Poster CML-1050

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ASC4FIRST Week 144 Analysis: Continued Superior Efficacy and Favorable Safety of Asciminib vs Investigator-Selected Tyrosine Kinase Inhibitors in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase

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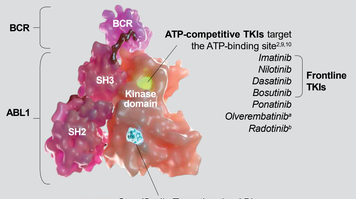
Introduction

- Asciminib is a *BCR::ABL1* inhibitor that works by Specifically Targeting the ABL Myristoyl Pocket (STAMP) and has demonstrated efficacy and safety in both newly diagnosed and previously treated patients with Ph+ CML-CP, including those with the T315I mutation[1-7] **(Figure 1)**
- Asciminib is approved for newly diagnosed Ph+ CML-CP in 64 countries across the globe[8]
- In the ASC4FIRST primary (week 48) and key secondary (week 96) analyses, asciminib demonstrated consistently superior efficacy and improved safety and tolerability compared with all IS-TKIs in newly diagnosed CML-CP[3,4]
  - The early molecular response rate at week 12 was higher with asciminib vs all IS-TKIs (89.6% vs 70.1%), asciminib vs IS-TKIs within the imatinib stratum (88.1% vs 59.8%), and asciminib vs IS-TKIs within the 2G TKI stratum (91.0% vs 80.4%)[3]
  - The MMR rate at week 96 remained superior with asciminib vs IS-TKIs within the imatinib stratum (76.2% vs 47.1%; adjusted 1-sided *P*<.001) and higher with asciminib vs IS-TKIs within the 2G TKI stratum (72.0% vs 56.9%; unadjusted 1-sided *P*<.05; the study was not designed to formally confirm statistical significance for this endpoint)[4]
- Here we report the ASC4FIRST week 144 analysis after a longer median follow-up of ≈3.1 years

Figure 1. Asciminib: Intentionally Designed to Improve Efficacy and Reduce Off-Target Effects vs Current ATP-Competitive TKIs[1,2]



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[a]Approved in China. [b]Approved in South Korea.

Methods

- ASC4FIRST is a phase 3, randomized, multicenter, open-label trial in adults with newly diagnosed Ph+ CML-CP randomly assigned 1:1 to receive asciminib 80 mg qd or an IS-TKI at standard label doses (imatinib 400 mg qd, nilotinib 300 mg bid, dasatinib 100 mg qd, or bosutinib 400 mg qd)[3,4] **(Figure 2)**
- Patients were stratified according to the prerandomization-selected TKI (IMA or 2G TKI) and ELTS risk category[3,4]
- The primary objectives of the trial were to compare the efficacy of asciminib with that of all IS-TKIs and with that of imatinib at week 48, and have been previously reported[3]
- The key secondary objectives of the trial were to compare the efficacy of asciminib with that of all IS-TKIs and with that of imatinib at week 96, and have been previously reported[4]

Figure 2. Study Design[3]

Selected secondary end points for:	**Efficacy**	• MMR at week 144 with asciminib vs all investigator-selected TKIs • MMR at week 144 with asciminib vs investigator-selected TKIs in the imatinib stratum • MMR at week 144 with asciminib vs investigator-selected TKIs in the 2G TKI stratum • MR[4] and MR[4.5] at and by data collection timepoints
	Safety	• Type, frequency, and severity of AEs, and other safety data

Permission granted by Massachusetts Medical Society.[3]
[a]Either imatinib, bosutinib, dasatinib, or nilotinib is allowed for up to 2 weeks prior to randomization. Treatment with other TKIs prior to randomization is not permitted.

Results

- At the data cutoff, more patients remained on treatment with asciminib than with imatinib or 2G TKIs **(Table 1)**

Table 1. Patient Disposition

	Asciminib			IS-TKIs		
	ASC (n = 201)	ASC^{IMA} (n = 101)	ASC^{2G} (n = 100)	All IS-TKIs (n = 204)	IS-TKI^{IMA} (n = 102)	IS-TKI^{2G} (n = 102)
Duration of follow-up, median, months	38.1	36.2	39.2	37.4	35.3	38.5
Treatment ongoing, %[a,b]	78.6	81.2	76.0	55.9	50.0	61.8
Discontinued from treatment, %	20.9	17.8	24.0	42.6	48.0	37.3
Unsatisfactory therapeutic effect	10.4	7.9	13.0	23.0	30.4	15.7
Treatment failure per ELN	5.0	5.9	4.0	13.7	18.6	8.8
Confirmed loss of MMR	2.5	2.0	3.0	2.5	2.9	2.0
Other[c]	3.0	0.0	6.0	6.9	8.8	4.9
Adverse event	7.5	6.9	8.0	13.2	12.7	13.7
Progressive disease	1.0	2.0	0.0	2.0	2.9	1.0
Physician decision	1.0	0.0	2.0	0.5	0.0	1.0
Protocol deviation	0.5	1.0	0.0	1.0	1.0	1.0
Patient decision	0.5	0.0	1.0	2.5	1.0	3.9
Pregnancy	0.0	0.0	0.0	0.5	0.0	1.0

[a]At data cutoff: September 29, 2025. [b]A patient stratified to imatinib as prerandomization selection of TKI received nilotinib as actual treatment. Hence, this patient is considered in the imatinib stratum for efficacy analysis and in the 2G TKI stratum for safety analysis. [c]Includes "Patient had not reached optimal response," "Treatment warning per ELN," "Patient not in MMR," and "Patient did not achieve MMR."

- The rate of MMR increased over time and remained superior at week 144 with asciminib compared with all IS-TKIs **(Figure 3A)** and with asciminib compared with imatinib in the imatinib stratum **(Figure 3B)**
- In the 2G TKI stratum, the rate of MMR continued to increase over time and remained consistently higher with asciminib compared with 2G TKIs **(Figure 3C)**

Figure 3. MMR Rates Over Time

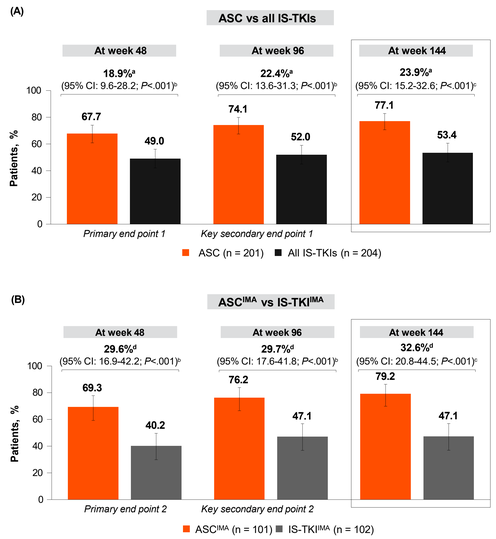
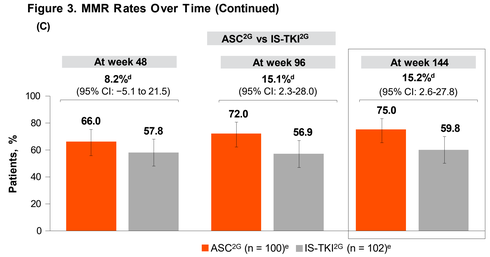


Figure 3. MMR Rates Over Time (Continued)



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Error bars represent 95% CIs.
[a]The common treatment difference and its 95% CI were estimated using the Mantel-Haenszel method after stratifying for prerandomization-selected TKI and baseline ELTS risk groups (IRT data). [b]Adjusted 1-sided *P* value was calculated based on the graphical gatekeeping procedure. The null hypothesis is rejected if the adjusted *P* value is ≤.025. [c]Unadjusted nominal 1-sided *P* value. [d]The common treatment difference and its 95% CI were estimated using the Mantel-Haenszel method after stratifying for baseline ELTS risk groups (IRT data). [e]At week 144, unadjusted nominal *P* value = 0.01.

- Deep molecular response rates were consistently higher with asciminib compared with all IS-TKIs, asciminib compared with imatinib, and asciminib compared with 2G TKIs **(Figures 4A-4C)**

Figure 4. Deep Molecular Response Rates

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- Probability of EFS by week 144 was higher with asciminib compared with all IS-TKIs, including imatinib and 2G TKIs **(Table 2)**
- Long-term outcomes, including OS and PFS were comparable with asciminib compared with all IS-TKIs, including imatinib and 2G TKIs

Table 2. KM Estimates of OS, PFS, and EFS

Patients (95% CI), %	Asciminib			IS-TKIs		
	ASC (n = 201)	ASC^{IMA} (n = 101)	ASC^{2G} (n = 100)	All IS-TKIs (n = 204)	IS-TKI^{IMA} (n = 102)	IS-TKI^{2G} (n = 102)
KM estimated probability of EFS 3 years after randomization[a]	85.0 (79.7-89.5)	83.0 (75.0-89.6)	87.0 (79.6-92.7)	69.2 (62.7-75.4)	63.0 (53.6-72.4)	75.2 (66.5-83.2)
KM estimated probability of OS 3 years after randomization	99.0 (96.0-99.7)	99.0 (92.9-99.9)	99.0 (93.0-99.9)	97.2 (93.5-98.9)	95.8 (89.1-98.4)	99.0 (92.8-99.9)
KM estimated probability of PFS 3 years after randomization[b]	98.0 (94.7-99.2)	97.0 (90.9-99.0)	99.0 (93.0-99.9)	94.8 (90.4-97.2)	92.8 (85.4-96.5)	97.0 (90.9-99.0)

[a]EFS was defined as the time from randomization to the earliest occurrence of treatment failure as defined by ELN criteria, confirmed loss of MMR in 2 consecutive tests at any time on study treatment, discontinuation of study treatment due to AE, progression to accelerated phase or blast crisis (including during the survival follow-up period), or death from any cause (including during the survival follow-up period). [b]PFS was defined as the time from randomization to the earliest occurrence of progression to accelerated phase or blast crisis (including during the survival follow-up period) or death from any cause (including during the survival follow-up period).

- No new postbaseline *BCR::ABL1* mutations emerged with asciminib after the week 96 analysis cutoff, whereas 1 was observed with imatinib (E459K) and 1 with a 2G TKI (F359V) **(Table 3)**

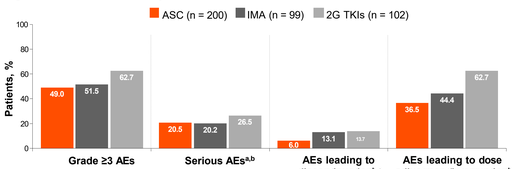
Table 3. Postbaseline Treatment-Emergent *BCR::ABL1* Mutations

By week 48 analysis cutoff[a]			Between weeks 48[a] and 96[b] analysis cutoffs		Between weeks 96[b] and 144 analysis cutoffs	
	Patient	Postbaseline mutations[c]	Patient	Postbaseline mutations[c]	Patient	Postbaseline mutations[c]
Asciminib	1	A337V,[d] V506M[e]	9	A337V[d]		
	2	A337T,[d] V506M[e]	10	A337T[d]		
	3	A433D[d]				
	4	A433D[d]				
	5	L340Q[d]				
	6	A337T,[d] A344P,[e] P465Q,[e] I502N[e]				
	7	A337T,[d] L340Q[d]				
	8	A337T,[e] F497L[e]				
Imatinib	1	L248V,[d] E450Q[e]	3	F317L[d]	5	E459K[d,f]
	2	L248V,[d] E255V,[e] G250E[e]	4	E459K[d]		
Nilotinib	1	Y253H[e]	3	Y253H[d]	4	F359V[d,g]
	2	Y253H[d]				

[a]Data cutoff: November 28, 2023. [b]Data cutoff: October 22, 2024. [c]A patient with multiple mutations is only counted once. Per protocol, *BCR::ABL1* mutations were assessed at baseline, weeks 24, 48, and 96, and at treatment or time of treatment failure, and per investigator's discretion if clinically indicated. Therefore, the number of patients who underwent mutation testing at week 48 was 173 with asciminib and 140 with all IS-TKIs, at week 96 was 164 and 123, respectively, and at week 144 was 158 and 114, respectively. [d]Variant allele frequency was ≥20%. [e]Variant allele frequency was <20%. [f]Patient discontinued treatment due to confirmed loss of MMR and received postprotocol therapy with imatinib. At data cutoff, the patient was in alive and in CP. [g]Patient discontinued treatment due to unsatisfactory therapeutic effect and received postprotocol therapy with dasatinib. At data cutoff, the patient was alive and in CP.

- Safety and tolerability remained favorable with asciminib vs imatinib and 2G TKIs by the week 144 data cutoff **(Figure 5)**
  - AEs leading to discontinuation were generally nonoverlapping with asciminib vs imatinib vs individual 2G TKIs
- No on-treatment deaths were reported during ASC4FIRST
- During the survival follow-up, 8 deaths occurred overall, including 3 in the asciminib arm, 4 in the imatinib arm, and 1 in the 2G TKI arm
  - Since the 96-week data cutoff, 1 death occurred and was in the asciminib arm; it was assessed by the investigator as unrelated to study treatment

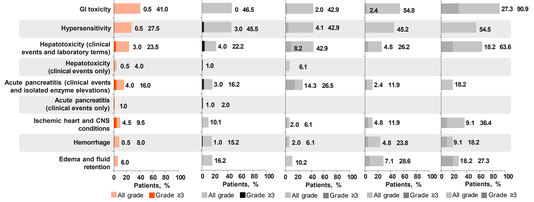
Figure 5. Overview of Safety



[a]A serious AE is defined as any AE (appearance of or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that are fatal or life-threatening. [b]Any grade. [c]Two patients who discontinued after the 30-day safety follow-up are not included and are counted under "AEs leading to dose interruption."

- The proportion of patients with all grade hypertension was 12.5% with asciminib vs 6.5% with all IS-TKIs, 16.0% with ASC^{IMA} vs 5.1% with IS-TKI^{IMA}, and 9.0% with ASC^{2G} vs 7.8% with IS-TKIs^{2G}. The proportion of patients with grade ≥3 hypertension was 6.0% with asciminib vs 3.5% with all IS-TKIs, 9.0% with ASC^{IMA} vs 2.0% with IS-TKI^{IMA}, and 3.0% with ASC^{2G} vs 4.9% with IS-TKIs^{2G}
- AEs of special interest were generally less frequent with asciminib compared with imatinib and individual 2G TKIs **(Figure 6)**

Figure 6. AEs of Special Interest[a]



[a]A patient with multiple severity grades for an AE is only counted under the maximum grade. [b]Myelosuppression includes erythropenia, leukopenia, thrombocytopenia, and cytopenias affecting >1 lineage.

- The rate of arterial occlusive events was low **(Table 4)**
- Of patients who experienced arterial occlusive events, 4 patients with asciminib and 3 with 2G TKIs had ongoing cardiovascular-related comorbidities; 1 patient with asciminib had a prior cardiovascular-related comorbidity

Table 4. Arterial Occlusive Events by the Weeks 48, 96, and 144 Data Cutoffs

	All ASC (n = 200)			IMA (n = 99)			2G TKIs (n = 102)		
Arterial occlusive events by data cutoff	Week 48[a]	Week 96[b]	Week 144	Week 48[a]	Week 96[b]	Week 144	Week 48[a]	Week 96[b]	Week 144
EAIR (per 100 patient-treatment years)	**0.8**	**1.0**	**1.3**	**0.0**	**0.0**	**0.5**	**1.5**	**1.5**	**1.1**
Cumulative number of patients with arterial occlusive events, n (%)[c]	**2.0 (1.0)**	**4.0 (2.0)**	**7.0 (3.5)**	**0.0**	**0.0**	**1.0 (1.0)**	**2.0 (2.0)**	**3.0 (2.9)**	**3.0 (2.9)**
Patients with new arterial occlusive events by the data cutoff, n (%)									
Arteriosclerosis coronary artery	1.0 (0.5)[d]	1.0 (0.5)[e]	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Cerebrovascular accident	1.0 (0.5)	0.0	2.0 (1.0)[f]	0.0	0.0	0.0	0.0	0.0	0.0
Vertebral artery arteriosclerosis	0.0	0.0	0.0	0.0	0.0	0.0	1.0 (1.0)	0.0	0.0
Myocardial infarction	0.0	0.0	1.0 (0.5)[e]	0.0	0.0	0.0	1.0 (1.0)[g]	0.0	0.0
Myocardial ischemia	0.0	0.0	1.0 (0.5)[f]	0.0	0.0	0.0	1.0 (1.0)[g]	0.0	0.0
Angina pectoris	0.0	1.0 (0.5)	1.0 (0.5)[f]	0.0	0.0	0.0	0.0	0.0	0.0
Peripheral arterial occlusive disease	0.0	1.0 (0.5)[d]	1.0 (0.5)[f]	0.0	0.0	0.0	0.0	0.0	0.0
Cerebral infarction	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0 (1.0)	0.0
Ischemic stroke	0.0	0.0	1.0 (0.5)[f]	0.0	0.0	0.0	0.0	0.0	0.0
Cerebral artery stenosis	0.0	0.0	1.0 (0.5)	0.0	0.0	0.0	0.0	0.0	0.0
Amaurosis fugax	0.0	0.0	0.0	0.0	0.0	1.0 (1.0)	0.0	0.0	0.0

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[a]Data cutoff: November 28, 2023. [b]Data cutoff: October 22, 2024. [c]Safety analyses were done in patients who received ≥1 dose of study drug. Patients were analyzed according to the study treatment received. [d]Arteriosclerosis coronary artery and peripheral arterial occlusive disease were reported in the same patient. [e]Arteriosclerosis coronary artery and myocardial infarction were reported in the same patient. [f]Cerebrovascular accident, myocardial ischemia, angina pectoris, peripheral arterial occlusive disease, and ischemic stroke were reported in the same patient. [g]Myocardial infarction and myocardial ischemia were reported in the same patients who received a 2G TKI (dasatinib).

Conclusions

- After ≈3.1 years of follow-up, results from the ASC4FIRST week 144 analysis continue to support the outcomes of the primary and key secondary analyses[3,4]
  - MMR rate increased over time with asciminib compared with the relatively stable rates observed with imatinib and 2G TKIs; at week 144, MMR rates with asciminib remained superior to those with imatinib and numerically higher than those with 2G TKIs
  - Deep molecular response rates increased over time with asciminib and remained higher than those with imatinib and 2G TKIs
  - There were no new postbaseline emergent *BCR::ABL1* mutations with asciminib since the week 96 analysis, whereas 1 was reported with imatinib and 1 with a 2G TKI
  - Asciminib's safety and tolerability profile continued to be more favorable than that of imatinib and 2G TKIs after longer follow-up
- Asciminib offers a continued favorable benefit-risk profile compared with current standard-of-care TKIs (imatinib and 2G TKIs) with sustained DMR rates potentially supporting expansion of future TFR eligibility as long-term follow-up continues

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This study was funded by Novartis Pharmaceuticals Corporation.
Poster presented at the Society of Hematologic Oncology (SOHO) 2026; September 9-12, 2026; Houston, Texas, USA.
Previously presented at:
2026 American Society of Clinical Oncology, Inc. Reused with permission. This abstract was accepted and previously presented at the 2026 ASCO Annual Meeting; May 29-June 2, 2026; Chicago, Illinois, USA.
2026 EHA Congress; June 11-14, 2026; Stockholm, Sweden.

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Abbreviations

2G, second generation; **AE**, adverse event; **ASC**, asciminib; **ATP**, adenosine triphosphate; **bid**, twice daily; **BOS**, bosutinib; **CML**, chronic myeloid leukemia; **CNS**, central nervous system; **CP**, chronic phase; **DAS**, dasatinib; **DMR**, deep molecular response; **EAIR**, exposure-adjusted incidence rate; **EFS**, event-free survival; **ELN**, European LeukemiaNet; **ELTS**, EUTOS long-term survival score; **EUTOS**, European Treatment and Outcome Study; **GI**, gastrointestinal; **IMA**, imatinib; **IRT**, interactive response technology; **IS-TKI**, investigator-selected TKI; **KM**, Kaplan-Meier; **LPFT**, last patient first treatment; **MMR**, major molecular response (*BCR::ABL*^{IS}≤0.1%); **MR**, molecular response; **MR^4**, *BCR::ABL*^{IS} ≤0.01%; **MR$^{4.5}$**, *BCR::ABL*^{IS} ≤0.0032%; **NIL**, nilotinib; **OS**, overall survival; **PFS**, progression-free survival; **Ph+**, Philadelphia-chromosome positive; **qd**, once daily; **R**, randomized; **SH**, Src homology; **TFR**, treatment-free remission; **TKI**, tyrosine kinase inhibitor.

Acknowledgments

The authors thank all study participants and their families, the study investigators, the staff at 113 participating study sites spanning 29 countries, and the independent data monitoring committee.

Medical writing support was provided by Debasri Mukherjee, PhD, CMPP, of Novartis Healthcare Pvt Ltd, Hyderabad, India funded by Novartis Pharmaceuticals Corporation.