Poster CML-345

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Tolerability of Asciminib vs Investigator-Selected Tyrosine Kinase Inhibitors in the Phase 3 ASC4FIRST Study in Newly Diagnosed Patients With Chronic Myeloid Leukemia in Chronic Phase

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KEY FINDINGS & CONCLUSIONS

- Results of this exploratory post hoc analysis from the ASC4FIRST trial demonstrated the markedly favorable tolerability profile of asciminib vs standard-of-care TKIs
- Patients receiving asciminib required fewer dose adjustments, interruptions, and discontinuations compared to imatinib or 2G TKIs, regardless of strata
- The duration of dose reductions was shorter for patients receiving asciminib compared to imatinib or 2G TKIs
- Grade 1/2 nonhematologic AEs leading to treatment discontinuation were higher in patients receiving imatinib and 2G TKIs, highlighting the impact these events have on a patient's ability to tolerate their CML treatment
- Overall, these results demonstrate the favorable tolerability profile of asciminib and its potential for patients with newly diagnosed CML
- Additional long-term follow-up and quality of life data from ASC4FIRST will further inform these findings

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

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BACKGROUND

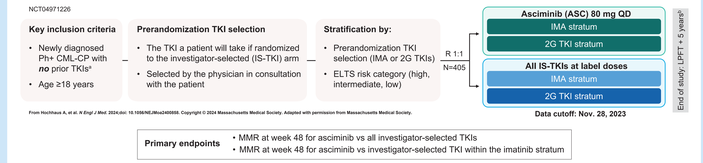
- Although TKIs have changed the course of CML,[1] nearly 25% of patients with newly diagnosed CML switch treatments within the first year, with more pronounced rates in the second year[2]
- Intolerance of ATP-competitive TKIs, which includes persistent, low-grade AEs that disrupt a patient's daily living,[3] contribute to frequent treatment switches[4-6]
- Intolerance may result in intentional nonadherence and may decrease a patient's probability of achieving response to treatment[7,8]
- In the phase 3 ASC4FIRST trial, asciminib demonstrated superior efficacy and favorable safety and tolerability vs investigator-selected TKIs (IS-TKIs) in patients with newly diagnosed CML-CP[9]
- Demographics were similar between arms; within stratum, patients within the imatinib stratum were older and at greater risk for CV disease than patients in the 2G TKI stratum[9]
- Here we present an exploratory post hoc analysis of ASC4FIRST week 48 data to further investigate the tolerability of asciminib compared with IS-TKIs within each strata

METHODS

Study Design

- As previously described, ASC4FIRST is a phase 3, multicenter, open-label randomized trial of asciminib vs IS-TKIs (imatinb and 2G TKIs [dasatinib, nilotinib, or bosutinib]) in patients with newly diagnosed CML-CP (**Figure 1**)[9]
- To compare asciminib to standard-of-care use of TKIs, dose modifications for IS-TKIs were done per local labeling and institutional practice at the investigator's discretion[9]
- Dose modifications for asciminib were recommended or mandated per protocol guidance[9]
- Exploratory tolerability analyses included frequency, duration, grade, and type of AEs, and dose reductions, interruptions, or discontinuations due to AEs
- To account for expected and observed differences in patient demographics between strata, tolerability analyses were conducted within strata to allow for comparisons in similar patient profiles

Figure 1. Study Design



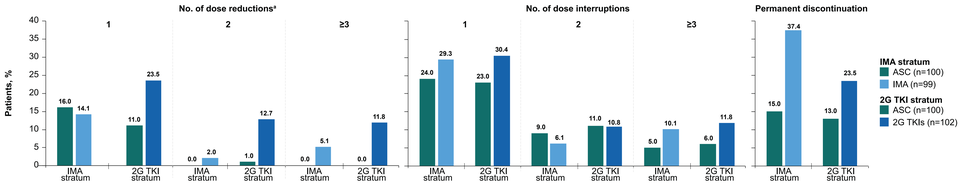
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2G, 2nd generation; AE, adverse event; ASC, asciminib; CML-CP, chronic myeloid leukemia in chronic phase; ELTS, EUTOS long-term survival; EUTOS, European Treatment and Outcome Study; IMA, imatinib; IS-TKI, investigator-selected tyrosine kinase inhibitor; LPFT, last patient first treatment; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); Ph, Philadelphia chromosome; QD, once daily; R, randomized; TKI, tyrosine kinase inhibitor.
*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. †Patients will remain on study for 5 years after the last patient's first dose, unless they have discontinued early due to treatment failure, disease progression, pregnancy, intolerance, or investigator or patient decision.

RESULTS

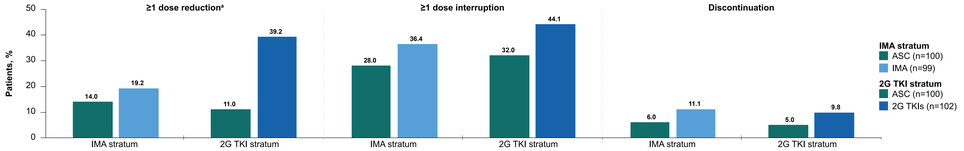
- Within the full analysis set, the median follow-up within the imatinib stratum was 14.3 months for asciminib and 13.7 months for imatinib. Within the 2G TKI stratum, the median follow-up was 17.4 months for asciminib and 17.0 months for 2G TKIs[9]
  - At the time of data cutoff, treatment was ongoing in 84.2% of patients receiving asciminib vs 61.8% receiving imatinib within the imatinib stratum, and in 88.0% receiving asciminib vs 75.5% receiving 2G TKIs within the 2G TKI stratum[9]
  - Of the patients who discontinued treatment, 5.9% of patients on asciminib vs 10.8% of patients on imatinib within the imatinib stratum and 5.0% on asciminib and 9.8% on 2G TKIs within the 2G TKI stratum discontinued due to AEs[9,10]
- Safety analyses were performed according to the actual treatments received; the safety population comprised 401 patients (200 patients receiving asciminib [asciminib in the imatinib stratum, n=100; asciminib in the 2G TKI stratum, n=100]; 99 receiving imatinib, and 102 receiving 2G TKIs)[9]
- Overall and within individual strata, patients receiving asciminib required fewer dose reductions, interruptions, and permanent discontinuations for any reason (**Figure 2**)
- Regardless of strata, patients receiving asciminib required fewer dose interruptions and dose reductions due to AEs compared with patients receiving imatinib or 2G TKIs (**Figure 3**)

Figure 2. Proportion of Patients Requiring Dose Adjustments and Discontinuations for Any Reason



2G, 2nd generation; AE, adverse event; ASC, asciminib; IMA, imatinib; TKI, tyrosine kinase inhibitor.
[a]Patients receiving asciminib were allowed no more than 2 dose reductions for a specific AE. Re-escalation was allowed only once for any specific AE but was permitted for different AEs.

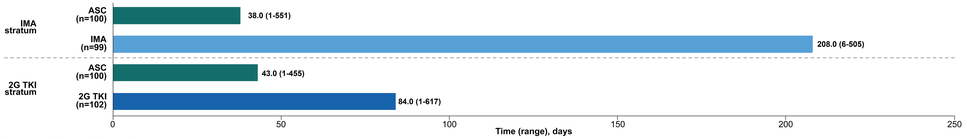
Figure 3. Proportion of Patients Requiring Dose Adjustments and Discontinuations Due to AEs



2G, 2nd generation; AE, adverse event; ASC, asciminib; IMA, imatinib; TKI, tyrosine kinase inhibitor.
[a]Patients receiving asciminib were allowed no more than 2 dose reductions for a specific AE. Re-escalation was allowed only once for any specific AE but was permitted for different AEs.

- Overall and within individual strata, patients receiving asciminib had a lower median duration of dose reductions compared with patients receiving imatinib or 2G TKIs (**Figure 4**)

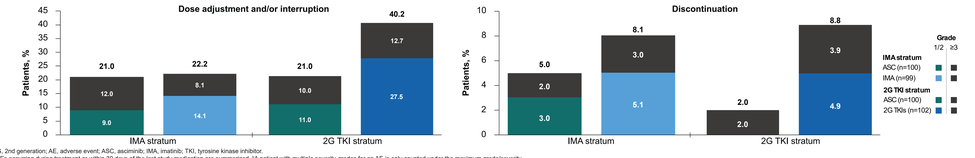
Figure 4. Median Duration of Dose Reductions[a]



2G, 2nd generation; ASC, asciminib; IMA, imatinib; TKI, tyrosine kinase inhibitor.
[a]Due to any cause.

- Overall, rates of dose adjustments, interruptions, and discontinuations were lower in patients receiving asciminib, including those resulting from grade 1/2 nonhematologic AEs (**Figure 5**)
  - Of patients receiving imatinib and 2G TKIs, 14.1% and 27.5%, respectively, experienced grade 1/2 nonhematologic AEs leading to dose adjustment and/or interruption
  - Approximately 5% of patients receiving imatinib and 2G TKIs experienced grade 1/2 nonhematologic AEs leading to treatment discontinuation

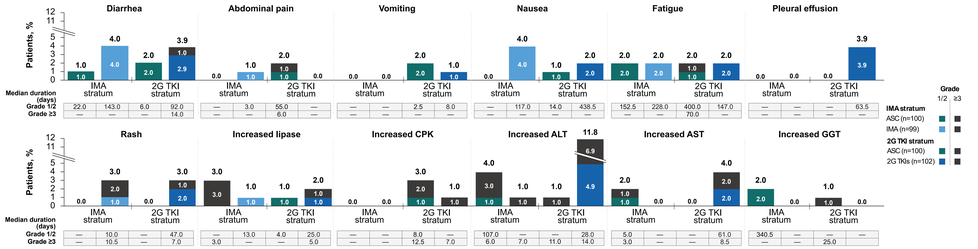
Figure 5. Grade 1/2 and Grade ≥3 Nonhematologic AEs Leading to Dose Adjustment and/or Interruption[a,b] and to Discontinuation[a,b]



2G, 2nd generation; AE, adverse event; ASC, asciminib; IMA, imatinib; TKI, tyrosine kinase inhibitor.
[a]AEs occurring during treatment or within 30 days of the last study medication are summarized. [b]A patient with multiple severity grades for an AE is only counted under the maximum grade/severity.

- Grade 1/2 and grade ≥3 nonhematologic AEs leading to dose adjustment and/or interruption in ≥2% of patients in any group are reported in **Figure 6**

Figure 6. Grade 1/2 and Grade ≥3 Nonhematologic AEs Leading to Dose Adjustment and/or Interruption in ≥2% of Patients in Any Group[a,b,c]



2G, 2nd generation; AE, adverse event; ALT, alanine aminotransferase; ASC, asciminib; AST, aspartate aminotransferase; CPK, creatine phosphokinase; GGT, gamma-glutamyl transferase; IMA, imatinib; TKI, tyrosine kinase inhibitor.
[a]AEs occurring during treatment or within 30 days of the last study medication are summarized. [b]Patients experiencing an AE of varying severity may be counted under both grade 1/2 and grade ≥3. [c]COVID-19 is not shown.

- Overall and within strata, fewer patients receiving asciminib experienced nonhematologic AEs leading to treatment discontinuation compared with imatinib and with 2G TKIs, as shown in **Table 1**

Table 1. Nonhematologic AEs Leading to Treatment Discontinuation[a,b]

IMA stratum	Event, %		All grade	Grade ≥3	2G TKI stratum	Event, %		All grade	Grade ≥3
ASC (n=100)	**Patients with ≥1 event**		**5.0**	**2.0**	ASC (n=100)	**Patients with ≥1 event**		**2.0**	**2.0**
	Nervous system	Cerebrovascular accident	1.0	1.0		Liver	Hepatotoxicity	1.0	1.0
	Psychiatric	Delirium	1.0	0		Nervous system	Neuralgia	1.0	1.0
	Pancreatic[c]	Acute pancreatitis	1.0	1.0					
		Increased lipase	3.0	1.0					
IMA (n=99)	**Patients with ≥1 event**		**8.1**	**3.0**	2G TKIs (n=102)	**Patients with ≥1 event**		**8.8**	**3.9**
	GI/metabolism	Diarrhea	2.0	0.0		Cardiac	Cardiac failure	1.0	1.0
		Nausea	1.0	0.0		GI	Colitis	1.0	1.0
		Decreased appetite	1.0	0.0		Investigations	Electrocardiogram QT prolonged	1.0	0.0
	Constitutional	Face edema	1.0	1.0		Constitutional	Generalized edema	1.0	1.0
		Asthenia	1.0	0.0			Hypersensitivity	1.0	0.0
		Pyrexia	1.0	0.0			Muscular weakness	1.0	1.0
		Myalgia	1.0	0.0		Respiratory	Pleural effusion	2.0	1.0
	Pancreatic	Pancreatitis	1.0	0.0		Skin/subcutaneous tissue	Rash	1.0	0.0
	Liver[c]	Hepatotoxicity	1.0	1.0			Rash maculopapular	1.0	0.0
		Increased ALT	1.0	1.0					
		Increased AST	1.0	1.0					
	Neoplasms	Metastatic gastric cancer	1.0	1.0					
		Prostate cancer	1.0	0.0					

2G, 2nd generation; AE, adverse event; ALT, alanine aminotransferase; ASC, asciminib; AST, aspartate aminotransferase; GI, gastrointestinal; IMA, imatinib; TKI, tyrosine kinase inhibitor.
[a]AEs occurring during treatment or within 30 days of the last study medication are summarized. [b]A patient with multiple severity grades for an AE is only counted under the maximum grade/severity. [c]Includes enzyme elevations.

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Abbreviations

2G: 2nd generation; AE, adverse event; ALT, alanine aminotransferase; ASC, asciminib; AST, aspartate aminotransferase; ATP, adenosine triphosphate; CML, chronic myeloid leukemia; CP, chronic phase; CPK, creatine phosphokinase; CV, cardiovascular; ELTS, EUTOS long-term safety; EUTOS, European Treatment and Outcome Study; GGT, gamma-glutamyl transferase; IMA, imatinib; IS-TKI, investigator-selected tyrosine kinase inhibitor; LPFT, last patient first treatment; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); Ph, Philadelphia chromosome; QD, once daily; R, randomized; TKI, tyrosine kinase inhibitor.