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Ehab L. Atallah, eatallah@mcw.edu

ASC2ESCALATE: a US, phase 2, single-arm, dose-escalation study of asciminib monotherapy in second-line and first-line treatment of patients with chronic myeloid leukemia in chronic phase

Presenter: Jorge E. Cortes

Ehab L. Atallah,[1] Michael J. Mauro,[2] Koji Sasaki,[3] Moshe Y. Levy,[4] Paul Koller,[5] Daisy Yang,[6] Dramane Laine,[6] John Sabo,[6] Ennan Gu,[7] Jorge E. Cortes[8]

[1]Medical College of Wisconsin, Milwaukee, WI; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]The University of Texas MD Anderson Cancer Center, Houston, TX; [4]Baylor Scott & White Health, Dallas, TX; [5]City of Hope National Medical Center, Duarte, CA; [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [7]Novartis Pharmaceuticals Corporation, Cambridge, MA; [8]Georgia Cancer Center, Augusta, GA

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Conclusions

ASC2ESCALATE is the **first** clinical trial designed to evaluate the safety and efficacy of asciminib monotherapy in **patients with CML-CP** in 2L therapy

ASC2ESCALATE is investigating the safety and efficacy of **asciminib dose escalation** in patients who have not achieved treatment milestone responses at 6 and 12 months in 2L and 1L

Dose escalation of asciminib (the first BCR::ABL1 inhibitor to **S**pecifically **T**arget the **A**BL **M**yristoyl **P**ocket) for patients with CML-CP could provide another treatment option for patients not meeting certain response milestones in 2L and 1L

ASC2ESCALATE is open to enrollment, with an anticipated final enrollment of approximately **92** and **60 to 90 patients** with CML-CP in the 2L and 1L cohorts, respectively, across **90 sites** in the United States

This study is sponsored by Novartis Pharmaceuticals Corporation.

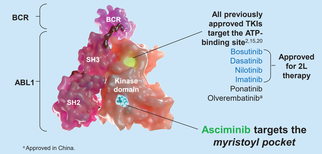
For more information, please refer to **https://clinicaltrials.gov/ct2/show/NCT05384587**

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Background

- ATP-competitive TKIs, such as imatinib and 2G TKIs, are the 1L standard of care for patients with CML-CP, with most patients on TKI therapy demonstrating **normal life expectancy**[1-4]
- However, **resistance and intolerance remain challenges** in 1L therapy, often necessitating a **switch to 2L therapy**, to which **resistance is typically higher**[5,6]
- Approximately 28% to 50% of patients discontinue their 1L therapy by 5 years,[7-10] and 20% to 30% discontinue their 2L therapy due to resistance or disease progression[11-13]
- Asciminib is the first BCR::ABL1 inhibitor **S**pecifically **T**argeting the **A**BL **M**yristoyl **P**ocket (STAMP) (**Figure 1**), allowing asciminib to have activity against most *BCR::ABL1* mutations that are resistant to ATP-competitive TKIs.[14-17] Additionally, asciminib has limited off-target activity[14,17,18]
- Here we present the **phase 2 ASCEMBLY** trial (NCT05384587) evaluating **asciminib** monotherapy with dose escalation in 2L and 1L treatment of **CML-CP**[19]

Figure 1. Asciminib is the first BCR::ABL1 inhibitor to Specifically Target the ABL Myristoyl Pocket (STAMP)[15]

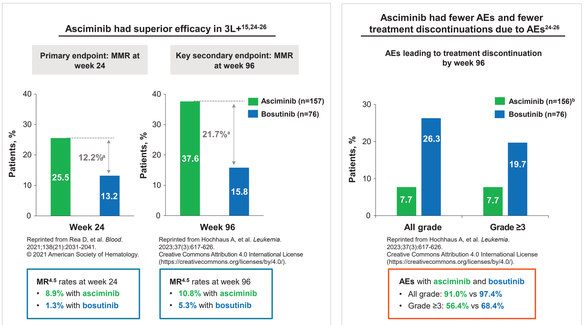


[a]Approved in China.

Asciminib overview

- Asciminib was first **approved** in the **United States** at 80 mg QD and 40 mg BID for the treatment of adults with Ph+ CML-CP previously treated with ≥2 TKIs and at 200 mg BID for adults with Ph+ CML-CP with the T315I mutation[21]
- In a large, phase 1, **dose-escalation trial**, asciminib demonstrated superior **efficacy** and **tolerability** across a **broad range of doses**[22]
  - **Longer-term follow-up** demonstrated the **durability** of response achieved with **asciminib**, with more than **two-thirds** of patients **remaining on therapy**[23]
- In the **phase 3 ASCEMBL** study, **asciminib** demonstrated **superior efficacy** and **better safety and tolerability** than bosutinib in adult patients with CML-CP treated with ≥2 prior TKIs (**Figure 2**)[15,24,25]
  - **MMR** (*BCR::ABL1*^{IS} ≤0.1%) rates continued to **increase over time** and **remained higher** with **asciminib** than bosutinib; deep molecular response rates were also higher with asciminib than bosutinib[15,24,25]
  - After longer follow-up, there were **no new or worsening safety findings** with **asciminib**, and its **safety and tolerability** continued to be **better** than those of bosutinib[24-26]

Figure 2. Efficacy and safety results from the phase 3 ASCEMBL study[15,24-26]



[a]The treatment difference after adjusting for baseline major cytogenic response status was 12.24% (95% CI, 2.19%-22.30%; 2-sided *P*=.029) at week 24 and 21.74% (95% CI, 10.53%-32.95%; 2-sided *P*=.001) at week 96.
[b]1 patient developed cytopenia after randomization and was not treated per investigator's decision.

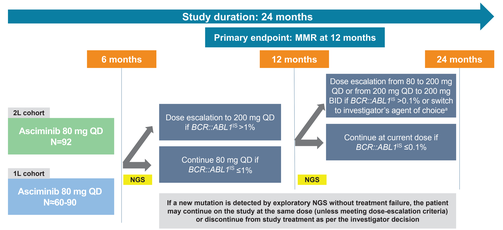
Study rationale

- Although several options are currently available for the treatment of patients who are **newly diagnosed** with CML-CP, some patients exhibit treatment **resistance** or **intolerance** to ATP-competitive TKIs, necessitating a **switch to 2L therapy**[2]
- Many patients **discontinue 1L treatment** due to resistance and intolerance and **switch to 2L therapy**, to which **resistance is typically higher**[5,6]
- The purpose of this study is to evaluate the **efficacy** and **safety** of **asciminib dose escalation** as **2L** and **1L treatment**
- A key question that this study is evaluating is whether patients with CML-CP with ***BCR::ABL1*^{IS} levels of >1%** and **>0.1%** at **6 and 12 months**, respectively, could benefit from asciminib **dose escalation**
- This study aims to provide valuable **practical guidance** for the **use of asciminib** in patients with CML-CP in **2L** and **1L** treatment

Study design and methods

- ASC2ESCALATE is a single-arm, multicenter, phase 2, open-label, **dose-escalation** study of **asciminib** in **2L** and **1L** treatment of **patients with non-T315I CML-CP** (**Figure 3**)
  - The **2L cohort** includes patients treated with **1 prior ATP-competitive TKI discontinued** for **warning response, resistance, or intolerance**
  - The **1L cohort** includes **newly diagnosed** patients and allows ≤**4 weeks of prior treatment with imatinib or a 2G TKI**
  - A **dose escalation** at **6 months** (to 200 mg QD) is allowed for patients not achieving *BCR::ABL1*^{IS} ≤1% and at **12 months** (to 200 mg QD if patients are on 80 mg QD or to 200 mg BID if patients are on 200 mg QD) if patients have not achieved MMR
    - Patients achieving these responses will continue with asciminib at their current dose
- The study goal and endpoints are summarized in **Table 1**
  - All primary and secondary analyses will be repeated for patients in the 1L cohort as secondary objectives of the study
- Key eligibility criteria are shown in **Table 2**

Figure 3. ASC2ESCALATE: a US, phase 2, single-arm, dose-escalation study of asciminib monotherapy in 2L and 1L treatment of patients with CML-CP



[a]Patients switching to investigator's choice will be withdrawn from the study.

Table 1. Study endpoints

The goal of this study is to evaluate the efficacy and safety of asciminib as 2L and 1L therapy in patients with CML-CP
Primary endpoint[a]
Proportion of patients achieving MMR (*BCR::ABL1*^{IS} ≤0.1%) at 12 months in the 2L setting
Secondary endpoints[a]
• Proportion of patients achieving MR$^{4.5}$ at 24 months
• MMR rate at all scheduled data collection time points (3, 6, 18, and 24 months)
• MR^2, MR^4, and MR$^{4.5}$ at all scheduled time points except for MR$^{4.5}$ at 24 months
• MR^2, MMR, MR^4, and MR$^{4.5}$ by scheduled time points (3, 6, 12, 18, and 24 months)
• Time to and duration of MMR
• Time to treatment failure
• Time from first dose of study treatment to earliest occurrence of documented disease progression to CML-AP/BC or date of death from any cause, before cutoff date
• Time from first dose of study treatment to death due to any cause during the study
• Type, frequency, and severity of AEs; changes in laboratory values that fall outside the predetermined ranges; and clinically notable ECG and other safety data (vital signs, physical examination findings)
Exploratory endpoint[b]
• *BCR::ABL1* mutations at baseline, during study treatment, and on confirmed loss of response (per ELN 2020)/end of treatment
• Change in symptom burden and interference from baseline over time according to the MDASI-CML PRO instrument
• Change in health utility from baseline over time according to EQ-5D-5L
• Measurement of healthcare resource utilization with number and percentage of patients hospitalized, total and average number of hospitalizations, reason for hospitalization, and type of hospital facility during 12 and 24 months

[a]All the primary and secondary analyses will be repeated for patients in the 1L cohort as secondary objectives of this study. [b]Exploratory endpoints apply to both the 2L and 1L cohorts.

Table 2. Key eligibility criteria

Both cohorts | 2L cohort | 1L cohort

Key inclusion criteria	Key exclusion criteria
• Adults (≥18 years of age) with CML-CP with no previous CML-AP/BC	• Known presence of the T315I mutation at any time prior to study entry
• ECOG performance status of 0, 1, or 2	• Known second CML-CP after previous progression to CML-AP/BC
• Adequate end-organ function within 14 days before the first dose of asciminib treatment (patients with mild to moderate renal and hepatic impairment are eligible if total bilirubin, AST, ALT, serum lipase, alkaline phosphatase, and creatinine clearance criteria are met)	• Previous treatment with asciminib
	• Previous treatment with an HSCT or plans to undergo allogeneic HSCT
• For patients with CML-CP with warning to 1L TKI, *BCR::ABL1*^{IS} at screening[2]: a. >1%-10% at 6 months after treatment initiation b. >0.1%-1% at 12 months after treatment initiation	• Cardiac or cardiac repolarization abnormality
	• History of acute pancreatitis within 1 year of study entry or medical history of chronic pancreatitis
• For patients with CML-CP with treatment failure or resistance to 1L TKI, *BCR::ABL1*^{IS} at screening[2]: a. >10% if 1L treatment duration between 6 and 12 months b. >1% if 1L treatment duration >12 months c. Loss of MMR >12 months after treatment initiation	• Treatment with strong inducers of CYP3A (for patients receiving asciminib 80 or 200 mg QD) or strong inducers and inhibitors of CYP3A (for patients receiving asciminib 200 mg BID)
	• Pregnant or lactating women, women of child-bearing potential not on highly effective contraception, or sexually active men unwilling to use barrier contraception while taking study treatment and for 7 days after stopping study
• For patients with CML-CP with intolerance of 1L TKI, *BCR::ABL1*^{IS} >0.1% at screening	• Previous treatment with ≥2 ATP-competitive TKIs
• Newly diagnosed patients with CML-CP[a]	• Previous treatment for >4 weeks with 1 ATP-competitive TKI

[a]Previous treatment for ≤4 weeks with 1 ATP-competitive TKI is allowed.

Current status

- ASC2ESCALATE is **open to enrollment** with an anticipated final enrollment of approximately 92 and 60 to 90 participants in the 2L and 1L cohorts, respectively, across approximately 90 sites
- As of July 10, 2023, a total of 6 patients have been enrolled in the 2L cohort
- The study is only recruiting in the **United States**
- The estimated primary analysis date is January 27, 2026, and the estimated study completion date is May 26, 2027

Abbreviations

1L, first line; 2G, second generation; 2L, second line; 3L, third line; ABL1, Abelson tyrosine kinase 1; AE, adverse event; ALT, alanine aminotransferase; AP, accelerated phase; AST, aspartate aminotransferase; ATP, adenosine triphosphate; BC, blast crisis; BID, twice daily; BCR, breakpoint cluster region; CML-CP, chronic myeloid leukemia in chronic phase; CYP3A, cytochrome P450 3A; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; ELN, European LeukemiaNet; MDASI-CML PRO, MD Anderson Symptom Inventory – Chronic Myelogenous Leukemia; HSCT, hematopoietic stem cell transplant; IS, International Scale; MMR, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); MR^2, *BCR::ABL1*^{IS} ≤1%; MR^4, *BCR::ABL1*^{IS} ≤0.01%; MR$^{4.5}$, *BCR::ABL1*^{IS} ≤0.0032%; NGS, next-generation sequencing; Ph, Philadelphia chromosome; PRO, patient-reported outcome; QD, once daily; SH, Src homology; TKI, tyrosine kinase inhibitor.

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