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What Is the Role of Asciminib in Chronic Myeloid Leukemia?

Jorge E. Cortes, MD
Director, Georgia Cancer Center
Cecil F. Whitaker Jr, GRA Eminent Scholar Chair in Cancer
Augusta, Georgia

H&O What is the mechanism of action of asciminib?

JC Asciminib (Scemblix, Novartis) is a tyrosine kinase inhibitor (TKI) that has a unique mechanism of action in comparison with other TKIs. Imatinib, which is a first-generation TKI, and dasatinib, bosutinib (Bosulif, Pfizer), and nilotinib, which are second-generation TKIs, inhibit kinase activity by competitively targeting adenosine triphosphate (ATP). In contrast, asciminib is a BCR::ABL1 inhibitor that works by specifically targeting the ABL myristoyl pocket (STAMP), regulating activity in native ABL. Because asciminib targets a different location than the other inhibitors do, the mutations that develop during treatment and reduce the effectiveness of other TKIs do not affect the activity of asciminib.

H&O Could you describe the approval history of asciminib?

JC The initial phase 1 study that looked at asciminib began in 2014, so we have been using this drug for a little more than 10 years. In that study, we determined a dose that was safe for patients and had activity in patients with chronic-phase chronic myeloid leukemia (CML-CP) overall and in those with a T315I mutation, who typically require a higher dose. The findings led to an expansion cohort of patients with CML-CP who had a T315I mutation and received a higher dose of the agent. It also led to the design of the phase 3 ASCEMBL trial for patients with CML-CP who had received multiple TKIs.[1] In that open-label study, a total of 233 patients with CML-CP who had previously been treated with at least 2 TKIs were randomized in a 2:1 ratio to receive asciminib at 40 mg twice daily or bosutinib at 500 mg once daily. Patients were stratified by major cytogenetic response (MCyR) status at baseline. The study did not include patients with a T315I mutation because bosutinib had been shown not to work in these patients.

After a median follow-up of 14.9 months, the major molecular response (MMR) rate was 25.5% with asciminib and 13.2% with bosutinib, a difference of 12.2 percentage points after adjustment for MCyR at baseline (95% CI, 2.19%-22.30%; 2-sided P=.029). These results led to the 2021 approval of asciminib in previously treated patients with Philadelphia chromosome–positive (Ph+) CML-CP. Asciminib also received a 2021 approval for use in patients who had Ph+ CML-CP with a T315I mutation, on the basis of results of the single-arm CABL001X2101 study.[2]

Asciminib received additional approval in 2024 for patients with newly diagnosed Ph+ CML-CP on the basis of results of the phase 3 ASC4FIRST trial, in which 405 patients with newly diagnosed CML were randomly assigned in a 1:1 ratio to receive either asciminib at 80 mg once daily or an investigator-selected TKI.[3] The MMR rate at week 48 was 67.7% in the asciminib group vs 49.0% in the investigator-selected TKI group (difference, 18.9 percentage points; 95% CI, 9.6%-28.2%; adjusted 2-sided P<.001). Within the imatinib stratum, the MMR rate at week 48 was 69.3% in the asciminib group vs

40.2% in the imatinib group (difference, 29.6 percentage points; 95% CI, 16.9%-42.2%; adjusted 2-sided *P*<.001). Within the second-generation TKI stratum, the MMR rate at week 48 was 66.0% with asciminib vs 57.8% with TKIs (difference, 8.2 percentage points; 95% CI, –5.1% to 21.5%) These results led to a new indication for asciminib for use in all lines of therapy and in patients with or without a T315I mutation.

In 4-year results from the ASCEMBL trial, published in mid-2025, asciminib continued to have better efficacy, safety, and tolerability in comparison with bosutinib. At week 156, the MMR rate remained higher with asciminib than with bosutinib, at 33.8% vs 10.5%, respectively. After adjustment for MCyR at baseline, the difference in the MMR rate was 23.2 percentage points (95% CI, 13.14%-33.18%; 2-sided *P*<.001).[4]

> When cost is not the primary concern, asciminib is the superior drug.

H&O In the in ASC4FIRST trial, is asciminib still statistically significantly superior to TKI treatment when imatinib is omitted from the TKI group?

JC The primary endpoints of ASC4FIRST were asciminib vs imatinib and asciminib vs all TKIs together. The study was not powered to show a statistically significant difference between asciminib and second-generation TKIs. We did, however, show a numerical difference between the groups in favor of asciminib of 8 percentage points at 48 weeks and of 15 percentage points at 96 weeks.

H&O What data exist regarding the effect of asciminib vs the effect of bosutinib on progression-free survival (PFS) and overall survival (OS)?

JC We do not yet have PFS and OS data from the ASCEMBL study, although the trends are in favor of asciminib. I expect it will take a long time until we can see a clear difference in survival, in part because the patients in this trial are able to switch to a different TKI if the initial one stops working. In the meantime, the most useful endpoints are the response rate and the rate of transformation to blast-phase CML.

H&O What adverse events (AEs) are seen with asciminib?

JC Asciminib is a relatively clean drug. In the 4-year results from ASCEMBL, asciminib continued to cause fewer grade 3 or higher AEs than bosutinib did, at 59.6% vs 68.4%, respectively, and fewer AEs leading to treatment discontinuation, at 8.3% vs 27.6%, respectively. In ASC4FIRST, grade 3 or higher AEs were less frequent with asciminib than with imatinib or second-generation TKIs, at 38.0% vs 44.4% and 54.9%, respectively. AEs leading to treatment discontinuation also were less frequent with asciminib than with imatinib or second-generation TKIs, at 4.5% vs 11.1% and 9.8%, respectively. We do see hematologic side effects with asciminib, especially thrombocytopenia, so that is an issue we need to manage. We especially see myelosuppression in patients who have more advanced disease and have previously received more therapies.

In terms of nonhematologic toxicity, we tend to see more hypertension with asciminib than with some of the other TKIs, such as imatinib or bosutinib, but this is usually grade 1 or 2. We also see lipase elevation in some patients. This is usually asymptomatic, meaning that the patients do not have clinical pancreatitis, but these patients still require monitoring. In ASC4FIRST, the incidence of lipase elevation with asciminib seems to be similar to that seen with imatinib and slightly lower than that seen with second-generation TKIs.

H&O Why was ASC4FIRST conducted as an open-label trial, and how might this trial design have affected AE reporting?

JC We designed ASC4FIRST as an open-label trial because of the logistics of having TKIs in the control group that had different schedules of administration. Some agents were given with food, and some without food; some were given once a day, and some twice a day. As a result, it was almost impossible to conduct a blinded study and at the same time use all the available TKIs that we wanted to. Could that have affected the reporting of AEs? It certainly had the potential to affect whether patients continued or discontinued a specific agent, so it is possible that this situation had a modest effect on AE reporting.

H&O What is your response to the point of view that imatinib should be the preferred first-line treatment for all patients with CML, given the increased cost and rate of adverse events with asciminib?[5]

JC If cost is your main consideration for therapy, imatinib is unquestionably the best choice because it is

the least expensive. But for many patients who have insurance coverage and other resources, asciminib provides a better chance of being able to discontinue treatment, a better quality of life, and fewer AEs. When cost is not the primary concern, asciminib is the superior drug.

H&O What do you consider the role of asciminib to be?

JC Asciminib represents another step forward in our goal to achieve cure in more patients. I know that this is an ambitious goal, but we need to be ambitious when it comes to cancer care. We also would like to get more patients to the point where they can stop therapy and be free of drugs. We have attempted to do this with ponatinib, but this agent is not suitable for frontline therapy because of the AE profile. Thanks to the better safety profile of asciminib, we now have another approach to aim for being able to stop therapy in more patients.

H&O What additional studies are looking at the use of asciminib in CML, either as monotherapy or in combination with other agents?

JC Data on the use of asciminib in second-line therapy are still limited, so we designed the phase 2 ASC2ESCALATE study to look at asciminib as first- and second-line treatment of CML-CP. This is a multicenter, single-arm, phase 2 dose-escalation study, and the first study to investigate asciminib in CML-CP following the failure of one prior TKI. Interim data on 63 patients that were presented at the American Society of Clinical Oncology Annual Meeting demonstrated an MMR rate of 44.4% at week 24.[6] We still need to see the final results of this study to determine the full potential of asciminib as a second-line option, but these interim results are very encouraging.

We also want to understand the role of asciminib in patients who start with imatinib and have a good but not great response. At that point, can we switch to asciminib to deepen the response to therapy? This is different from switching because of resistance to or intolerance of therapy. The ASC4MORE study is currently looking at this question as well.[7]

Several studies are also looking at asciminib in combination with other agents. One is looking at a combination of asciminib and nilotinib in patients with CML as initial therapy. A subset analysis showed that in patients with *ASXL1* mutations, the combination yielded responses that were at least equivalent to, if not better than, the responses in patients with no additional mutations or with mutations in genes other than *ASXL1*.[8]

H&O What other questions remain to be answered?

JC It would be very useful to devise algorithms that factored in patient and disease characteristics to define the best drug for each patient. We also need more studies that focus on quality of life. No matter how effective our treatments are for CML, most patients today must remain on TKIs for the rest of their life.

Disclosures

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