CML-423

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ASC4FIRST Trial in Progress: A Phase III Study of Asciminib vs an Investigator-Selected Tyrosine Kinase Inhibitor in Patients With Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase

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CONCLUSIONS

- Asciminib's unique mechanism of action and significantly positive results in 3L CML-CP (ASCEMBL), encourage further evaluation of asciminib in 1L CML vs standard therapy in ASC4FIRST, a phase III study, that is now enrolling
- Asciminib is a potent and specific allosteric inhibitor of BCR::ABL1 that **Specifically Targets the ABL Myristoyl Pocket (STAMP)**
- Asciminib's specificity offers the potential to reduce off-target effects and thus improve safety and tolerability in 1L therapy vs approved TKIs
- In clinical studies, the efficacy and safety of asciminib led to long treatment durations and deeper responses in heavily pretreated patients, indicating the potential benefits of asciminib in 1L
- Asciminib, through STAMP, has the potential to transform 1L standard of care for newly diagnosed patients with CML-CP

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For more information, please refer to https://clinicaltrials.gov/ct2/show/NCT04971226.

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INTRODUCTION

- Patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) may be treated with 1 of 4 tyrosine kinase inhibitors (TKIs) approved for first-line (1L) use: the first-generation (1G) TKI imatinib or one of the second-generation (2G) TKIs, bosutinib, dasatinib, and nilotinib[1-4]
- The goals for patients starting 1L therapy are to achieve cytogenetic and molecular responses, minimize treatment toxicity, maintain quality of life, prevent disease progression, prolong survival, and have the opportunity to achieve treatment-free remission[5]
- However, many patients do not achieve long-term disease control[6]
  - **>50%** develop resistance to or intolerance of imatinib
  - **30%** to **40%** of patients treated with a 2G TKI in 1L need to change therapy within 5 years
- Only ≈**30%** to **55%** of patients treated with TKIs in 1L achieve MR[4.5] (*BCR::ABL1*^{IS} ≤0.0032%), a measure of deep molecular response (**Table 1**)[1-4,7-10]
- While 2G TKIs have higher major molecular response (MMR) rates compared with imatinib (**Table 2**), they are associated with more adverse events (AEs), which can include arterio-occlusive events[5-10]
  - Many AEs associated with either imatinib or 2G TKIs have been linked to their lack of specificity, which leads to off-target effects[11-13]
  - Off-target effects of ATP-binding TKIs may lead to intolerance and treatment switch, which may increase the burden of AEs and longer-term health issues, including the accumulation of resistance mutations[5,6]
  - AEs impacting quality of life can also lead to non-compliance and loss of disease control[5,6]
- Disease control for most patients with CML-CP potentially requires lifelong treatment; therefore, more effective and safer treatment options are needed[14]
  - Poor disease control can lead to progression to advanced-phase CML
- Here we present the ongoing phase III **ASC4FIRST trial** evaluating asciminib monotherapy vs available 1G and 2G TKIs in **1L CML-CP**

Table 1. Deep Molecular Response With TKIs in 1L CML-CP

		Percentage with MR[4.5] (*BCR::ABL1*^{IS} ≤0.0032%)				
TKIs		**1 Year**	**2 Years**	**3 Years**	**4 Years**	**5 Years**
1G	Imatinib 400 mg QD[1,7,8]	1-3	8-9	13-15	23	31-33
	Bosutinib 400 mg QD[7,8,10]	8	13	NA	NA	47
2G	Dasatinib 100 mg QD[7,8]	5	19	24	34	42
	Nilotinib 300 mg BID[4,7]	11	25	32	40	54

Table 2. 2G TKIs Have Improved MMR Rates Compared With Imatinib in 1L CML-CP

		MMR by 12 months, %		MMR by 24 months, %	
Trial name	**2G TKI**	**1G TKI: imatinib**	**2G TKI**	**1G TKI: imatinib**	**2G TKI**
BFORE	Bosutinib[9]	36	47	51	61
DASISION	Dasatinib[8]	28	46	46	64
ENESTnd	Nilotinib[7]	27	55	44	71

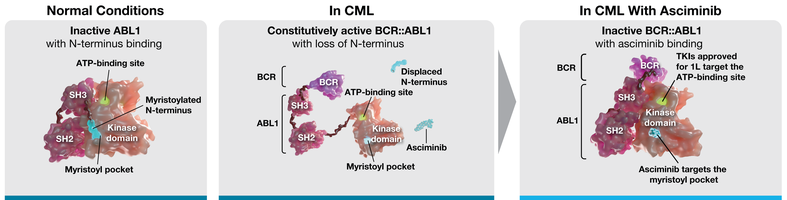
ASCIMINIB OVERVIEW

Asciminib was first **approved by the US Food and Drug Administration** for the treatment of adults with Philadelphia chromosome–positive (Ph+) CML-CP previously treated with ≥2 TKIs and in those with the T315I mutation[15]

Novel Mechanism of Action

- Asciminib is a potent allosteric inhibitor of BCR::ABL1 that works by Specifically Targeting the ABL Myristoyl Pocket (STAMP)[16-18] (**Figure 1**)
  - The specificity of asciminib is intended to avoid off-target effects from inhibition of other kinases, potentially leading to reduced toxicity

Figure 1. Asciminib Specifically Targets the ABL Myristoyl Pocket (STAMP)



Native ABL1 is inhibited by the interaction of its N-terminus and the myristoyl pocket, which helps regulate and control cell proliferation in the bone marrow[19,20,50]

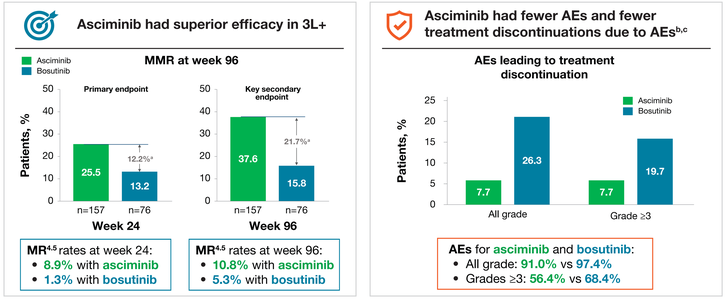
In the BCR::ABL1 fusion protein, the ABL1 N-terminal region is replaced with BCR, and this loss results in a constitutively open/active conformation, resulting in uncontrolled proliferation of immature abnormal blood cells[16,18]

Unlike ATP-competitive TKIs, by Specifically Targeting the ABL Myristoyl Pocket (STAMP), asciminib restores inhibition of BCR::ABL1, preventing unregulated cell proliferation[18]

Asciminib Efficacy and Safety in 3L+

- In the phase III ASCEMBL study, asciminib demonstrated superior efficacy and safety in adult patients with CML-CP treated with ≥2 prior TKIs (**Figure 2**)[21-23]

Figure 2. Efficacy and Safety Results From the Primary Analysis of the Phase III ASCEMBL Study[22,23]



MR[4.5] rates at week 24:
- 8.9% with **asciminib**
- 1.3% with **bosutinib**

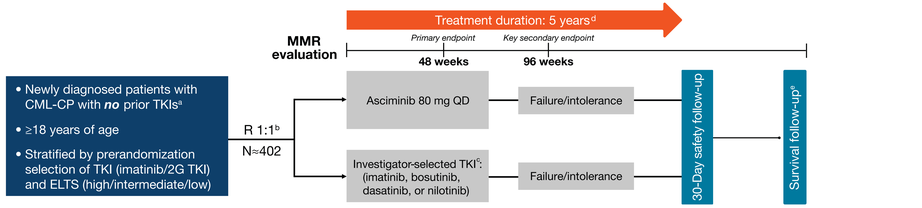
MR[4.5] rates at week 96:
- 10.8% with **asciminib**
- 5.3% with **bosutinib**

AEs for **asciminib** and **bosutinib**:
- All grade: **91.0%** vs **97.4%**
- Grades ≥3: **56.4%** vs **68.4%**

[a] The treatment difference after adjusting for baseline MCyR status was 12.24% (95% CI, 2.19%-22.30%; 2-sided *P*=.029) at week 24, 16.09% (95% CI, 5.69%-26.49%; 2-sided *P*=.007) at week 48, and 21.74% (95% CI, 10.53%-32.95%; 2-sided *P*=.001) at week 96. [b] Grade 1/2 AEs leading to discontinuation with bosutinib (n=5) included ALT/AST level increased, blood creatinine level increased, diarrhea, drug eruption, and pleural effusion. [c] Median duration of exposure: 23.7 months (range, 0.0-46.2 months) for asciminib and 7.0 months (range, 0.2-43.3 months) for bosutinib.

STUDY DESIGN AND METHODS

Figure 3. Study Design of ASC4FIRST: Phase III Trial of 1L Asciminib vs Investigator-Selected TKI in Newly Diagnosed Patients With CML-CP



[a] Either imatinib, bosutinib, dasatinib, or nilotinib ≤2 weeks is allowed. No treatment with other TKIs prior to randomization is permitted. [b] Patients will be randomized so that 50% of patients with imatinib as the prerandomization selected TKI will receive imatinib and 50% will receive asciminib; 50% of patients with a 2G TKI as the prerandomization selected TKI will be randomized to receive the 2G TKI and 50% will receive asciminib. [c] At the approved dose. [d] 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, intolerance, or investigator or patient decision. [e] Patients who discontinue early will continue to be followed up for survival and disease progression until the end of the study.

- ASC4FIRST is a multicenter, open-label, randomized, phase III, 1L study in adult patients with newly diagnosed Ph+ CML-CP
- Patients are randomized to receive asciminib 80 mg QD or an investigator-selected TKI at the approved dose (**Figure 3**)
- The goal of this study is to compare the efficacy of asciminib in 1L CML-CP therapy with all TKIs that are currently approved for this indication
- The study endpoints are summarized in **Table 3**
- The key eligibility criteria are shown in **Table 4**

Table 3. Study Endpoints

Primary endpoints[a]
- Multiple primary endpoints are:
  - MMR at week 48 with asciminib vs investigator-selected TKI
  - MMR at week 48 with asciminib vs imatinib within the stratum of patients with imatinib as the prerandomization investigator-selected TKI

Secondary endpoints
- Key secondary endpoint is MMR at week 96
- Safety endpoint is the time to discontinuation of study treatment due to AEs
- Other secondary endpoints include:
  - CHR, *BCR::ABL1*^{IS} ≤1%, MMR, MR[4], and MR[4.5] at and by scheduled time points
  - TTF, FFS, EFS, PFS, and OS
  - Patient-reported outcomes
  - PK measures
  - Time to first and duration of MMR, MR[4], and MR[4.5]
  - CCyR by weeks 48 and 96
  - Type, frequency, and severity of AEs

[a] The study will be positive if either of these endpoints are met.

Table 4. Key Eligibility Criteria

Key inclusion criteria	Key exclusion criteria
Adults (≥18 years of age) with CML-CP[a]	Previous treatment of CML with any other anticancer agents, including chemotherapy and/or biologic agents or prior stem cell transplant[a] – Treatment with imatinib, bosutinib, dasatinib, or nilotinib for ≤2 weeks is allowed[d]
CML-CP within 3 months of diagnosis that meets ELN 2020 criteria[a]	Cardiovascular impairment or cardiac repolarization abnormality
ECOG performance status of 0 or 1	Cytopathologically confirmed CNS infiltration
Evidence of typical *BCR::ABL1* transcript[b] at the time of screening quantified by RQ-PCR	Severe and/or uncontrolled concurrent medical disease that in the opinion of the investigator could cause unacceptable safety risks or compromise compliance with the protocol
Acceptable laboratory values at screening, electrolytes within normal limits, and adequate end-organ function	History of acute pancreatitis within 1 year of study entry, history of chronic pancreatitis, or history of chronic liver disease leading to severe hepatic impairment, or ongoing acute liver disease
No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly	

[a] Cytogenetic confirmation of Ph+ metaphases. [b] *BCR::ABL1* e14a2 and/or e13a2 transcripts. [c] Previous treatment with hydroxyurea and/or anagrelide is allowed. [d] No other treatment with TKIs prior to study entry is permitted.

CURRENT STATUS

- ASC4FIRST is currently recruiting and will enroll approximately 402 patients
- 134 study sites in the 29 countries shown in **Table 5** are participating
- As of September 8, 2022, 282 patients were randomized and receiving treatment

Table 5. List of Participating Countries

Countries (29)			
France	Austria	Denmark	South Korea
Italy	Norway	Sweden	Singapore
Germany	Switzerland	Portugal	India
Spain	Slovakia	Japan	Malaysia
Russia	Belgium	United States	Taiwan
United Kingdom	Bulgaria	Canada	
Czechia	Finland	China	
Israel	Hungary	Australia	

Abbreviations

1G, first generation; **1L**, first line; **2G**, second generation; **3L**, third line; **ABL1**, Abelson tyrosine kinase 1; **AE**, adverse event; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **ATP**, adenosine triphosphate; **BCR**, breakpoint cluster region; **BFORE**, Bosutinib Trial in First Line Chronic Myelogenous Leukemia Treatment; **BID**, twice daily; **CCyR**, complete cytogenetic response; **CHR**, complete hematologic response; **CML-CP**, chronic myeloid leukemia in chronic phase; **CNS**, central nervous system; **DASISION**, Dasatinib Versus Imatinib Study in Treatment-Naive Chronic Myeloid Leukemia Patients; **ECOG**, Eastern Cooperative Oncology Group; **EFS**, event-free survival; **ELN**, European LeukemiaNet; **ELTS**, ELTS2.0 long-term survival score; **ENESTnd**, Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Newly Diagnosed Patients; **EUTOS**, European Treatment and Outcome Study; **FFS**, failure-free survival; **IS**, International Scale; **MCyR**, major cytogenetic response; **MMR**, major molecular response (BCR::ABL1^{IS} ≤0.1%); **MR[4]**, 4-log red (BCR::ABL1^{IS} ≤0.01%; **MR[4.5]**, (BCR::ABL1^{IS} ≤0.0032%; **NA**, not available; **OS**, overall survival; **PFS**, progression-free survival; **Ph**, Philadelphia chromosome; **PK**, pharmacokinetic; **QD**, once daily; **R**, randomized; **RQ-PCR**, real-time quantitative polymerase chain reaction; **SH**, Src homology; **TKI**, tyrosine kinase inhibitor; **TTF**, time to treatment failure.

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