MR^{4.5} rate by that timepoint was 28.6% (90% CI, 10.4–54.0).

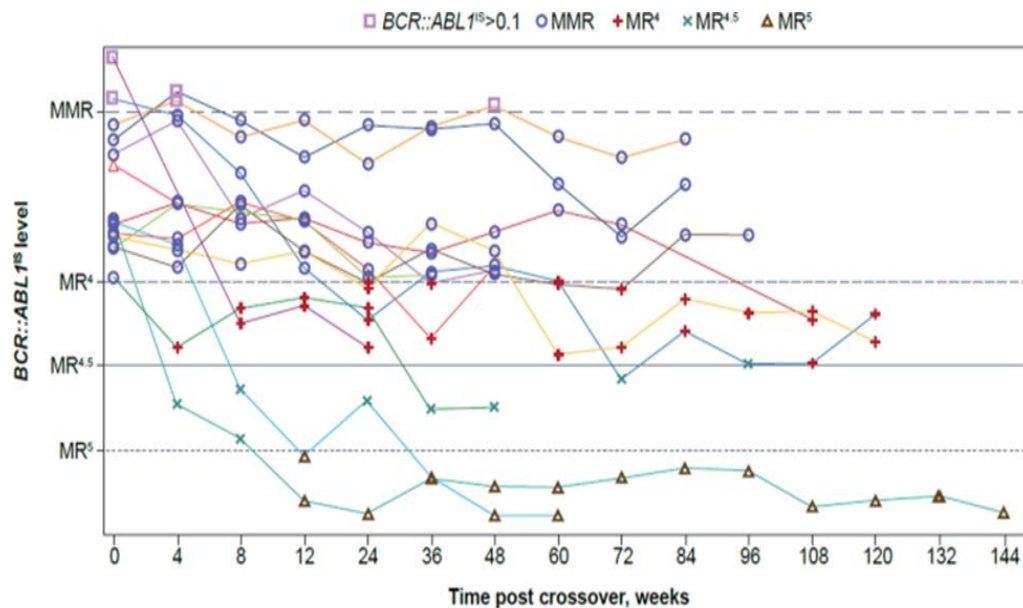


Figure 5. Changes in BCR::ABL1IS transcript levels over time among patients after crossing over to asciminib 60 mg combination therapy. ABL1, ABL proto-oncogene 1; BCR, breakpoint cluster region; IS, International Scale; MMR, major molecular response; MR⁴, BCR::ABL1^{IS} ≤ 0.01%; MR^{4.5}, BCR::ABL1^{IS} ≤ 0.0032%; MR⁵, BCR::ABL1^{IS} ≤ 0.001%.

a Patients in the imatinib arm were allowed to switch to the asciminib 60 mg + imatinib arm if they had not achieved MR^{4.5} at week 48. At crossover, 2 patients had BCR::ABL1IS ≥ 0.1% and 12 were in MMR. Each line on the graph represents BCR::ABL1IS levels over time for an individual patient

Safety

The overall safety profile of the regimens remained stable throughout the observation period, with no substantial shifts observed. Combining asciminib (40 mg or 60 mg QD) with imatinib resulted in notably fewer grade ≥ 3 adverse events and treatment discontinuations caused by toxicity than observed after switching to nilotinib. The incidence of patients experiencing at least

one adverse event was highest in the asciminib 40 mg QD add-on group (100%), the asciminib 60 mg QD add-on group (90.5%), and the nilotinib switch group (100%), while it was lowest with continued imatinib (75.0%) (**Figure 6**). Safety observations aligned closely with those from prior asciminib monotherapy trials, revealing no novel concerns or aggravation of known risks (**Figure 6**) [14, 18].

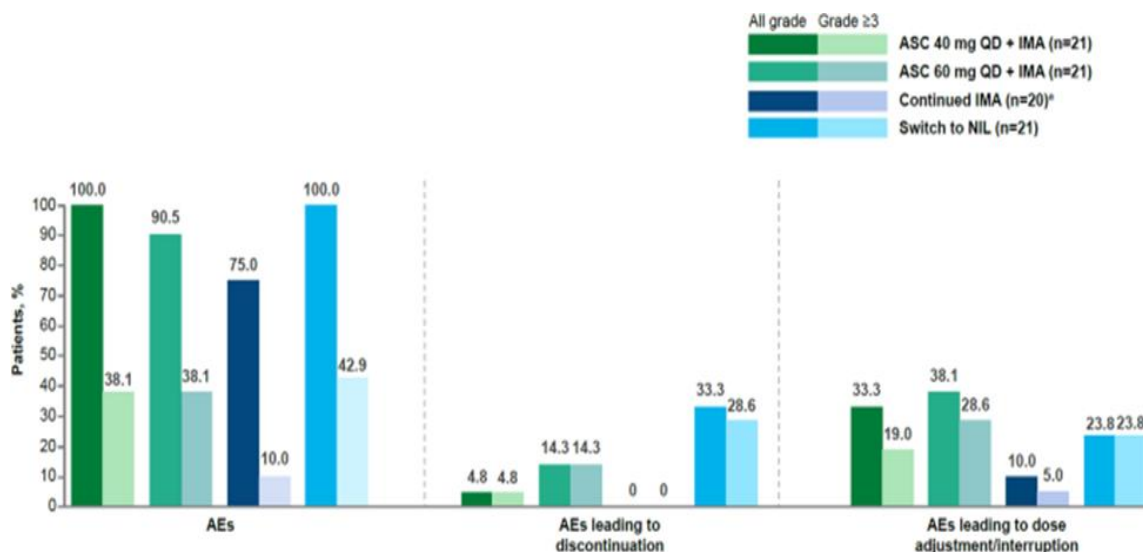


Figure 6. Overview of adverse events occurring in study participants according to assigned treatment. AE, adverse event; ASC, asciminib; IMA, imatinib; NIL, nilotinib; QD, once daily. a One patient in the IMA arm was not treated due to patient decision

Grade ≥ 3 adverse events affected eight patients (38.1%) in each asciminib add-on arm, two patients (10.0%) continuing imatinib, and nine patients (42.9%) who switched to nilotinib (**Figure 6**).

No dose-related pattern was evident in the adverse events reported among patients receiving asciminib in combination with imatinib (**Figure 7**). Predominant adverse events of any grade consisted of nausea (33.3%),

diarrhea (23.8%), and myalgia (23.8%) with asciminib 40 mg QD add-on; COVID-19 (42.9%), lipase elevation (19.0%), and alopecia (19.0%) with asciminib 60 mg QD add-on; diarrhea (15.0%), lipase elevation (15.0%), and hypophosphatemia (15.0%) with continued imatinib; and rash (38.1%), COVID-19 (28.6%), and alanine aminotransferase elevation (23.8%) with nilotinib.

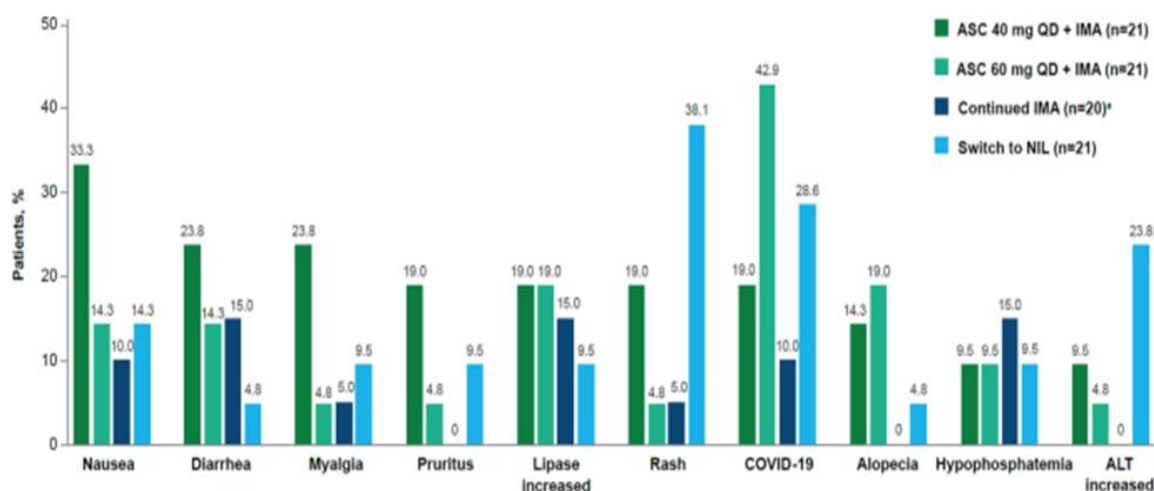


Figure 7. Frequent treatment-emergent adverse events (incidence $\geq 15\%$ in any group) across treatment arms. AE, adverse event; ALT, alanine aminotransferase; ASC, asciminib; IMA, imatinib; NIL, nilotinib; QD, once daily. a One patient in the IMA arm was not treated due to patient decision

Discontinuation rates due to adverse events were 4.8% (n = 1) in the asciminib 40 mg QD add-on arm, 14.3% (n

= 3) in the asciminib 60 mg QD add-on arm, 0% with continued imatinib, and 33.3% (n = 7) with nilotinib

(Figure 6). Adverse events prompting dose adjustments or interruptions occurred in 7 patients on asciminib 40 mg QD add-on, 8 on asciminib 60 mg QD add-on, 2 on continued imatinib, and 5 on nilotinib. Within the asciminib 60 mg QD add-on group, three discontinuations occurred due to grade 3 skin hyperesthesia, grade 3 pancreatitis, and a combination of grade 4 lipase and grade 3 amylase elevations in one case. In the nilotinib group, seven discontinuations were attributed to adverse events, with lipase increases being the most common cause (2 cases).

Adverse events of special interest arising at any severity most commonly involved gastrointestinal toxicity (42.9%), hypersensitivity reactions (23.8%), pancreatic enzyme increases (19.0%), and hepatotoxicity (19.0%) in the asciminib 40 mg QD add-on arm, and gastrointestinal toxicity (42.9%), pancreatic enzyme increases (23.8%), and ischemic heart or central nervous system issues (14.3%) in the asciminib 60 mg QD add-on arm (**Figure 8**).

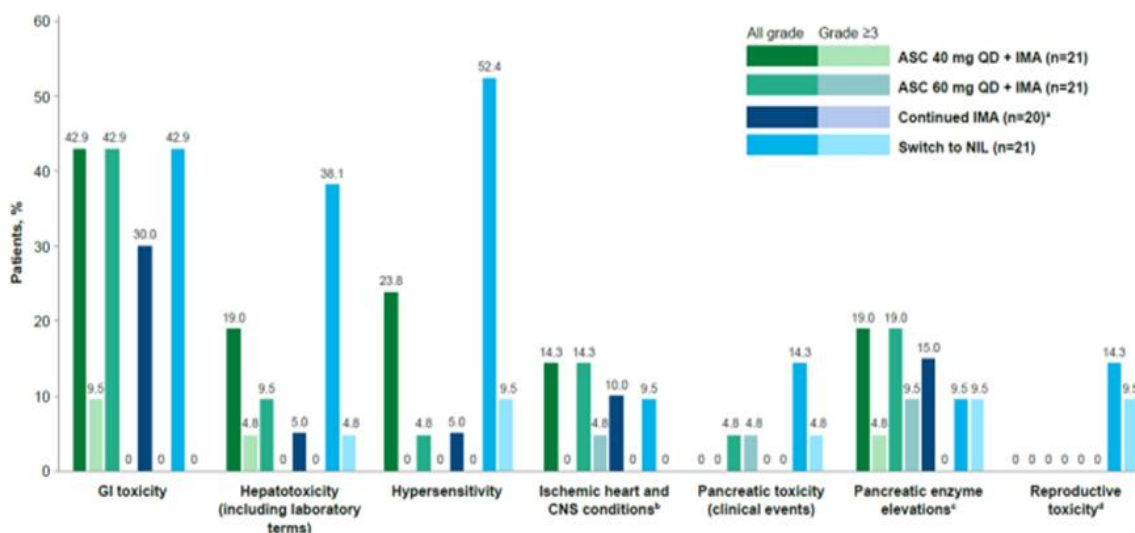


Figure 8. Selected adverse events of special interest by assigned regimen. AE, adverse event; ASC, asciminib; CNS, central nervous system; GI, gastrointestinal; IMA, imatinib; NIL, nilotinib; QD, once daily.

^a One patient in the IMA arm was not treated due to the patient's decision. ^b In the ASC arms, these events were increased blood creatine phosphokinase level. ^c In the ASC 40-mg QD add-on, ASC 60-mg QD add-on, continued imatinib, and switch to nilotinib arms, 19.0%, 19.0%, 15.0%, and 9.5% of patients, respectively, had increased lipase levels. In comparison, 4.8%, 4.8%, 10.0%, and 4.8%, respectively, had increased amylase levels. ^d All events in the reproductive toxicity category were cases of Gilbert syndrome

Three patients (14.3%) in each asciminib add-on arm developed elevated creatine phosphokinase, classified as ischemic heart and central nervous system. Five of the six events were grade 1 or 2, with the other being grade 3 or 4. Musculoskeletal complaints did not accompany these elevations. The continued imatinib arm showed frequent gastrointestinal toxicity (30.0%), pancreatic enzyme elevations (15.0%), and ischemic heart or central nervous system conditions (10.0%). The nilotinib switch arm had prominent hypersensitivity (52.4%), gastrointestinal toxicity (42.9%), and hepatotoxicity (38.1%). Arterial occlusive events were absent in both asciminib add-on groups, whereas one case (4.8%) of carotid artery stenosis occurred in the nilotinib arm.

During active treatment, one fatal event took place in the asciminib 40 mg QD add-on arm, caused by cardiac arrest. The patient, a 70-year-old man diagnosed with CML in 2008, had been managed with imatinib from 2008 until 2020. His history encompassed hypertension, type II diabetes, hypercholesterolemia, coronary stent implantation, and gastric cancer surgery combined with cholecystolithiasis treatment in February 2021. About six months after initiating study drugs and three months post-gastric operation, he presented with abdominal discomfort and breathing difficulties, leading to hospitalization and death from cardiac arrest five days afterward.

Taken together, the results of this trial indicate that adding asciminib to imatinib offers a valuable therapeutic option for promoting deep molecular response in patients with CML-CP who have not attained DMR despite at least 1 year of imatinib treatment. Such a combination approach appears promising for helping patients meet key therapeutic milestones, notably eligibility for treatment-free remission.

Superior performance of asciminib add-on therapy was evident for the primary endpoint of MR^{4.5} at week 48, with 19.0% of patients in the 40 mg QD arm and 28.6% in the 60 mg QD arm reaching this level, as opposed to 0.0% in those continuing imatinib and 4.8% in those switching to nilotinib. It is noteworthy that, even though a larger share of patients in the imatinib continuation group started in MMR, none advanced to MR^{4.5} by week 48. By contrast, participants receiving asciminib add-on presented with higher baseline BCR::ABL1 transcript levels. Data for the secondary endpoint at week 96 reinforced the effectiveness of both asciminib doses in driving deep molecular responses, yielding higher MR^{4.5} rates than either comparator. Remarkably, among patients who crossed over from continued imatinib to asciminib 60 mg QD add-on after failing to achieve MR^{4.5} at week 48, 28.6% subsequently achieved this response. No such achievement occurred in the imatinib-only arm. This pattern may stem from the study cohort's prolonged prior imatinib exposure (median 2.4 years, range 1.1–18.2 years) without DMR, coupled with the relatively small sample. Consistent with this, the CML-study IV reported that only 6.0% of patients in MMR at 18 months on imatinib reached MR^{4.5} by year 5 [22], underscoring that limited numbers may eventually attain deeper responses with extended imatinib use. These observations highlight the potential benefit of introducing asciminib promptly after one year of inadequate response to imatinib, thereby accelerating progress toward deep remission. Given the widespread initial use of imatinib worldwide and the fact that only about 30% of patients become eligible for TFR within 10 years on this agent [10], asciminib add-on therapy is a reasonable option to bridge this gap. Additionally, the combination strategy may hold advantages over nilotinib switch, particularly given the complete absence of arterial occlusive events in the add-on groups.

Deep responses with asciminib add-on occurred swiftly in many cases. By week 24, MR^{4.5} rates reached 14.3% and 19.0% in the 40 mg and 60 mg QD add-on arms, respectively, compared with 0.0% and 9.5% in the

continued imatinib and nilotinib arms. Nonetheless, heterogeneity in BCR::ABL1IS response kinetics was observed across subgroups. Certain patients exhibited a steady, gradual transcript decline; although DMR had not yet been achieved, prolonged treatment might allow them to reach this goal, warranting further evaluation. Another subset displayed persistently stable BCR::ABL1IS levels. Such a lack of response could reflect resistance mutations, although protocol-mandated mutational testing is restricted to cases of response loss. Asciminib added to imatinib exhibited acceptable tolerability. As anticipated, rates of any-grade adverse events, grade ≥ 3 adverse events, and discontinuations due to toxicity exceeded those seen with imatinib monotherapy alone. This difference is understandable, as all enrolled patients had already demonstrated tolerance to imatinib 400 mg daily for at least 1 year.

When benchmarked against nilotinib, the asciminib 40 mg and 60 mg QD add-on regimens displayed a more advantageous safety profile. Grade ≥ 3 adverse events occurred in approximately 38% of patients in either combination arm, compared with 10.0% on continued imatinib and 42.9% after nilotinib switch. Corresponding discontinuation rates due to adverse events were 4.8% and 14.3% for the 40 mg and 60 mg asciminib add-on arms, 0% for continued imatinib, and 33.3% for nilotinib. Pancreatic enzyme elevations arose at similar frequencies in the asciminib combination arms and the nilotinib group. These safety findings align with earlier asciminib monotherapy data and corroborate the generally favorable tolerability of asciminib when combined with imatinib [13, 14, 16, 18]. Long-term monitoring revealed no new safety signals with asciminib 40 mg or 60 mg QD added to imatinib, compared with previous monotherapy experience [13, 14, 16, 18]. Overall, the evidence supports a manageable safety profile for asciminib add-on therapy in patients with CML-CP.

The recommended monotherapy dose of asciminib for patients with CML-CP lacking the T315I mutation is 80 mg QD or 40 mg BID [11, 12]. Earlier phase I investigations, however, revealed that coadministration with imatinib increases asciminib exposure, as reflected by higher area under the curve and maximum concentration values. At the same time, asciminib itself does not affect imatinib pharmacokinetics [21]. When combined with imatinib, asciminib 40 mg QD yielded C_{max} values similar to asciminib 40 mg BID but reduced AUC by up to 40%. In parallel, asciminib 60 mg QD plus

imatinib produced AUC values comparable to those of the BID regimen, accompanied by a 1.5- to 1.85-fold increase in C_{max}. Although these pharmacokinetic variations were noted, the current study was not powered to directly compare the two asciminib add-on doses. It did not identify meaningful differences in efficacy or safety between them.

An alternative approach for patients failing to reach DMR after at least one year of imatinib could involve transitioning to asciminib monotherapy. The incorporation of a dedicated asciminib monotherapy cohort into the ASC4MORE trial will provide important insights into whether single-agent asciminib is sufficient to meet therapeutic targets in this setting, while simultaneously evaluating its safety and tolerability profile following prior TKI exposure.

Although the BCR:: *ABL1*^{IS} transcript dynamics captured by polymerase chain reaction analysis appear to corroborate the observed clinical advantages, the trial was not structured for formal head-to-head efficacy comparisons between arms and lacked blinding. Moreover, the study was not statistically powered for hypothesis testing, and the limited number of participants restricts deeper interpretation of these encouraging outcomes. These constraints should be borne in mind when considering the efficacy data; nonetheless, the trial was intentionally conducted to obtain preliminary evidence regarding the feasibility of asciminib add-on as a safe and active alternative to switching to a second-generation TKI. The asciminib monotherapy arm was implemented after recruitment for the other groups was completed, precluding direct comparisons with the add-on arms and thereby limiting broader conclusions from the study. Additional confirmatory research will be essential before widespread adoption of the asciminib add-on approach in routine practice.

Treatment choices should emerge from collaborative discussions between patients and clinicians, taking multiple considerations into account. Although second-generation TKIs demonstrate superior efficacy compared with imatinib, this advantage has not resulted in markedly better survival [23]. Higher frequencies of adverse events and discontinuations due to toxicity were noted in the asciminib add-on groups relative to continued imatinib, which was anticipated given the participants' established tolerance to prolonged imatinib therapy. Asciminib add-on also exhibited a more favorable safety profile than nilotinib, with faster and

deeper molecular responses than either imatinib continuation or nilotinib switch. Clinicians and patients should nevertheless weigh the increased pill burden associated with combination therapy when deciding on a regimen. Ultimately, decisions regarding asciminib add-on should be individualized based on a careful assessment of benefits and risks.

The ongoing phase II ASC2ESCALATE trial (NCT05384587) is exploring alternative dosing regimens of asciminib in patients with CML-CP who have stopped their initial TKI [24]. In addition to ASC4FIRST, multiple other investigations are evaluating asciminib as initial monotherapy, including ASCEND, ASC4START (NCT05456191), and ASC2ESCALATE, the latter also enrolling newly diagnosed patients [19, 24-26].

Conclusion

Collectively, the present results indicate that adding asciminib to imatinib is a promising option that enables more patients to achieve rapid and profound molecular responses safely and expeditiously.

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References

1. Sasaki K, Strom SS, O'Brien S, Jabbour E, Ravandi F, Konopleva M, et al. Relative survival in patients with chronic-phase chronic myeloid leukaemia in the tyrosine-kinase inhibitor era: analysis of patient data from six prospective clinical trials. *Lancet Haematol.* 2015;2(5):e186-93.
2. Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia.* 2020;34(4):966-84.
3. Shah NP, Bhatia R, Altman JK, Amaya M, Begna KH, Berman E, et al. Chronic myeloid leukemia, version 2.2024, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw.* 2024;22(1):43-69.

4. Branford S, Seymour JF, Grigg A, Arthur C, Rudzki Z, Lynch K, et al. BCR-ABL messenger RNA levels continue to decline in patients with chronic phase chronic myeloid leukemia treated with imatinib for more than 5 years and approximately half of all first-line treated patients have stable undetectable BCR-ABL using strict sensitivity criteria. *Clin Cancer Res.* 2007;13(23):7080-5.
5. Colombat M, Fort MP, Chollet C, Marit G, Roche C, Preudhomme C, et al. Molecular remission in chronic myeloid leukemia patients with sustained complete cytogenetic remission after imatinib mesylate treatment. *Haematologica.* 2006;91(2):162-8.
6. Cortes J, Rea D, Lipton JH. Treatment-free remission with first- and second-generation tyrosine kinase inhibitors. *Am J Hematol.* 2019;94(3):346-57.
7. Brümmendorf TH, Cortes JE, Milojkovic D, Gambacorti-Passerini C, Clark RE, le Coutre P, et al. Bosutinib versus imatinib for newly diagnosed chronic phase chronic myeloid leukemia: final results from the BFORE trial. *Leukemia.* 2022;36(7):1825-33.
8. Cortes JE, Saglio G, Kantarjian HM, Baccarani M, Mayer J, Boque C, et al. Final 5-year study results of DASISION: the dasatinib versus imatinib study in treatment-naïve chronic myeloid leukemia patients trial. *J Clin Oncol.* 2016;34(20):2333-40.
9. Hochhaus A, Saglio G, Hughes TP, Larson RA, Kim DW, Issaragrisil S, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. *Leukemia.* 2016;30(5):1044-54.
10. Kantarjian HM, Hughes TP, Larson RA, Kim DW, Issaragrisil S, le Coutre P, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. *Leukemia.* 2021;35(2):440-53.
11. Novartis Pharmaceuticals Corporation. Scemblix (asciminib) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2023.
12. Novartis Europharm Limited. Scemblix (asciminib) [summary of product characteristics]. Dublin, Ireland: Novartis Europharm Limited; 2024.
13. Hughes TP, Mauro MJ, Cortes JE, Minami H, Rea D, DeAngelo DJ, et al. Asciminib in chronic myeloid leukemia after ABL kinase inhibitor failure. *N Engl J Med.* 2019;381(24):2315-26.
14. Mauro MJ, Hughes TP, Kim D-W, Rea D, Cortes JE, Hochhaus A, et al. Asciminib monotherapy in patients with CML-CP without BCR::ABL1 T315I mutations treated with at least two prior TKIs: 4-year phase 1 safety and efficacy results. *Leukemia.* 2023;37(5):1048-59.
15. Manley PW, Barys L, Cowan-Jacob SW. The specificity of asciminib, a potential treatment for chronic myeloid leukemia, as a myristate-pocket binding ABL inhibitor and analysis of its interactions with mutant forms of BCR-ABL1 kinase. *Leuk Res.* 2020;98:106458.
16. Rea D, Mauro MJ, Boquimpani C, Minami Y, Lomaia E, Voloshin S, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. *Blood.* 2021;138(21):2031-41.
17. Wylie AA, Schoepfer J, Jahnke W, Cowan-Jacob SW, Loo A, Furet P, et al. The allosteric inhibitor ABL001 enables dual targeting of BCR-ABL1. *Nature.* 2017;543(7647):733-7.
18. Hochhaus A, Réa D, Boquimpani C, Minami Y, Cortes JE, Hughes TP, et al. Asciminib vs bosutinib in chronic-phase chronic myeloid leukemia previously treated with at least two tyrosine kinase inhibitors: longer-term follow-up of ASCEMBL. *Leukemia.* 2023;37(3):617-26.
19. Hochhaus A, Wang J, Kim DW, Kim DDH, Mayer J, Goh YT, et al. Asciminib in newly diagnosed chronic myeloid leukemia. *N Engl J Med.* 2024;391(10):885-98.
20. Hughes T, Cortes JE, Réa D, Mauro MJ, Hochhaus A, Kim D-W, et al. P704: Asciminib provides durable molecular responses in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP) with the T315I mutation: updated efficacy and safety data from a phase I trial. *HemaSphere.* 2022;6:599-600.
21. Cortes J, Lang F, Kim D-W, Réa D, Mauro MJ, Minami H, et al. Combination therapy using asciminib plus imatinib (IMA) in patients (pts) with chronic myeloid leukemia (CML): results from a phase 1 study. *HemaSphere.* 2019;3(S1):397.
22. Hehlmann R, Muller MC, Lauseker M, Hanfstein B, Fabarius A, Schreiber A, et al. Deep molecular response is reached by the majority of patients treated with imatinib, predicts survival, and is

- achieved more quickly by optimized high-dose imatinib: results from the randomized CML-study IV. *J Clin Oncol*. 2014;32(5):415-23.
23. Chen KK, Du TF, Wu KS, Yang W. First-line treatment strategies for newly diagnosed chronic myeloid leukemia: a network meta-analysis. *Cancer Manag Res*. 2018;10:3891-910.
24. ClinicalTrials.gov. A study of asciminib plus imatinib in patients with newly diagnosed chronic myeloid leukemia (CML) in chronic phase (CP) [Internet]. Bethesda (MD): National Library of Medicine; 2024 [cited 2024 Mar 19]. Available from: <https://clinicaltrials.gov/ct2/show/NCT05384587>
25. ClinicalTrials.gov. A study of asciminib in combination with imatinib in patients with newly diagnosed chronic myeloid leukemia (CML) [Internet]. Bethesda (MD): National Library of Medicine; 2024 [cited 2024 Mar 19]. Available from: <https://clinicaltrials.gov/ct2/show/NCT05456191>
26. ClinicalTrials.gov. A study of asciminib plus imatinib in patients with chronic myeloid leukemia (CML) in chronic phase [Internet]. Bethesda (MD): National Library of Medicine; 2024 [cited 2024 Mar 19]. Available from: <https://clinicaltrials.gov/ct2/show/NCT04971226>