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CHRONIC MYELOID LEUKEMIA

Asciminib in combination with imatinib, nilotinib, or dasatinib in patients with chronic myeloid leukemia in chronic or accelerated phase: phase 1 study final results

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Data from in vitro and animal studies suggest that asciminib, the first BCR::ABL1 inhibitor that Specifically Targets the ABL Myristoyl Pocket (STAMP), synergizes with adenosine triphosphate (ATP)-competitive tyrosine kinase inhibitors (TKIs) to prevent emergence of and overcome resistance. Combination therapy may provide new treatment options for patients with chronic myeloid leukemia (CML) with suboptimal responses to ATP-competitive TKI monotherapy. Preliminary analysis of asciminib combined with nilotinib, imatinib, or dasatinib in a phase 1 dose-escalation study suggested promising efficacy and safety for patients with CML in chronic phase or accelerated phase treated with prior ATP-competitive TKIs; herein, we present final results from the 3 combination therapy arms. Asciminib, in combination with ATP-competitive TKIs, demonstrated rapid efficacy offset by a decreased tolerability compared with asciminib monotherapy. Based on these safety, tolerability, and preliminary efficacy results, asciminib 40 mg twice daily (BID) plus nilotinib 300 mg BID, asciminib 40 or 60 mg once daily (QD) plus imatinib 400 mg QD, and asciminib 80 mg QD plus dasatinib 100 mg QD were identified as recommended doses for expansion. The maximum tolerated dose was reached at asciminib 60 mg QD plus imatinib 400 mg QD and was not reached with asciminib plus nilotinib or dasatinib.

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INTRODUCTION

Adenosine triphosphate (ATP)-competitive tyrosine kinase inhibitors (TKIs; first-generation imatinib; second-generation nilotinib, dasatinib, and bosutinib; and third-generation ponatinib) targeting the BCR::ABL1 ATP-binding site have extended life expectancy of patients with chronic phase chronic myeloid leukemia (CML-CP) to near that of the general population [1, 2]. However, up to 25% and 24% of patients in clinical trials and real-world studies (across all lines of therapy with varying follow-up), respectively, discontinue ATP-competitive TKIs due to lack of efficacy (i.e., resistance) [3–13]. Resistance to ATP-competitive TKIs can increase disease progression risk and may be conferred by treatment-emergent mutations (e.g., T315I) [1, 14, 15].

Multiple lines of therapy, particularly when required due to TKI resistance, are associated with lower probabilities of response, higher disease progression risk, and decreased survival [16–18]. Overall survival rates at 8 years were significantly decreased for patients receiving ≥3 TKIs (22%) versus those remaining on imatinib as their first therapy (83%) [17]. Use of a second-generation TKI after failure with a prior second-generation TKI may have limited clinical benefit [19]. Ponatinib use may be limited by its safety profile and patients' comorbidities [1, 11, 20, 21]. Sequential use of TKIs can result in resistant mutations, including T315I [22]. Different treatment strategies offering stronger efficacy are needed for patients with ATP-competitive TKI resistance.

Asciminib, the first BCR::ABL1 inhibitor that Specifically Targets the ABL Myristoyl Pocket (STAMP) [23–25], is indicated for adults with previously treated Philadelphia chromosome-positive CML-CP in >60 countries and regions and in some countries for patients with the T315I mutation [26–31]. Asciminib recently received

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accelerated approval for the treatment of adults with newly diagnosed Philadelphia chromosome-positive CML-CP [26]. Asciminib maintains activity against most BCR::ABL1 ATP-binding site mutations [32], including T315I, and has improved specificity versus ATP-competitive TKIs [23–25]. This novel mechanism of action allows asciminib to be used in combination with ATP-competitive TKIs to overcome drug resistance, offering new treatment options for patients with CML not responding to ATP-competitive TKI monotherapy. Using agents with distinct mechanisms of action may synergistically inhibit BCR::ABL1 [33, 34]. Studies of asciminib combined with ATP-competitive TKIs showed suppression of resistant outgrowth in BCR::ABL1 mutant cell lines [33, 34], and asciminib combined with ponatinib demonstrated effectiveness against compound mutations at clinically relevant concentrations [33].

Asciminib has shown rapid, durable molecular responses with favorable safety and tolerability [27–29]. The first report of the phase 1 trial (median follow-up, ≈14 months) established asciminib's favorable safety and tolerability profile in patients with CML-CP or accelerated phase (AP) without T315I with ≥2 prior TKIs or with T315I with ≥1 prior TKI [27]. Asciminib continued to demonstrate favorable efficacy, safety, and tolerability in patients with CML-CP without T315I (4-year follow-up) [28] and with T315I (2-year follow-up) [35]. The phase 3 ASCEMBL trial demonstrated asciminib's superior efficacy versus bosutinib in patients with CML-CP with ≥2 prior TKIs [29, 36]. In the phase 3 ASC4FIRST trial, asciminib demonstrated superior efficacy and favorable safety and tolerability versus standard-of-care TKIs in frontline patients with CML-CP [37].

Preliminary analyses from the phase 1 study of asciminib in combination with nilotinib (ASC + NIL), imatinib (ASC + IMA), or dasatinib (ASC + DAS) (median follow-up, ≤88.3 weeks; cutoff: July 15, 2018) showed durable responses and adequate tolerability in patients without T315I with ≥2 prior TKIs or with T315I with ≥1 prior TKI [38, 39]. We report final results after ≈4.7 years' additional follow-up in these combination arms.

METHODS

Study oversight

The study was designed collaboratively by the sponsor (Novartis Pharma AG) and study investigators. The protocol was approved by the sites' institutional review boards or independent ethics committees (see supplementary appendix) and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent. The sponsor collected and analyzed the data. The sponsor and the authors interpreted the data. All authors contributed to the development and writing of the manuscript. All authors and representatives of the sponsor reviewed and amended the manuscript and vouch for the accuracy and completeness of the data and fidelity of the study to the protocol.

Study design

Methods were previously described [27, 28]. Briefly, this analysis focuses on the combination arms of the phase 1, multicenter, open-label study of asciminib monotherapy and combination therapy with imatinib, nilotinib, or dasatinib (NCT02081378) [40]. Monotherapy results are published separately [27, 28, 35, 41, 42]. Adults (aged ≥18 years) with Philadelphia chromosome-positive CML-CP/AP with an Eastern Cooperative Oncology Group performance status of 0–2, with ≥2 prior TKIs, or with T315I with ≥1 prior TKI, were eligible.

Patients were assigned to study arms by the sponsor. Doses administered were based on available asciminib monotherapy dose-escalation data and the anticipated risk when combined with nilotinib, imatinib, or dasatinib. The provisional doses of combination agents satisfied the escalation-with-overdose-control criteria [27]. An adaptive Bayesian logistic regression model (5 parameters) guided by the escalation-with-overdose-control principle was used to make dose recommendations and estimate the maximum tolerated dose (MTD) and recommended dose for expansion (RDE); separate Bayesian logistic regression models were used for each combination arm. Patients in the ASC + NIL arm received standard-dose nilotinib (300 mg twice daily [BID]) [21] plus asciminib 20 mg or 40 mg BID. Based on the asciminib monotherapy dose-escalation data, the provisional starting dose of asciminib was 20 mg BID; however, asciminib 40 mg BID starting dose was selected when the ASC + NIL cohort was opened, satisfying escalation-with-overdose-control criteria. In the ASC + IMA arm, patients received standard-dose imatinib (400 mg once daily [QD]) [21] plus asciminib 40 mg BID or 40, 60, or 80 mg QD. Patients in the ASC + DAS arm received standard-dose dasatinib (100 mg QD) [21] plus asciminib 40 mg BID or 80 or 160 mg QD. Dosing was administered in continuous 28-day cycles. Patients who experienced adverse events (AEs) resulting in treatment discontinuation could continue with asciminib monotherapy if the AEs were clearly not asciminib-related and patients were benefiting from treatment (Figure S1).

The primary objective was to determine the MTD and/or RDE via the incidence of dose-limiting toxicities during the first treatment cycle. Secondary objectives included safety, tolerability, preliminary efficacy, and pharmacokinetics (PK). End-of-treatment period was declared when all patients enrolled were followed for ≥64 weeks or discontinued from treatment, whichever occurred first, and had post-trial access options available.

Study assessments

Assessments were previously described [27, 28].

Statistical analyses

MTD and RDE were previously described [27]. Data for this report were based on an end-of-study (EOS) cutoff date of March 14, 2023. Safety and efficacy analyses included patients who received ≥1 dose of study treatment. The dose-determining analysis set included patients from the safety set who either received ≥75% of the planned doses of treatment in the first cycle and had sufficient safety evaluations during the first cycle of dosing or discontinued earlier due to dose-limiting toxicities.

RESULTS

Patients

This analysis included 26, 25, and 32 patients with CML-CP/AP in the ASC + NIL, ASC + IMA, and ASC + DAS arms, respectively. Patient demographics and clinical characteristics are summarized in Table 1. Data for each dose cohort (described in the methods) are in Table S1. Patients were heavily pretreated; 61.5%, 60.0%, and 46.9% of patients receiving ASC + NIL, ASC + IMA, and ASC + DAS, respectively, received ≥3 prior TKIs. Of patients receiving ASC + NIL, 69.2% previously received nilotinib; with ASC + IMA, 68.0% previously received imatinib; and with ASC + DAS, 56.3% previously received dasatinib. At screening, most patients had *BCR::ABL1*^{IS} >1% (69.2%, 60.0%, and 59.4% receiving ASC + NIL, ASC + IMA, and ASC + DAS, respectively), while some were in MMR (15.4%, 12.0%, and 12.5% receiving ASC + NIL, ASC + IMA, and ASC + DAS, respectively). Of patients receiving ASC + NIL, ASC + IMA, and ASC + DAS, 26.9%, 16.0%, and 6.3%, respectively, were not in complete hematologic response. The T315I mutation was detected at screening in 2 patients (6.3%) receiving ASC + DAS.

At data cutoff, ≈40–66% of patients in each arm continued to receive post-trial asciminib (Table 2; Table S2). Throughout the study, with ASC + NIL, ASC + IMA, and ASC + DAS, 10, 6, and 12 patients discontinued nilotinib, imatinib, and dasatinib, respectively, and remained on asciminib monotherapy. With ASC + NIL, ASC + IMA, and ASC + DAS, 12 (46.2%), 10 (40.0%), and 21 (65.6%) patients received treatment until EOS and continued to receive post-trial asciminib: 7, 7, and 10 patients in combination with the ATP-competitive TKI, and 5, 3, and 11 patients with asciminib monotherapy, respectively.

By EOS, the median duration of exposure (range) with ASC + NIL, ASC + IMA, and ASC + DAS, respectively, was 3.0 (0.2–7.4), 5.2 (0.5–6.6), and 2.8 (0.2–6.3) years for asciminib and 1.6 (0.0–7.2), 1.6 (0.0–6.6), and 1.7 (0.2–5.8) years for nilotinib, imatinib, and dasatinib, respectively. While all patients began treatment with

Table 1. Baseline patient demographics and clinical characteristics.

Variable	ASC + NIL, all patients (*n* = 26)	ASC + IMA, all patients (*n* = 25)	ASC + DAS, all patients (*n* = 32)
Median age, years (range)	55.5 (23-78)	57 (22-79)	53 (19-76)
Male, *n* (%)	16 (61.5)	12 (48.0)	24 (75.0)
Race, *n* (%)			
Black or African American	2 (7.7)	1 (4.0)	1 (3.1)
White	21 (80.8)	17 (68.0)	20 (62.5)
Asian	2 (7.7)	4 (16.0)	7 (21.9)
Other	1 (3.8)	3 (12.0)	4 (12.5)
Ethnicity, *n* (%)			
Hispanic or Latino	1 (3.8)	3 (12.0)	1 (3.1)
East Asian	2 (7.7)	3 (12.0)	2 (6.3)
Southeast Asian	0 (0)	0 (0)	5 (15.6)
Other	19 (73.1)	12 (48.0)	13 (40.6)
Not reported	4 (15.4)	4 (16.0)	10 (31.3)
Unknown	0 (0)	3 (12.0)	1 (3.1)
ECOG performance status, *n* (%)			
0	19 (73.1)	17 (68.0)	25 (78.1)
1	7 (26.9)	8 (32.0)	7 (21.9)
CML-CP/AP, *n* (%)	25 (96.2)/1 (3.8)	25 (100)/0 (0)	31 (96.9)/1 (3.1)
Prior TKI therapy, *n* (%)			
2	10 (38.5)	10 (40.0)	17 (53.1)
3	6 (23.1)	5 (20.0)	9 (28.1)
4	8 (30.8)	6 (24.0)	5 (15.6)
≥5	2 (7.7)	4 (16.0)	1 (3.1)
Prior TKIs, *n* (%)			
Bosutinib	10 (38.5)	12 (48.0)	10 (31.3)
Dasatinib	23 (88.5)	19 (76.0)	18 (56.3)
Imatinib	18 (69.2)	17 (68.0)	24 (75.0)
Nilotinib	18 (69.2)	23 (92.0)	24 (75.0)
Ponatinib	8 (30.8)	7 (28.0)	9 (28.1)
Radotinib	2 (7.7)	1 (4.0)	1 (3.1)
T315I mutation reported at screening, *n* (%)	0 (0)	0 (0)	2 (6.3)
BCR::ABL1^{IS} at screening, *n* (%)			
>10%	13 (50.0)	10 (40.0)	13 (40.6)
>1% to ≤10%	5 (19.2)	5 (20.0)	6 (18.8)
>0.1% to ≤1%	4 (15.4)	5 (20.0)	7 (21.9)
>0.01% to ≤0.1%	2 (7.7)	3 (12.0)	4 (12.5)
>0.0032% to ≤0.01%	1 (3.8)	0 (0)	0 (0)
≤0.0032%	1 (3.8)	0 (0)	0 (0)
Atypical/e1a2/ unknown transcripts	0 (0)	2 (8.0)	2 (6.3)

AP accelerated phase, *ASC* asciminib, *CML* chronic myeloid leukemia, *CP* chronic phase, *DAS* dasatinib, *ECOG* Eastern Cooperative Oncology Group, *IS* International Scale, *IMA* imatinib, *NIL* nilotinib, *TKI* tyrosine kinase inhibitor.

nilotinib, imatinib, or dasatinib simultaneously with asciminib, the end dates for the ATP-competitive TKI and asciminib could have been different, as patients could discontinue their ATP-competitive TKI due to AEs and remain on asciminib monotherapy.

Safety

The safety set included 26, 25, and 32 patients receiving ASC + NIL, ASC + IMA, and ASC + DAS, respectively. All-grade AEs (≥30% of patients) are shown in Fig. 1 and Table S3. Grade ≥3 AEs reported in ≥15% of patients were thrombocytopenia (26.9%) and increased lipase (19.2%) with ASC + NIL, hypertension (16.0%) with ASC + IMA, and thrombocytopenia (18.8%) and increased lipase (15.6%) with ASC + DAS.

AEs led to dose adjustments or interruptions of asciminib in 17 (65.4%), 15 (60.0%), and 22 (68.8%) patients with ASC + NIL, ASC + IMA, and ASC + DAS, respectively. Most frequent AEs (≥10% of patients) requiring dose adjustment or interruption were thrombocytopenia (15.4%), lipase increase (11.5%), and amylase increase (11.5%) with ASC + NIL; nausea and pancreatitis (12.0% each) with ASC + IMA; and pleural effusion (15.6%), fatigue, lipase increase, and thrombocytopenia (12.5% each) with ASC + DAS.

AEs requiring additional therapy (concomitant medications treating AEs and cancer-related symptoms) occurred in 21 (80.8%), 24 (96.0%), and 30 (93.8%) patients with ASC + NIL, ASC + IMA, and ASC + DAS, respectively. AEs requiring additional therapy (≥10% of patients) were required in all 3 arms. With ASC + NIL, these included arthralgia (19.2%), anemia, constipation, pneumonia, pain in extremity, nausea (15.4% each), atrial fibrillation, upper abdominal pain, hyperuricemia, bone pain, sleep disorder, thrombocytopenia, and vomiting (11.5% each). With ASC + IMA, these included peripheral edema (20.0%), dry eye (16.0%), arthralgia, constipation, hypertension, influenza, pyrexia, rash, anemia, and upper respiratory tract infection (12.0% each). With ASC + DAS, these included hypertension, pleural effusion (21.9% each), nausea, upper respiratory tract infection (18.8% each), cough, pneumonia, pyrexia (15.6% each), anemia, COVID-19, diarrhea, and headache (12.5% each).

AEs led to treatment discontinuation in 3 (11.5%), 5 (20.0%), and 4 (12.5%) patients with ASC + NIL, ASC + IMA, and ASC + DAS, respectively (Table S4). With ASC + NIL, 1 patient experienced cardiac dysfunction; 1 patient experienced arteriosclerosis, extremity necrosis, and peripheral arterial occlusive disease; 1 patient experienced neutropenia and myelodysplastic syndrome. With ASC + IMA, 1 patient experienced leukocytosis and blast crisis, and 1 patient each experienced dysphagia, anemia, myopathy, and pruritus. With ASC + DAS, 1 patient each experienced pregnancy, lung adenocarcinoma, and peripheral ischemia; 1 patient experienced peripheral sensory neuropathy and fluid retention.

All-grade AEs of special interest (≥ 30% of patients in any arm) were gastrointestinal toxicity (61.5%, 84.0%, 65.6%), hypersensitivity (46.2%, 48.0%, 40.6%), myelosuppression (42.3%, 48.0%, 43.8%), hepatotoxicity (including laboratory terms; 34.6%, 36.0%, 18.8%), thrombocytopenia (30.8%, 32.0%, 37.5%), edema and fluid retention (26.9%, 28.0%, 43.8%), and pancreatic events (including isolated pancreatic enzyme elevations; 42.3%, 36.0%, 34.4%) with ASC + NIL, ASC + IMA, and ASC + DAS, respectively; 3.8%, 12.0%, and 0% of patients, respectively, experienced pancreatitis (clinical events) (Fig. 2; Table S5). Gastrointestinal and hypersensitivity events were managed with additional therapy or dose adjustment/interruption. While most myelosuppression events were managed by dose adjustment/interruption, 1 patient each with ASC + NIL and ASC + IMA discontinued due to decreased neutrophil count and anemia, respectively.

All-grade arterial occlusive events (AOEs) were reported in 3 (11.5%), 1 (4.0%), and 1 (3.1%) patients with ASC + NIL, ASC + IMA, and ASC + DAS, respectively (Table 3). In the asciminib 40 mg BID plus nilotinib 300 mg BID cohort, the patient who experienced

Table 2. Patient disposition at end of study.

Variable, *n* (%)	ASC + NIL, all patients (*n* = 26)	ASC + IMA, all patients (*n* = 25)	ASC + DAS, all patients (*n* = 32)
Patients enrolled			
Treated	26 (100.0)	25 (100.0)	32 (100.0)
Reason for discontinuation of study treatment			
Adverse event	3 (11.5)	4 (16.0)	3 (9.4)
Physician decision prior to end of study	8 (30.8)	5 (20.0)	7 (21.9)
Lack of efficacy	7 (26.9)	5 (20.0)	3 (9.4)
Other reasons[a]	1 (3.8)	0 (0)	4 (12.5)
Progressive disease	1 (3.8)	2 (8.0)	1 (3.1)
Patient/guardian decision	2 (7.7)	1 (4.0)	0 (0)
Death	0 (0)	1 (4.0)	0 (0)
Pregnancy	0 (0)	1 (4.0)	0 (0)
Lost to follow-up	0 (0)	1 (4.0)	0 (0)
Discontinuation of ATP-competitive TKI	10	6	12
Reason for discontinuation of ATP-competitive TKI, *n*			
Adverse event	6	2	10
Physician decision	4	1	2
Patient decision	0	2	0
Progressive disease	0	1	0
Completed study and continued in PTA[b]	12 (46.2)	10 (40.0)	21 (65.6)

ASC asciminib, *ATP* adenosine triphosphate, *DAS* dasatinib, *IMA* imatinib, *NIL* nilotinib, *PTA* post-trial access, *TKI* tyrosine kinase inhibitor.
[a]Includes in the ASC + NIL arm, intolerance ($n = 1$); in the ASC + DAS arm, intolerance safety precaution, planned pregnancy, unable to comply with study procedures, and not indicated to continue in the study ($n = 1$ each). [b]Study allowed continuation on treatment based on physician's assessment of benefit.

grade 3 angina pectoris, grade 3 peripheral arterial occlusive disease, grade 1 cerebral arteriosclerosis, and grade 1 cerebrovascular accident was a 76-year-old man previously treated with imatinib, nilotinib, dasatinib, and bosutinib; active, controlled medical conditions included coronary artery disease, hypertension, and cardiac failure. A 73-year-old woman with previous nilotinib, dasatinib, and ponatinib treatment in the asciminib 20 mg BID plus nilotinib 300 mg BID cohort experienced grade 1 angina pectoris; no relevant prior or active cardiovascular medical conditions were noted. In the asciminib 20 mg BID plus nilotinib 300 mg BID cohort, a 41-year-old man previously treated with dasatinib and imatinib experienced grade 2 peripheral arterial occlusive disease; no relevant prior cardiovascular medical history was noted; active, controlled conditions included hypertension. A 75-year-old man previously treated with dasatinib, nilotinib, and bosutinib in the asciminib 40 mg BID plus imatinib 400 mg QD cohort experienced grade 1 arterial embolism; no relevant prior cardiovascular medical history was noted; active, controlled conditions included arterial hypertension, aortic valve disease, mitral valve disease, and pulmonary valve disease. A 71-year-old man in the asciminib 40 mg BID plus dasatinib 100 mg QD cohort with prior imatinib, bosutinib, and nilotinib treatment experienced grade 2 cerebrovascular accident; relevant prior medical history included cerebrovascular disease and peripheral artery bypass; active, controlled conditions included angina pectoris, type 2 diabetes mellitus, arterial hypertension, coronary artery disease, and peripheral vascular disease (Table S6).

Dose-limiting toxicities were reported in 1 (6.3%), 6 (24.0%), and 2 (9.1%) patients with ASC + NIL, ASC + IMA, and ASC + DAS, respectively (Table 4; Table S7) [43]. With ASC + NIL, 1 patient in the asciminib 20 mg BID cohort experienced maculopapular rash. With ASC + IMA, 1 patient in the asciminib 40 mg QD cohort experienced neutropenia, 1 patient each in the asciminib 60 mg QD cohort experienced abdominal pain and nausea, 1 patient each in the asciminib 80 mg QD cohort experienced increased lipase and pancreatitis, and 1 patient in the asciminib 40 mg BID cohort experienced pancreatitis. With ASC + DAS, 1 patient in the asciminib 40 mg BID cohort experienced increased lipase and 1 patient in the asciminib 160 mg QD cohort experienced thrombocytopenia.

No on-treatment (occurring during treatment or ≤30 days after last treatment) deaths were reported; 1 patient in the asciminib 60 mg QD plus imatinib 400 mg QD cohort died due to pneumonia and 1 patient in the asciminib 40 mg BID plus nilotinib 300 mg BID cohort died due to leukemia during the safety follow-up (death occurring >30 days after treatment discontinuation).

Overall, median dose intensity was similar to the starting doses in each treatment arm (Table 5).

Pharmacokinetics

PK assessment showed a moderate increase in exposure of asciminib plus imatinib or nilotinib. Dasatinib plus asciminib 80 mg QD showed a moderate increase in exposure of asciminib, whereas dasatinib plus asciminib 40 mg BID had no effect on asciminib's PK (Table S8). The MTD for ASC + IMA was reached at asciminib 60 mg QD plus imatinib 400 mg QD; MTD for ASC + NIL and ASC + DAS was not reached. Based on the safety, tolerability, PK, and preliminary efficacy data observed, the following were the RDE: asciminib 40 or 60 mg QD plus imatinib 400 mg QD, asciminib 40 mg BID plus nilotinib 300 mg BID, and asciminib 80 mg QD plus dasatinib 100 mg QD.

Efficacy

Of 26, 25, and 32 patients receiving ASC + NIL, ASC + IMA, and ASC + DAS, respectively, 0, 2, and 2 patients were not evaluable for MMR due to atypical/unknown transcripts at screening; 4, 3, and 4, respectively, were excluded due to being in MMR at baseline. Overall (by any time point during the study), 8/22, 11/20, and 15/26 patients achieved MMR with ASC + NIL, ASC + IMA, and

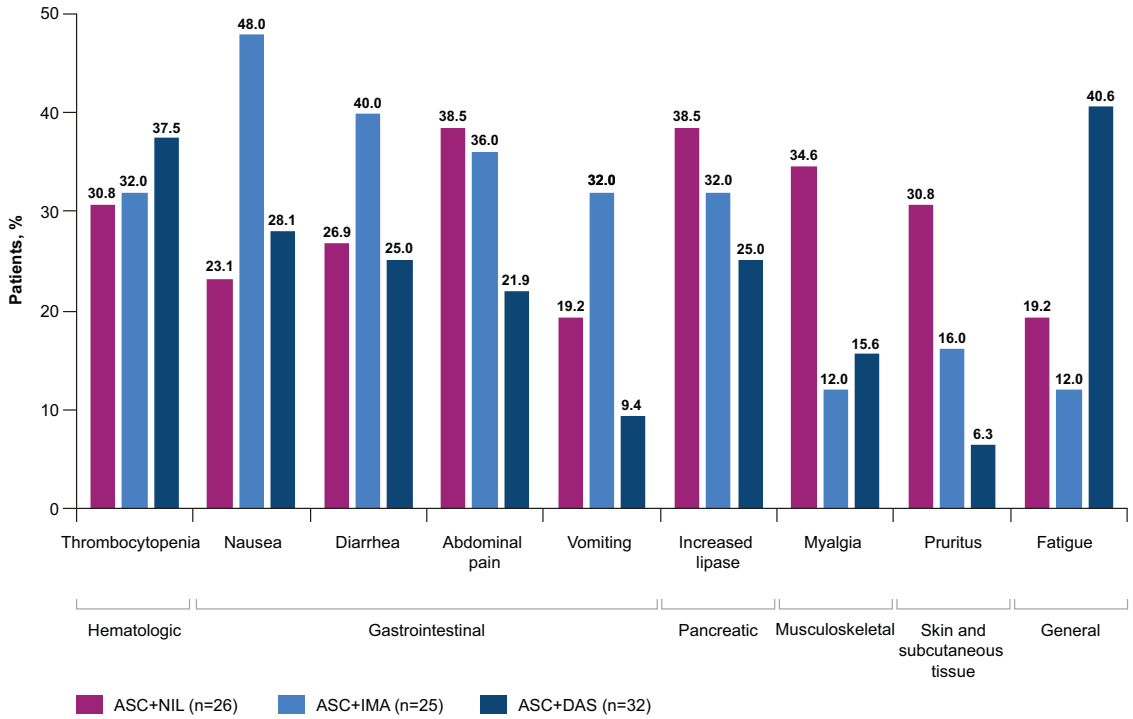

Fig. 1 Treatment-emergent all-grade AEs occurring in ≥ 30% of patients in any arm.[a] ASC asciminib, DAS dasatinib, IMA imatinib, NIL nilotinib. [a]AEs were counted if they occurred after treatment initiation through 30 days after the end of treatment.

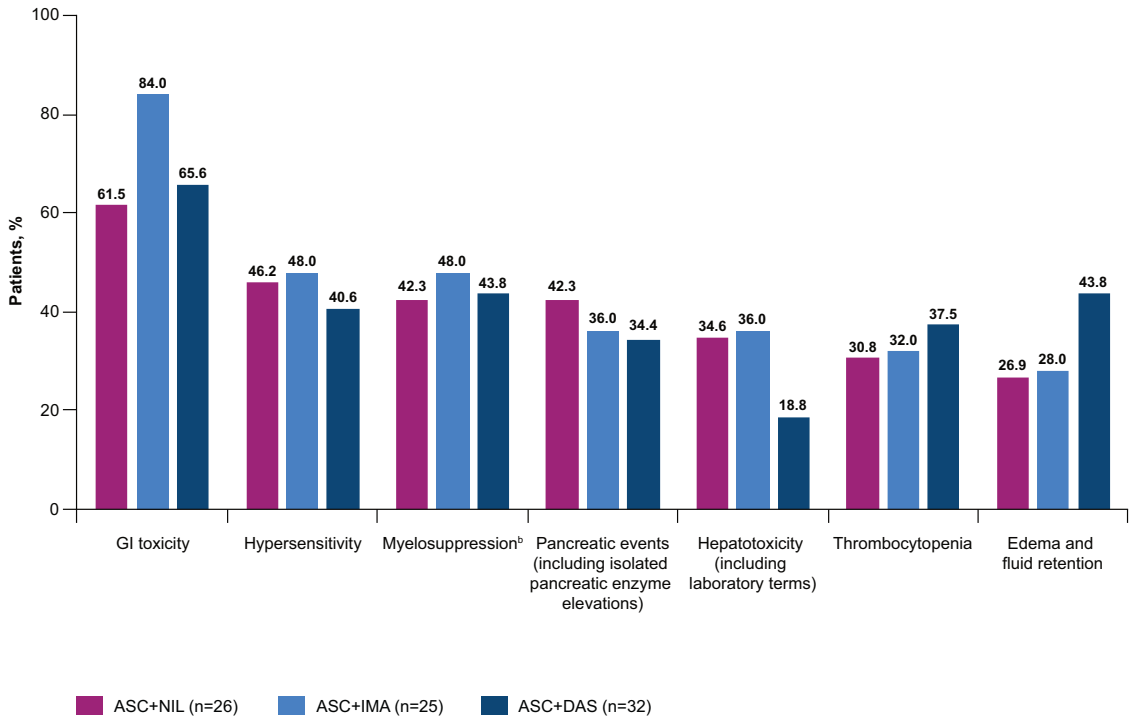

Fig. 2 AEs of special interest in ≥ 30% in any arm.[a] ASC asciminib, DAS dasatinib, GI gastrointestinal, IMA imatinib, NIL nilotinib. [a]A patient with multiple severity grades for an AE was only counted under the maximum grade. [b]Myelosuppression includes anemia, leukopenia, thrombocytopenia, and cytopenias affecting >1 lineage.

ASC + DAS, respectively. Responses were achieved rapidly: median time to first MMR was 20.1, 20.9, and 22.1 weeks with ASC + NIL, ASC + IMA, and ASC + DAS, respectively. By week 96, 31.8%, 45.0%, and 46.2% of MMR-evaluable patients with ASC + NIL, ASC + IMA, and ASC + DAS, respectively, achieved MMR. By week 432, 36.4%, 55.0%, and 57.7% of patients with ASC + NIL, ASC + IMA, and ASC + DAS, respectively, achieved MMR (Fig. 3).

With ASC + NIL, ASC + IMA, and ASC + DAS, among 8/22, 11/20, and 15/26 patients who achieved MMR, 7, 7, and 13 patients, respectively, maintained or improved this response to a deeper

Table 3. Arterial occlusive events[a].

Variable, *n* (%)	ASC + NIL (*n* = 26)		ASC + IMA (*n* = 25)		ASC + DAS (*n* = 32)	
	All grade	Grade ≥ 3	All grade	Grade ≥ 3	All grade	Grade ≥ 3
AOEs, total no. of patients[b]	3 (11.5)	1 (3.8)	1 (4.0)	0 (0)	1 (3.1)	0 (0)
Cardiac events	2 (7.7)	1 (3.8)[c]	0 (0)	0 (0)	0 (0)	0 (0)
Angina pectoris	2 (7.7)[c]	1 (3.8)[c]	0 (0)	0 (0)	0 (0)	0 (0)
Cerebrovascular events	2 (7.7)	0 (0)	0 (0)	0 (0)	1 (3.1)	0 (0)
Cerebral arteriosclerosis	1 (3.8)[c]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cerebrovascular accident	1 (3.8)[c]	0 (0)	0 (0)	0 (0)	1 (3.1)	0 (0)
Peripheral arterial occlusive disease	2 (7.7)	1 (3.8)[c]	1 (4.0)	0 (0)	0 (0)	0 (0)
Peripheral arterial occlusive disease	2 (7.7)[c]	1 (3.8)[c]	0 (0)	0 (0)	0 (0)	0 (0)
Embolism arterial	0 (0)	0 (0)	1 (4.0)	0 (0)	0 (0)	0 (0)
Exposure-adjusted AOE rate, *n* (incidence rate per 100 patient treatment-years)	3 (4.5)		1 (1.2)		1 (1.0)	
Cardiac failure (clinical events)	1 (3.8)[d]	0 (0)	2 (8.0)[e]	0 (0)	1 (3.1)[f]	0 (0)

AE adverse event, *AOE* arterial occlusive event, *ASC* asciminib, *BID* twice daily, *DAS* dasatinib, *IMA* imatinib, *NIL* nilotinib, *QD* once daily.
[a]A patient with multiple severity grades for an AE is only counted under the maximum grade. [b]AOEs include the following Medical Dictionary for Regulatory Activities terms: myocardial infarction; embolic and thrombotic events, arterial; ischemic central nervous system vascular conditions; ischemic heart disease.
[c]One patient in the ASC + NIL arm experienced angina pectoris, cerebral arteriosclerosis, cerebrovascular accident, and peripheral arterial occlusive disease.
[d]One patient in the ASC 20 mg BID plus NIL 300 mg BID cohort experienced cardiac failure. [e]One patient each in the ASC 40 mg BID plus IMA 400 mg QD and ASC 60 mg QD plus IMA 400 mg QD cohorts experienced cardiac failure. [f]One patient in the ASC 40 mg BID plus DAS 100 mg QD cohort experienced 2 pulmonary edema events.

level up to the cutoff. By week 444, 61.5%, 69.6%, and 80.0% of patients with ASC + NIL, ASC + IMA, and ASC + DAS, respectively, achieved *BCR::ABL1*^{IS} ≤1% (Fig. 4).

DISCUSSION

This study provides evidence of asciminib plus nilotinib, imatinib, or dasatinib as potential treatment strategies that may help some patients with limited therapeutic options after several lines of therapy achieve their goals (e.g. durability of response, deeper molecular response, and preventing resistance emergence) [18, 44, 45]. Combination therapy in patients with CML-CP/AP with ≥2 prior TKIs ($n = 81$) or with T315I with ≥1 prior TKI ($n = 2$) demonstrated rapid responses with adequate tolerability.

MMR, a well-established treatment goal [1, 21], can be associated with improved outcomes, including overall survival and progression-free survival [46, 47]. Within separate study comparison limits, MMR rates by week 96 with ASC + IMA (45.0%) and ASC + DAS (46.2%) were similar to those observed with asciminib monotherapy (42.7%, ASCEMBL study) with relatively similar durations of exposure (≈2.0–3.0 years) [36]. However, patients receiving combination treatment with asciminib plus nilotinib or imatinib were more heavily pretreated [36]. These data suggest that the efficacy of asciminib in combination with ATP-competitive TKIs is comparable with that of asciminib monotherapy.

ASC + NIL had the lowest MMR rate and the highest incidence of AOEs. While no hypothesis testing was done and comparisons were not powered to detect significant differences between arms, these results suggest that ASC + IMA or ASC + DAS may be safer combinations providing higher rates of responses.

In this analysis, 66–77% of patients experienced grade ≥3 AEs. Lower rates occurred with asciminib monotherapy in ASCEMBL (56.4%) with similar duration of exposure [36]. By EOS, 9.4–16% of patients discontinued treatment due to AEs. Rates were lower with asciminib monotherapy in ASCEMBL in patients with ≥2 prior TKIs (7.0%) [36], suggesting that combination therapy in pretreated patients with CML-CP may be associated with slightly higher AE burden versus asciminib monotherapy [27, 28, 36]. It remains to be seen if the possible increased benefit justifies the minor increase in AEs and treatment discontinuation. Future studies should compare monotherapy to combination therapy and define patient populations where combination therapy is preferable, such as those with limited therapeutic options due to tolerability or resistance.

Unique AEs are associated with ATP-competitive TKIs [48, 49]. Notably, nilotinib is associated with increased risk of cardiovascular events [48]. AOEs were higher with ASC + NIL than with asciminib monotherapy (11.5% with ASC + NIL vs 5.1% and 8.7% with asciminib in the 2.3-year ASCEMBL follow-up and 4-year phase 1 follow-up, respectively) [28, 36]. Accordingly, it is important to evaluate a patient's risk factors for AOE development when considering treatment with ASC + NIL.

Although imatinib is generally well tolerated, it is associated with gastrointestinal disturbances (including nausea, vomiting, and diarrhea) [49, 50]. Grade ≥3 nausea has been reported in ≈1–3% of newly diagnosed patients with CML receiving imatinib [51, 52]. Grade ≥3 nausea was reported at 8.0% with ASC + IMA. With asciminib monotherapy, grade ≥3 nausea was experienced by 0.6% of patients in the 2.3-year ASCEMBL follow-up and 1.7% of patients in the phase 1 4-year follow-up [28, 36].

Pleural effusion is commonly associated with dasatinib treatment [49]. After 6 years' follow-up in the phase 3 CA180-034 study (dasatinib in imatinib-resistant/intolerant patients), 5.3% of patients experienced grade ≥3 pleural effusion and 1.8% discontinued treatment due to grade ≥3 pleural effusion [53]. At 5 years' follow-up in the DASISION study (dasatinib vs imatinib in newly diagnosed patients), 3% of patients with dasatinib experienced grade 3/4 drug-related pleural effusion and 6% discontinued dasatinib due to pleural effusion [7]. Higher rates were seen with ASC + DAS, with 4 patients (12.5%) experiencing grade ≥3 pleural effusion. Three of the 4 patients with grade ≥3 pleural effusion permanently discontinued dasatinib and continued asciminib; 2 of these 3 patients had pleural effusion resolved by EOS. The fourth patient (in the asciminib 160 mg QD plus dasatinib 100 mg QD cohort) temporarily interrupted dasatinib treatment until the pleural effusion resolved to grade 1; dasatinib was restarted at a reduced dose of 70 mg QD and the pleural

Table 4. DLTs in patients eligible for dose-determining analysis set.

	DLT[a]	Patients, *n* (%)	Asciminib starting dose
ASC + NIL, all patients (*n* = 16)[b]	Rash maculopapular	1 (6.3)	20 mg BID
ASC + IMA, all patients (*n* = 25)[b]	Neutropenia	1 (4.0)	40 mg QD
	Abdominal pain	1 (4.0)	60 mg QD
	Nausea	1 (4.0)	60 mg QD
	Increased lipase	1 (4.0)	80 mg QD
	Pancreatitis	2 (8.0)	80 mg QD & 40 mg BID (*n* = 1 each)
ASC + DAS, all patients (*n* = 22)[b]	Increased lipase	1 (4.5)	40 mg BID
	Thrombocytopenia	1 (4.5)	160 mg QD

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ASC asciminib, *BID* twice daily; *DAS* dasatinib, *DLT* dose-limiting toxicity, *IMA* imatinib, *NIL* nilotinib, *QD* once daily.
[a]DLTs during the first cycle of treatment were considered. [b]The dose-determining analysis set consisted of all patients from the safety set who either met the minimum exposure criterion (e.g., if they received at least 75% of the planned doses of the study treatment in the first 28 days of dosing) and had sufficient safety evaluations during the first 28 days (Cycle 1) of dosing or discontinued earlier due to DLT.

Table 5. Dose intensity.

A. Asciminib plus nilotinib

Median dose intensity, mg/day	ASC 20 mg BID + NIL 300 mg BID (*n* = 12)		ASC 40 mg BID + NIL 300 mg BID (*n* = 14)	
	ASC	NIL	ASC	NIL
	48.6	597.7	78.9	591.2

B. Asciminib plus imatinib

Median dose intensity, mg/day	ASC 40 mg BID + IMA 400 mg QD (*n* = 6)		ASC 40 mg QD + IMA 400 mg QD (*n* = 9)		ASC 60 mg QD + IMA 400 mg QD (*n* = 6)		ASC 80 mg QD + IMA 400 mg QD (*n* = 4)	
	ASC	IMA	ASC	IMA	ASC	IMA	ASC	IMA
	74.1	395.9	40.0	398.5	60.0	389.3	60.1	390.7

C. Asciminib plus dasatinib

Median dose intensity, mg/day	ASC 40 mg BID + DAS 100 mg QD (*n* = 11)		ASC 80 mg QD + DAS 100 mg QD (*n* = 15)		ASC 160 mg QD + DAS 100 mg QD (*n* = 6)	
	ASC	DAS	ASC	DAS	ASC	DAS
	79.1	91.6	79.9	99.4	157.3	75.4

ASC asciminib, *BID* twice daily, *DAS* dasatinib, *IMA* imatinib, *NIL* nilotinib, *QD* once daily.

effusion was ongoing at cutoff. No pleural effusion events with asciminib were reported in the ASCEMBL 2.3-year follow-up or the phase 1 4-year follow-up [28, 36].

Myelosuppression events are often experienced by patients with CML receiving TKIs, sometimes resulting in treatment discontinuation [28, 36, 49]. Thrombocytopenia and neutropenia are hematologic toxicities associated with asciminib therapy [26, 28, 36]. Here, grade ≥3 thrombocytopenia and neutropenia were reported in 26.9%, 12.0%, and 18.8% and 15.4%, 16.0%, and 9.4% of patients receiving ASC + NIL, ASC + IMA, and ASC + DAS, respectively. In the 2.3-year ASCEMBL follow-up, 22.4% and 18.6% of patients experienced grade ≥3 thrombocytopenia and neutropenia with asciminib monotherapy; in the phase 1 4-year follow-up, 13.9% and 12.2% of patients experienced thrombocytopenia and neutropenia, respectively [28, 36]. Discontinuation due to thrombocytopenia and neutropenia events here (0% and 0–3.8%, respectively) was similar to that with asciminib monotherapy (3.2% and 2.6%, respectively, in the ASCEMBL 2.3-year follow-up; 1.7% and 0%, respectively, in the phase 1 4-year follow-up), and most events were managed by dose adjustment/interruption, or additional therapy [28, 36].

Elevated lipase and clinical pancreatitis are important to consider with ATP-competitive TKIs and asciminib [28, 36, 49, 50]. Levels of elevated lipase were relatively similar between the combination arms (38.5%, 31.0%, and 25.0% with ASC + NIL, ASC + IMA, and ASC + DAS, respectively) and asciminib monotherapy in the phase 1 4-year follow-up (37.4%) [28]; in the ASCEMBL 2.3-year follow-up, 5.1% of patients receiving asciminib experienced elevated lipase [36]. While all-grade clinical pancreatitis was slightly lower with ASC + NIL (3.8%) and ASC + DAS (0%) than with asciminib monotherapy in the phase 1 4-year follow-up (7.0%) [28], more patients with ASC + IMA experienced clinical pancreatitis (12.0%). Levels of clinical pancreatitis were not reported in the ASCEMBL 2.3-year follow-up [36].

Taken together, these data suggest patients treated with asciminib plus conventional TKIs may experience the unique AEs of ATP-competitive TKI monotherapy. Therefore, patient comorbidities and risk factors should be considered when selecting combination regimens. As asciminib's safety and tolerability profile has been established at 80 mg daily [26, 36, 37], and to decrease the risk of developing ATP-competitive TKI-associated AEs, patients may benefit from combination therapy with the approved dose of asciminib and reduced doses of ATP-

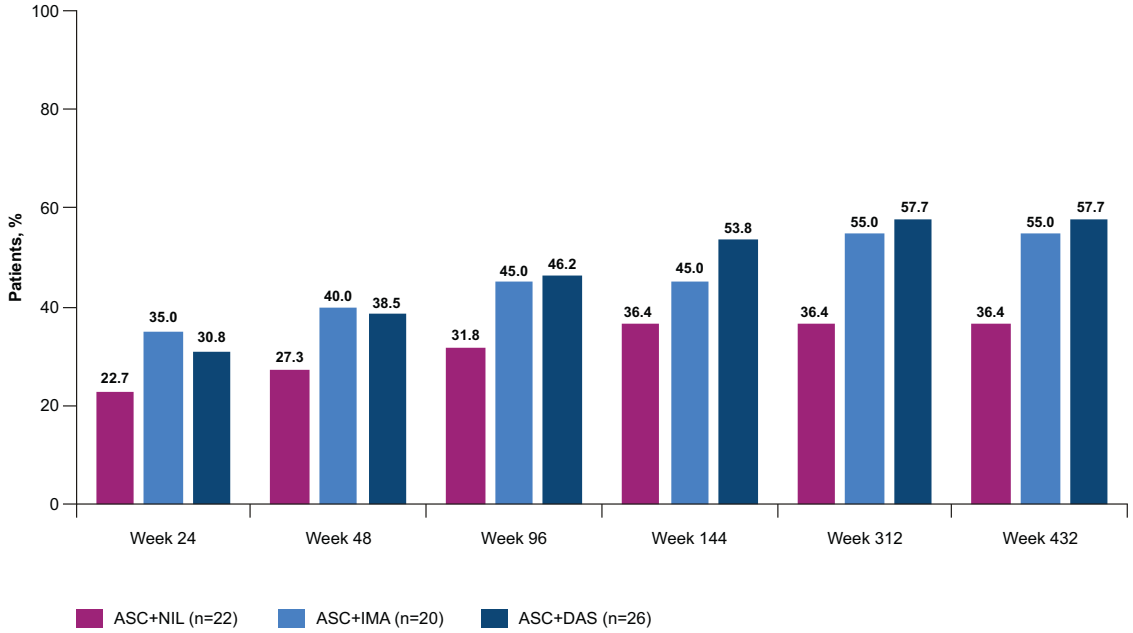

Fig. 3 MMR by time point in patients not in MMR at screening.[a] ASC asciminib, DAS dasatinib, IMA imatinib, MMR major molecular response (*BCR::ABL1*^{IS} ≤ 0.1%), NIL nilotinib. [a]Excludes patients with atypical transcripts and those in MMR at baseline.

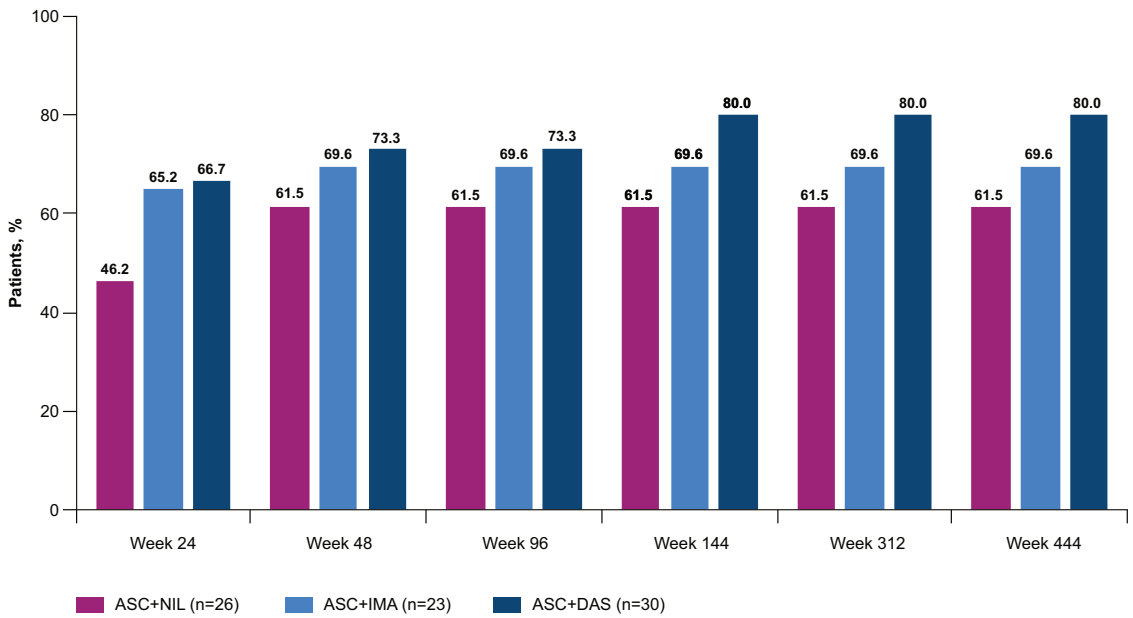

Fig. 4 *BCR::ABL1*^{IS} ≤ 1% by time point.[a] ASC asciminib, DAS dasatinib, IMA imatinib, NIL nilotinib. [a]Excludes patients with atypical/*p190* (*e1a2* or *e1a3*)/unknown transcripts and those with a missing evaluation at screening.

competitive TKIs. Combination strategies with asciminib may reduce the emergence of resistance mutations, but larger studies will need to be conducted.

In this heavily pretreated population, ≈40–66% of patients with combination therapy were receiving combination treatment at EOS; only 9–16% discontinued due to AEs. Treatment discontinuation due to progressive disease occurred in 1 patient each with ASC + NIL and ASC + DAS and in 2 patients with ASC + IMA. Therefore, patients with multiple prior treatments may benefit from the rapid responses afforded by combination therapy. However, the benefits and risks of combination therapy will need to be carefully considered for patients at higher risk of developing AEs [54]. Exploring reduced standard dose (escalating as necessary) of ATP-competitive TKIs in combination with asciminib 80 mg daily could be a safer approach.

Preclinical data suggest that asciminib plus ponatinib combination therapy may be more effective in patients with compound mutations (including T315I) than asciminib with other ATP-competitive TKIs, including nilotinib [33]. Asciminib paired with ponatinib could be a treatment option for patients with the T315I mutation [33], but its effectiveness and safety remain to be determined.

The MTD was reached only with ASC + IMA (asciminib 60 mg QD plus imatinib 400 mg QD). Based on the safety, tolerability, PK, and preliminary efficacy data, the RDE for each arm was as follows: asciminib 40 mg BID plus nilotinib 300 mg BID; asciminib

40 or 60 mg QD plus imatinib 400 mg QD; and asciminib 80 mg QD plus dasatinib 100 mg QD. The ASC + IMA dose combinations are being evaluated as recommended phase 2 doses in ASC4MORE (NCT03578367), a phase 2 study of asciminib add-on to imatinib, versus continued imatinib, versus switch to nilotinib in patients with CML-CP without deep molecular response with ≥1 year of imatinib as their first TKI [55, 56]. At week 96 in ASC4MORE, more patients with asciminib add-on to imatinib achieved *BCR::ABL1*^{IS} ≤ 0.0032% than with continued imatinib or switch to nilotinib [56]. At early time points, more patients with asciminib add-on to imatinib achieved MMR than with continued imatinib or switch to nilotinib [57]. No AOEs were reported with asciminib add-on, which may be safer than switching to nilotinib [56].

Patients with resistance to earlier lines of treatment (with imatinib or second-generation TKIs) may have limited subsequent treatment options, particularly if they have contraindicated mutations, comorbidities, or specific toxicity profiles [1, 18, 45, 58, 59]. These patients may benefit from asciminib plus imatinib or dasatinib to achieve treatment goals (durability of response, deeper molecular response to increase the likelihood of treatment-free remission eligibility, and preventing emergence of resistance) [1, 18, 21, 44, 45]. This population of patients may respond to combination therapy offering stronger efficacy versus monotherapy, thus preventing TKI switching, which may result in treatment-resistant mutations [22, 60]. The results presented in this final analysis of the combination arms of the phase 1 study, supported by ASC4MORE results, provide evidence for asciminib combination therapy as a potential strategy that may help patients with limited therapeutic options achieve their treatment goals.

DATA AVAILABILITY

Novartis is committed to sharing access to patient-level data and supporting clinical documents from eligible studies to qualified external researchers. These requests will be reviewed and approved by an independent review panel based on scientific merit. All data provided will be anonymized to respect the privacy of patients who have participated in the trial consistent with applicable laws and regulations. This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

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AUTHOR CONTRIBUTIONS

JEC, FL, DR, AH, MB, YTG, MCH, TPH, JJWMJ, PIC, HM, KS, DJD, GSO, NP, MC, MH, and MJM contributed to the data acquisition and interpretation, writing, and reviewing the manuscript, and reviewing and approving the final manuscript.

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COMPETING INTERESTS

JEC: Novartis, Pfizer, and Bristol Myers Squibb: grants, consulting fees. FL: Bristol Myers Squibb, Incyte, and Celgene: consultancy, honoraria; Novartis: consultancy, honoraria, and research funding. DR: Novartis, Pfizer, and Incyte: personal fees. AH: Bristol Myers Squibb, Pfizer: institutional research support; Novartis and Incyte: institutional research support, personal honoraria. MB: Bristol Myers Squibb, Celgene, Pfizer, Incyte, and Novartis: consultancy and honoraria; AbbVie: consultancy. YTG: Pfizer, Johnson & Johnson, Amgen, MSD Pharma, EUSA Pharma, Roche, Bristol Myers Squibb, and AbbVie: honoraria. MCH: Novartis, Deciphera, Theseus, and Blueprint Medicines: consultancy; Deciphera: speakers bureau; Jonathan David Foundation, VA Merit Review Grant (I01BX005358), and NCI R21 grant (R21CA263400): partial salary support. Prior to 2019, MCH held an equity interest in MolecularMD. MCH holds multiple patents on the diagnosis and/or treatment of gastrointestinal stromal tumors; 1 patent on treatment has been licensed by Oregon Health & Science University to Novartis. TPH: Novartis, Bristol Myers Squibb, and Enliven: consultancy, research funding. JJWMJ: Novartis and Bristol Myers Squibb: research funding; Incyte: speakers fee; AbbVie, Novartis, Pfizer, and Incyte: honoraria; AbbVie, Alexion, Amgen, Astellas, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Janssen-Cilag, Olympus, Incyte, Sanofi Genzyme, Servier, Jazz, and Takeda: support for Apps for Care and Science nonprofit foundation, of which JJWMJ is president. PIC: Pfizer, Novartis, and Incyte: honoraria. HM: Chugai Pharma, Daiichi Sankyo, Eisai, Genmab, Guardant Health, Kyowa Kirin, Lilly Japan, Meiji Seika Kaisha, Miyarisan Pharmaceutical, Novartis, Otsuka Pharmaceutical, Pfizer, Shionogi, Rakuten Medical, Taiho Pharmaceutical, and Takeda: honoraria; Asahi Kasei Pharma, Chugai Pharma, Dainippon Sumitomo Pharma, Kyowa Kirin, Otsuka Pharmaceutical, Taiho Pharmaceutical, Nihonkayaku, and Teijin Pharma: research funding. KS: Novartis: research funding, honoraria. DJD: AbbVie, Novartis, Blueprint, and GlycoMimetics: grants; AbbVie, Novartis, Blueprint, and GlycoMimetics: research funding; AbbVie, Amgen, Autolus, Blueprint, Forty-Seven, GlycoMimetics, Incyte, Jazz, Kite, Novartis, Pfizer, Servier, and

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