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ORAL ABSTRACTS

632.CHRONIC MYELOID LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

With up to 8 Years of Therapy, Asciminib (ASC) Monotherapy Demonstrated Continued Favorable Efficacy, Safety, and Tolerability in Patients (Pts) with Philadelphia Chromosome-Positive Chronic Myeloid Leukemia in Chronic Phase (Ph+ CML-CP) without the T315I Mutation: Final Results from the Phase 1 X2101 Study

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INTRODUCTION Tyrosine kinase inhibitors (TKIs) have extended the life expectancy for pts with CML, approximating that of the general population, and established BCR::ABL1-targeted therapies as the standard of care for CML. However, multi-TKI resistance and intolerance remain challenges that may lead to treatment (Tx) discontinuation. ASC is the first and only approved BCR::ABL1 inhibitor that Specifically Targets the ABL Myristoyl Pocket (STAMP) with higher selectivity for ABL, reducing off-target effects seen with TKIs. A follow-up analysis (median exposure: 4.2 y) of the phase 1 ASC study in pts with CML-CP without T315I after receiving ≥2 TKIs demonstrated durable efficacy and favorable tolerability, with nearly one-third of pts achieving deep molecular response by cutoff (Jan 6, 2021). Here we present final end-of-study (EOS) efficacy and safety results from the phase 1 ASC study in pts with CML-CP without the T315I mutation (cutoff: Mar 14, 2023).

METHODS This analysis included adults with Ph+ CML-CP without the T315I mutation and an ECOG performance status of 0-2 who had relapsed disease or were refractory to or intolerant of ≥2 prior TKIs. Pts received ASC monotherapy at starting doses of 10-200 mg twice daily (BID) or 80-200 mg once daily (QD). The study started with dose escalation to estimate the maximum tolerated dose (MTD), followed by expansion to establish safety and tolerability of ASC. Dose adjustments were allowed if pts did not tolerate the dosing schedule. The EOS was declared when all pts completed ≥64 wks within the study or discontinued Tx; pts continuing to receive ASC at the EOS were provided continued access to ASC.

RESULTS A total of 115 pts were enrolled between Apr 2014 and Mar 2023. Across all starting doses, the median exposure duration was 5.9 y, with a maximum exposure of 8.4 y; 112 pts (97.4%) had received ≥2 prior TKIs and 82 (71.3%) had received ≥3 prior TKIs. By data cutoff, 70 pts (60.9%) who completed the study on ASC were provided continued access to ASC. Among 45 pts who ended Tx early, 15 (13.0%) and 8 (7.0%) ended due to adverse events (AEs) and disease progression, respectively. Efficacy of ASC at EOS was sustained and consistent with previous reports, with the majority of pts (65.1%) achieving major molecular response (MMR) by the cutoff. While most responses were observed by wk 48, cumulative MMR rates continued to increase up to wk 144 (Figure 1). The median time to MMR (range) was 58.3 (2-360) wks among pts who achieved MMR but were not in MMR at screening. Among the 56 pts who achieved MMR, 50 maintained or improved the response up to data cutoff. At wks 24, 48, and 96, respectively, 18.9%, 17.9%, and 23.6% of pts achieved MR ^{4} and 13.2%, 15.1%, and 18.9% achieved MR $^{4.5}$.

Safety and tolerability of ASC improved with longer durations of exposure. The most frequent all-grade AEs included arthralgia (40.9%), increased lipase (39.1%), fatigue (38.3%), and headache (38.3%), and only 13.0% of pts experienced AEs leading to Tx discontinuation. Even with longer durations of Tx, AEs were less likely to occur after the first year on ASC (Figure 2). The safety and tolerability of ASC remained consistent with prior analyses; there were no new or worsening safety issues compared with those already known for ASC and no new on-Tx deaths.

The MTD of ASC was not reached. Based on safety, tolerability, efficacy, and pharmacokinetic data, ASC 40 mg BID was selected as the recommended dose for expansion in adults with CML-CP without the T315I mutation.

CONCLUSIONS In this final analysis of the phase 1 ASC trial in pts with CML-CP without the T315I mutation, ASC continued to show favorable efficacy and sustained safety and tolerability over a median exposure duration of 5.9 y, with a maximum exposure of 8.4 y. Pts achieved high rates of MMR with nearly one-fourth of pts achieving deep molecular responses at wk 96, demonstrating durable efficacy of ASC over time. Even with longer exposures, the risk of AEs did not increase and there were no new or worsening safety issues. With ASC, most AEs occurred early, and no new late-emerging safety issues were seen, supporting ASC as a safe and tolerable long-term Tx, highly clinically relevant in the management of resistant/intolerant CML-CP. Based on results from this and the ASCEMBL study, 40 mg BID and 80 mg QD have since been approved for use in this pt population.

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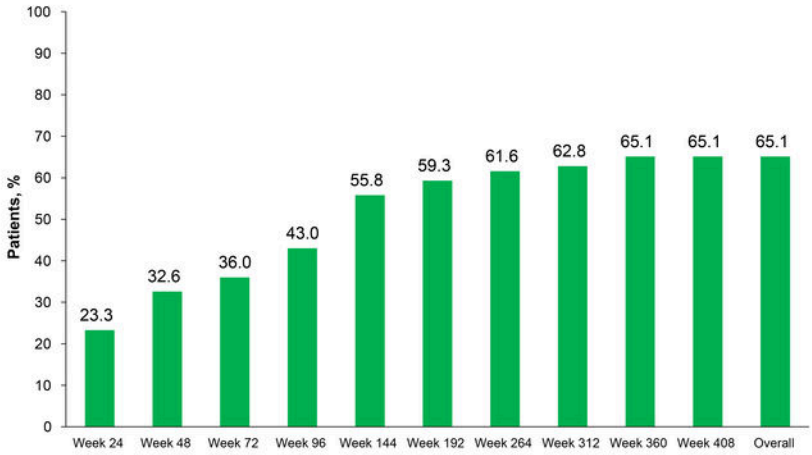
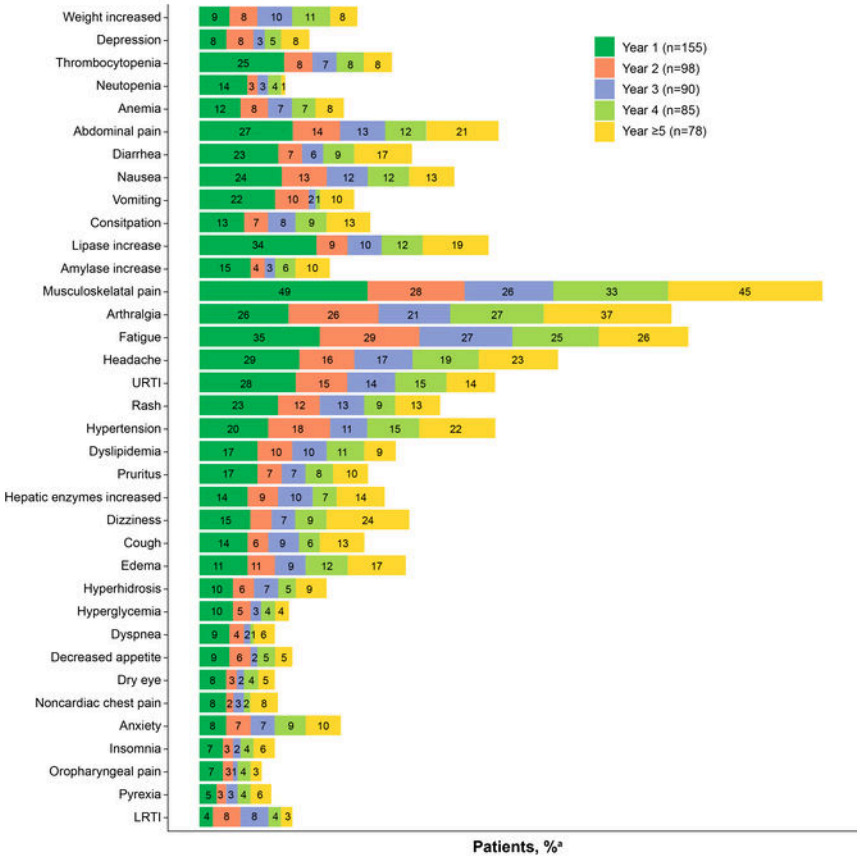
Figure 1. Cumulative MMR rate in patients not in MMR at screening (n=86)[a]



MMR, major molecular response (*BCR::ABL1*[IS] ≤0.1%).
[a] Excludes patients in MMR or who had atypical/unknown transcripts at screening.

Figure 2. Prevalence of AEs over time



LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection.
[a] Patients with multiple occurrences of an event within the same time interval were counted only once in that time interval.

Figure 1

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