Poster CML-387

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ASC4FIRST, a Pivotal Phase 3 Study of Asciminib vs Investigator-Selected Tyrosine Kinase Inhibitors in Newly Diagnosed Patients With Chronic Myeloid Leukemia: Primary Results

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KEY FINDINGS & CONCLUSIONS

- After almost 1.5 years of median follow-up, asciminib demonstrated superior efficacy and favorable safety and tolerability compared with IS-TKIs and imatinib in patients with newly diagnosed CML-CP
- Both **primary objectives in ASC4FIRST were met** with high statistical significance
  1. Asciminib demonstrated superior MMR rates at week 48 vs all IS-TKIs
  2. Asciminib demonstrated superior MMR rates at week 48 vs IS-TKIs within the imatinib stratum
- Asciminib had a markedly favorable safety and tolerability profile, with fewer grade ≥3 AEs and half the rate of AEs leading to treatment discontinuation vs all IS-TKIs
- With these data, asciminib has the potential to become a therapy of choice for patients with newly diagnosed CML-CP
- Longer follow-up will further elucidate the benefits of asciminib as a treatment for newly diagnosed CML

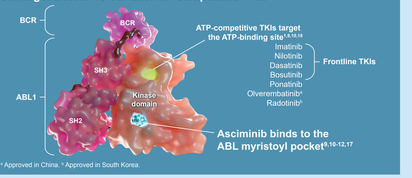
This study is sponsored by Novartis Pharmaceuticals Corporation. For more information, please refer to https://www.clinicaltrials.gov/study/NCT04971226.

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BACKGROUND

- Patients with CML require treatments that optimize safety, tolerability, and efficacy[1]
- Many newly diagnosed patients do not achieve optimal responses with standard TKI therapy,[1-7] and up to approximately 25% require treatment change within 12 months[8]
- Asciminib is a BCR::ABL1 inhibitor that, unlike ATP-competitive TKIs, inhibits kinase activity by binding to the ABL myristoyl pocket[9-12] (**Figure 1**)
- Asciminib demonstrated long-term efficacy and safety in pretreated patients with CML-CP in the phase 3 ASCEMBL and phase 1 X2101 trials and was approved for the treatment of adults with CML-CP who received ≥2 prior TKIs, and patients with CML-CP harboring the T315I mutation[10,11,13-15]
- We report primary results from the phase 3 randomized ASC4FIRST (NCT04971226) trial of asciminib vs investigator-selected (IS) TKIs in patients with newly diagnosed CML-CP[16]

Figure 1. Asciminib: designed to improve efficacy and reduce off-target effects vs current ATP-competitive TKIs[8,10,17]



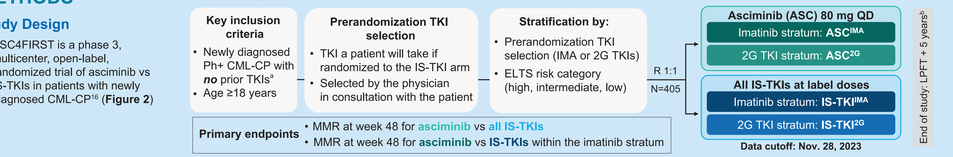
[a] Approved in China. [b] Approved in South Korea.

METHODS

Study Design

- ASC4FIRST is a phase 3, multicenter, open-label, randomized trial of asciminib vs IS-TKIs in patients with newly diagnosed CML-CP[16] (**Figure 2**)

Figure 2. Study Design



[a] Either imatinib, bosutinib, dasatinib, or nilotinib is allowed for up to 2 weeks prior to randomization. Treatment with other TKIs prior to randomization was not permitted. [b] Patients will remain on study for 5 years after the last patient first dose, unless they have discontinued early due to treatment failure, disease progression, pregnancy, intolerance, or investigator or patient decision.

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RESULTS

- Between November 5, 2021, and December 20, 2022, a total of 405 patients were randomized in the ASC4FIRST trial
- A total of 201 patients were randomized to receive asciminib, and 204 patients were randomized to receive IS-TKIs
- Baseline characteristics were well balanced between asciminib and all IS-TKIs and within strata, and were generally representative of the population affected by CML (**Table 1**)
  - More patients in the imatinib stratum vs the 2G TKI stratum were age ≥65 years, with higher cardiovascular disease risk, and tended towards a lower ELTS risk score, reflecting physician preference for imatinib in these subgroups

Table 1. Baseline Characteristics

Variable	Asciminib			IS-TKI		
	All asciminib (n=201)	Imatinib stratum (n=101)	2G TKI stratum (n=100)	All IS-TKI (n=204)	Imatinib stratum (n=102)	2G TKI stratum (n=102)
Median age (range), years	52.0 (18.0-79.0)	56.0 (21.0-79.0)	43.0 (18.0-76.0)	50.5 (19.0-86.0)	54.5 (20.0-86.0)	43.0 (19.0-83.0)
Age group, %						
18 to <65 years	77.1	68.3	86.0	76.0	68.6	83.3
65 to <75 years	17.9	23.8	12.0	16.7	21.6	11.8
≥75 years	5.0	7.9	2.0	7.4	9.8	4.9
Male, %	65.2	61.4	69.0	61.3	63.7	58.8
Framingham CV risk score, %[a]						
Low risk (<10%)	54.2	40.6	68.0	54.9	39.2	70.6
Intermediate risk (10%-20%)	15.9	20.8	11.0	21.6	28.4	14.7
High risk (≥20%)	29.9	38.6	21.0	23.5	32.4	14.7
ELTS, %[b]						
Low	60.7	61.4	60.0	61.3	62.7	59.8
Intermediate	27.9	29.7	26.0	27.9	29.4	26.5
High	11.4	8.9	14.0	10.8	7.8	13.7

[a] Framingham estimated 10-year cardiovascular disease risk categories. [b] Based on randomization data.

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- The median duration of follow-up was 16.3 months with asciminib and 15.7 months with all IS-TKIs
- At the data cutoff, more patients were receiving treatment with asciminib (86.1%) than imatinib (61.8%) and 2G TKIs (75.5%) (**Table 2**)
- Fewer patients had discontinued treatment with asciminib (13.4%) compared with imatinib (36.3%) and 2G TKIs (23.5%)

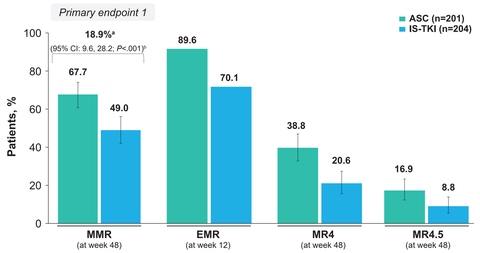
Table 2. Patient Disposition

Randomized patients, %	Asciminib			IS-TKI		
	All asciminib (n=201)	Imatinib stratum (n=101)	2G TKI stratum (n=100)	All IS-TKI (n=204)	Imatinib stratum (n=102)	2G TKI stratum (n=102)
Treatment ongoing[a]	86.1	84.2	88.0	68.6	61.8	75.5
Discontinued from treatment	13.4	14.9	12.0	29.9	36.3	23.5
Unsatisfactory therapeutic effect	6.0	5.9	6.0	15.2	20.6	9.8
Treatment failure per ELN	5.0	5.9	4.0	11.8	15.7	7.8
Confirmed loss of MMR	0.5	0	1.0	0	0	0
Physician decision	0.5	0	1.0	3.4	4.9	2.0
Progressive disease	1.0	2.0	0	2.0	2.9	1.0
Adverse event	5.5	5.9	5.0	10.3	10.8	9.8
Protocol deviation	0.5	1.0	0	1.0	1.0	1.0
Patient decision	0.5	0	1.0	1.0	1.0	1.0
Pregnancy	0	0	0	0.5	0	1.0

[a] Ongoing at the time of the data cutoff date November 28, 2023.

- The MMR rate at week 48 was superior with asciminib (67.7%) vs all IS-TKIs (49.0%), meeting the first primary endpoint (**Figure 3**)
- A higher proportion of patients achieved early and deep molecular responses with asciminib than with all IS-TKIs (**Figure 3**)

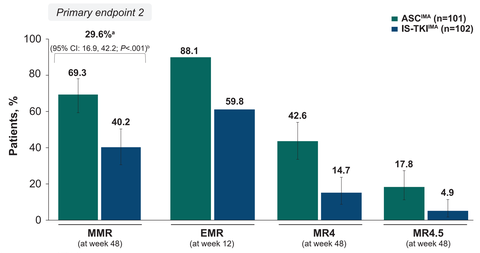
Figure 3. Molecular Response With Asciminib vs All IS-TKIs



Error bars represent 95% CIs.
[a] The common treatment difference and its 95% CI are estimated using the Mantel-Haenszel method after stratifying for (a) pre-randomization selected TKI, and (b) baseline ELTS risk groups (both IRT data). [b] Adjusted 1-sided p-value calculated based on the graphical gatekeeping procedure. The null hypothesis is rejected if the adjusted p-value is ≤0.025.

- The MMR rate at week 48 was superior with ASC^{IMA} (69.3%) vs IS-TKI^{IMA} (40.2%), meeting the second primary endpoint (**Figure 4**)
- A higher proportion of patients achieved early and deep molecular responses with ASC^{IMA} than with IS-TKI^{IMA} (**Figure 4**)

Figure 4. Molecular Response With ASC^{IMA} vs IS-TKI^{IMA}



Error bars represent 95% CIs.
[a] The common treatment difference and its 95% CI are estimated using the Mantel-Haenszel method after stratifying for baseline ELTS risk groups (IRT data). [b] Adjusted 1-sided p-value calculated based on the graphical gatekeeping procedure. The null hypothesis is rejected if the adjusted p-value is ≤0.025.

- The MMR rate at week 48 was numerically higher with ASC^{2G} (66.0%) vs IS-TKI^{2G} (57.8%) (**Figure 5**)
- A higher proportion of patients achieved early and deep molecular responses with ASC^{2G} than IS-TKI^{2G} (**Figure 5**)

Figure 5. Molecular Response With ASC^{2G} vs IS-TKI^{2G}

Error bars represent 95% CIs.
[a] The common treatment difference and its 95% CI are estimated using the Mantel-Haenszel method after stratifying for baseline ELTS risk groups (IRT data).

- Asciminib had higher MMR rates across all demographic and prognostic subgroups vs all IS-TKIs (**Figure 6**)

Figure 6. Subgroup Analyses

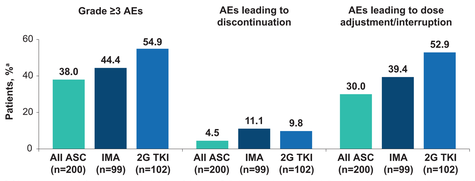
Subgroup	MMR ASC, %	MMR All IS-TKIs, %	Favors all IS-TKIs	Favors ASC	Treatment difference (95% CI)
All patients	67.7	49.0			18.6 (9.2 to 28.1)
ELTS					
Low	72.1	57.6			14.5 (2.8 to 26.3)
Intermediate	64.3	36.8			27.4 (9.7 to 45.2)
High	52.2	31.8			20.4 (−7.9 to 48.6)
Sex					
Female	64.3	54.4			9.9 (−5.8 to 25.6)
Male	69.5	45.6			23.9 (12.1 to 35.6)
Age category					
18 to <65 years	64.5	48.4			16.1 (5.2 to 27.0)
65 to <75 years	75.0	55.9			19.1 (−2.8 to 41.0)
≥75 years	90.0	40.0			50.0 (19.0 to 81.0)

-20 0 20 40 60 80

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- Asciminib demonstrated favorable safety and tolerability vs imatinib and 2G TKIs (**Figure 7**)
- The median dose intensity was 80.0 mg/day with asciminib, 400.0 mg/day with imatinib, 595.1 mg/day with nilotinib, 98.9 mg/day with dasatinib, and 341.8 mg/day with bosutinib
- The most common AEs leading to treatment discontinuation were increased lipase with asciminib (1.5%), diarrhea and lymphopenia with imatinib (2.0% each), and pleural effusion with 2G TKIs (2.0%)

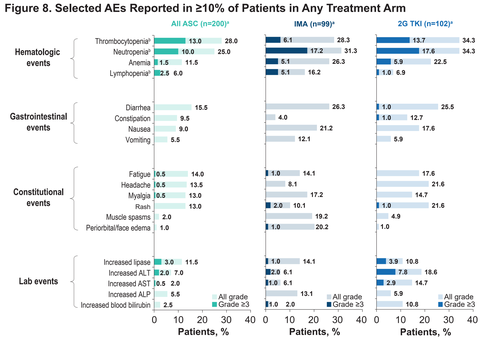
Figure 7. Overview of Safety



[a] Safety analyses consisted of patients who received ≥1 dose of study drug. Patients were analyzed according to the study treatment received. A patient with multiple severity grades for an AE is only counted under the maximum grade.

- Rates of most hematologic and non-hematologic AEs were lower with asciminib than imatinib and 2G TKIs (**Figure 8**)

Figure 8. Selected AEs Reported in ≥10% of Patients in Any Treatment Arm



[a] The safety set comprised all patients who received ≥1 dose of a study drug. The numbers represent counts of patients. Shown are AEs that occurred during treatment or within 30 days after receiving the last dose of study medication. A patient with multiple severity grades for an AE is only counted under the maximum grade. AEs are ordered in groups by system organ class. Rates of leukopenia, COVID-19, and upper respiratory tract infection are not shown. [b] Thrombocytopenia includes thrombocytopenia and decreased platelet count; neutropenia includes neutropenia and decreased neutrophil count; lymphopenia includes lymphopenia and decreased lymphocyte count.

- AOEs were infrequently observed in ASC4FIRST (**Table 3**)
  - As the incidence of AOEs is known to increase with longer exposure, longer follow-up is needed to better assess the long-term risk of AOEs
  - In the phase 3 ASCEMBL trial, AOEs occurred in 5.1% treated with asciminib and 1.3% of patients treated with bosutinib after a median of 2.3 years follow-up, with exposure-adjusted rates for asciminib decreasing with longer follow-up[10,13]

Table 3. Arterial Occlusive Events

Patients, n (%)	All ASC (n=200)[a]		IMA (n=99)[a]		2G TKI (n=102)[a]	
	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3
No. of patients with AOEs	2 (1.0)	1 (0.5)	0	0	2 (2.0)	1 (1.0)
Arteriosclerosis coronary artery	1 (0.5)	0	0	0	0	0
Cerebrovascular accident	1 (0.5)	1 (0.5)	0	0	0	0
Myocardial infarction	0	0	0	0	1 (1.0)[b]	1 (1.0)[b]
Myocardial ischemia	0	0	0	0	1 (1.0)[b]	0
Vertebral artery arteriosclerosis	0	0	0	0	1 (1.0)	0

[a] Safety analyses consisted of patients who received ≥1 dose of study drug. Patients were analyzed according to the study treatment received. [b] Myocardial infarction and myocardial ischemia occurred in the same patient with 2G TKIs.

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Abbreviations

2G, second generation; ABL1, Abelson tyrosine kinase 1; AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AOE, arterial occlusive event; ASC, asciminib; ASP, alkaline phosphatase; AST, asparate aminotransferase; ATP, adenosine triphosphate; BCR, breakpoint cluster region; CML, chronic myeloid leukemia; CP, chronic phase; CV, cardiovascular; ELN, European LeukemiaNet; ELTS, EUTOS long-term survival score; EMR, early molecular response; EUTOS, European Treatment and Outcome Study; IMA, imatinib; IRT, interactive response technology; IS, International Scale, IS-TKI, investigator-selected TKI; LPFT, last person first treatment; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); MR4, *BCR::ABL1*^{IS} ≤0.01%; MR4.5, *BCR::ABL1*^{IS} ≤0.0032%; Ph, Philadelphia chromosome; QD, once daily; R, randomized; TKI, tyrosine kinase inhibitor.