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ORAL ABSTRACTS

632.CHRONIC MYELOID LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Asciminib (ASC) in Combination with Imatinib (IMA), Nilotinib (NIL), or Dasatinib (DAS) May be a Potential Treatment (Tx) Option in Patients (Pts) with Philadelphia Chromosome-Positive Chronic Myeloid Leukemia in Chronic Phase or Accelerated Phase (Ph+ CML-CP/AP): Final Results from the Asciminib Phase 1 Study

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INTRODUCTION ATP-competitive tyrosine kinase inhibitors (TKIs) have extended the life expectancy of pts with CML. However, Tx resistance remains an issue with ATP-competitive TKIs. ASC is the only approved BCR::ABL1 inhibitor that Specifically Targets the ABL Myristoyl Pocket (STAMP), differing from ATP-competitive TKIs, which bind the ATP-binding site. Preclinical studies of ASC combined with ATP-competitive TKIs showed suppression of *BCR::ABL1* mutants, suggesting the potential for enhanced BCR::ABL1 inhibition via combination therapy.
In a phase 1 study (NCT02081378), ASC monotherapy showed durable and deepening responses and favorable tolerability in pts who received ≥2 prior TKIs. Analysis of ASC in combination with IMA, NIL, or DAS suggested favorable efficacy and safety for pts not achieving adequate responses with single ATP-competitive TKIs. We present final results from the ASC + IMA, ASC + NIL, and ASC + DAS arms (end of study [EOS] cutoff: Mar 14, 2023).

METHODS Adults with Ph+ CML-CP/AP without T315I treated with ≥2 prior TKIs and an ECOG performance status ≤2 were allocated to ASC + IMA, ASC + NIL, and ASC + DAS arms. Pts with T315I and Tx with ≥1 TKI were eligible if no other effective therapy existed. Pts were enrolled between July 2015 and May 2021. Pts received IMA 400 mg once daily (QD) + ASC 40 mg twice daily (BID), 40 mg QD, 60 mg QD, or 80 mg QD; NIL 300 mg BID + ASC 20 mg or 40 mg BID; or DAS 100 mg QD + ASC 40 mg BID, 80 mg QD, or 160 mg QD. Maximum tolerated dose (MTD) was estimated by the incidence of dose-limiting toxicities (DLTs) in cycle 1. In case of discontinuation of combination Tx, pts could receive ASC monotherapy. EOS was when all enrolled pts had completed Tx, which was when pts had been followed for ≥64 wks within the study or had discontinued Tx, whichever occurred first.

RESULTS Of 25, 26, and 32 pts in the ASC + IMA, ASC + NIL, and ASC +DAS arms, 25, 25, and 31, respectively, had CML-CP and 0, 1, and 1, respectively, had CML-AP. Only 2 pts in the ASC + DAS arm had the T315I mutation at screening.
At EOS, duration of combination Tx was 2.9, 2.1, and 2.2 y for pts in the ASC + IMA, ASC + NIL, and ASC + DAS arms, respectively. The median duration of exposure (range) in the ASC + IMA, ASC + NIL, and ASC + DAS arms, respectively, was 5.2 (0.5-6.6), 3.0 (0.2-7.4), and 2.8 (0.2-6.3) y for ASC and 1.6 (0.0-6.6), 1.6 (0.0-7.2), and 1.7 (0.2-5.8) y, respectively, for IMA, NIL, and DAS. During the study, 3, 6, and 7 pts discontinued IMA, NIL, and DAS, respectively, and continued receiving ASC.
In the ASC + IMA, ASC + NIL, and ASC + DAS arms, 10 (40.0%), 12 (46.2%), and 21 (65.6%) were receiving Tx until the EOS and continued to receive post-trial ASC: 7, 7, and 10 with combination therapy and 3, 5, and 11 with ASC monotherapy, respectively.
All pts experienced ≥1 all-grade AE with ASC + IMA, ASC + NIL, or ASC + DAS, most frequently nausea (48.0%), abdominal pain and increased lipase (38.5% each), and fatigue (40.6%), respectively; 72.0%, 76.9%, and 65.6% of pts, respectively, reported grade ≥3 AEs; and 20.0%, 11.5%, and 12.5% of pts had AEs leading to Tx discontinuation, respectively (Figure). All grade arterial occlusive events (AOEs) were experienced by 3 (12.0%), 2 (7.7%), and 3 (9.4%) pts in the ASC + IMA, ASC + NIL, and ASC + DAS arms, respectively; 1 pt in each arm reported a grade ≥3 AOE. There were no on-Tx deaths.
DLTs were reported in 6, 1, and 2 pts in the ASC + IMA, ASC + NIL, or ASC + DAS arms, respectively (Table). Pharmacokinetic (PK) assessment showed a moderate increase in exposure of ASC in combination with IMA or NIL; DAS had no effect on the PK of ASC.
By wk 96, major molecular response (MMR) was achieved by 45.0%, 31.8%, and 46.2% of MMR-evaluable pts (excluding pts with atypical transcripts and those in MMR at baseline) in the ASC + IMA, ASC + NIL, and ASC + DAS arms, respectively. Responses were achieved rapidly, with a median time to first MMR of 20.9, 20.1, and 22.1 wks in the ASC + IMA, ASC+ NIL, and ASC + DAS arms, respectively.

CONCLUSIONS ASC in combination with ATP-competitive TKIs, while associated with a higher AE burden vs ASC monotherapy, demonstrated rapid efficacy in the enrolled pt population. The MTD for ASC + IMA was reached at ASC 60 mg QD + IMA 400 mg QD (Table); the MTD for ASC + NIL or DAS was not reached. ASC 40 or 60 mg QD + IMA 400 mg QD, ASC 40 mg BID + NIL 300 mg BID, and ASC 80 mg QD + DAS 100 mg QD were recommended doses for expansion. Combination therapy with ASC is a novel Tx strategy that may help some pts achieve Tx goals.

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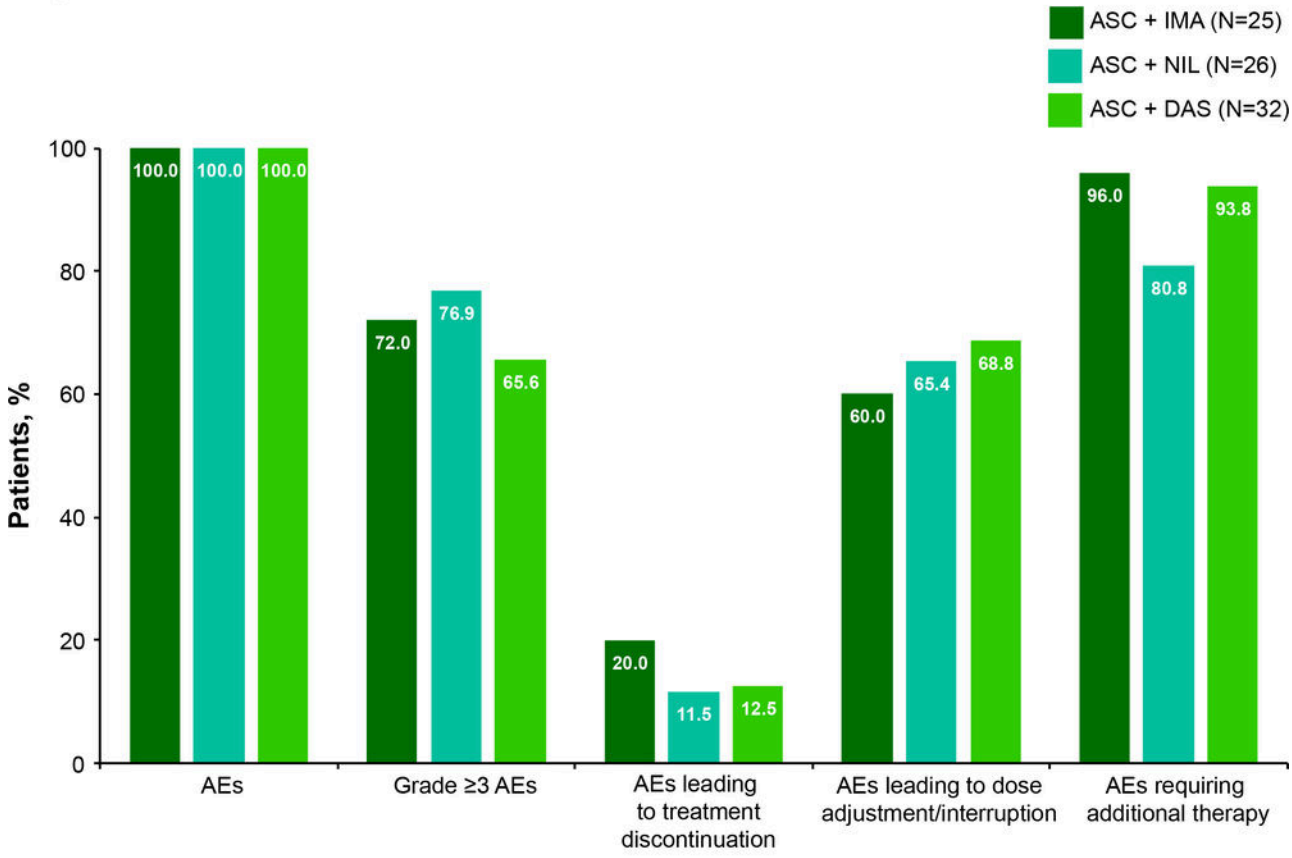
OffLabel Disclosure: Asciminib is a BCR: ABL1 inhibitor that Specifically Targets the ABL Myristoyl Pocket (STAMP). It is approved in over 50 countries for patients with Ph+ CML-CP who have received at least 2 prior TKIs and in some countries for patients with Ph+ CML-CP harboring the T315I mutation

Figure. Overview of AEs



AE, adverse event; ASC, asciminib; DAS, dasatinib; IMA, imatinib; NIL, nilotinib.

Table. Dose-limiting toxicities by PT

Category, n (%)	ASC + IMA N=25	ASC + NIL N=26	ASC + DAS N=32
Pancreatitis	2 (8.0)	0 (0.0)	0 (0.0)
Abdominal pain	1 (4.0)	0 (0.0)	0 (0.0)
Nausea	1 (4.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	0 (0.0)	0 (0.0)	1 (4.5)
Rash maculopapular	0 (0.0)	1 (6.3)	0 (0.0)
Lipase increased	1 (4.0)	0 (0.0)	1 (4.5)
Neutrophil count decreased	1 (4.0)	0 (0.0)	0 (0.0)

ASC, asciminib; DAS, dasatinib; IMA, imatinib; NIL, nilotinib; PT, preferred term.

Figure 1

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