Title

Imatinib remains the best frontline therapy in patients with chronic myeloid leukemia: Critical analysis of the ASC4FIRST trial

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CORRESPONDENCE

Imatinib remains the best frontline therapy in patients with chronic myeloid leukemia: Critical analysis of the ASC4FIRST trial

To the Editor:

A recent study—ASC4FIRST[1]—builds the case that the novel drug, asciminib, a BCR::ABL1 inhibitor, is superior to current tyrosine kinase inhibitors (TKIs) for the treatment of chronic phase (CP) chronic myeloid leukemia (CML). Some have even taken to social media to announce a post-imatinib era.

As the first TKI to be approved in oncology, imatinib has been a transformative oral anti-cancer drug, improving survival for patients with CP CML. Imatinib, and subsequent drugs—dasatinib, bosutinib, and nilotinib—have increased the life expectancy of patients diagnosed with CML to essentially the same length as the general population without CML.[2]

Will asciminib further improve upon existing TKIs? We consider this alongside three questions raised by the ASC4FIRST trial: does it establish superiority over second-generation TKIs (dasatinib, bosutinib, and nilotinib), does the improvement in major molecular milestones mean the drug will improve survival or quality of life, and what can we conclude about adverse effects in this open-label study?

A primary concern with the ASC4FIRST trial is its approach to comparing asciminib with other TKIs, as a combined entity. The trial's design included two primary comparisons: asciminib versus all TKIs (a combined group of imatinib and second-generation TKIs) and asciminib versus imatinib alone. However, a direct comparison between asciminib and second-generation TKIs was relegated to a "secondary objective" and "not compared [...] as a primary objective." This design choice raises critical questions about the validity and clinical relevance of the findings.

Combining imatinib and second-generation TKIs into a single control group undermines the distinct therapeutic profiles and efficacy of these drugs. It is well-established that second-generation TKIs, such as dasatinib and nilotinib, outperform imatinib in achieving significant molecular responses in CML patients.[3] By lumping these agents together, the trial essentially sets up a comparison that is guaranteed to favor asciminib. This strategy, which we have called the use of "nested groups" as opposed to "adjacent groups," is a common tactic in clinical trials which creates confusion about precisely which groups benefit or which comparisons are significant.[4,5] In this case it lacks clinical justification and can mislead stakeholders about the true efficacy of the investigational drug.

In the ASC4FIRST trial, the difference in the 48-week major molecular response (MMR) between asciminib and the combined TKI group (a nested group) was significant. Yet, the more relevant comparison—asciminib versus second-generation TKIs (omitting imatinib, an adjacent subgroup)—revealed no significant difference (66.0% vs. 57.8%, respectively).[1] This finding is crucial because it highlights that asciminib may not offer a substantial improvement over current second-generation TKIs. We have depicted this in Figure 1. Therefore, the trial's conclusion that asciminib is superior to imatinib does not mean it is superior to all available treatment options.

Another concern is the choice of the primary endpoint. The ASC4FIRST trial used the 48-week MMR as its primary measure of efficacy. While achieving MMR is an important milestone in the management of CML, its correlation with long-term clinical outcomes is not absolute.[5] Molecular milestones like the 48-week MMR are often used in clinical trials due to their convenience and shorter timeline for assessment. However, these milestones are not definitive indicators of long-term survival or overall clinical benefit.

Data showing that switching or escalating therapy based on MMR improves outcomes like overall survival (OS) are lacking.[6] MMR's importance originated from the IRIS study, which correlates MMR with progression-free survival and not OS or quality of life. Studies have not conclusively shown that MMR correlates with improved patient-centered outcomes. For instance, various analyses, such as those between second-generation TKIs and imatinib, revealed no significant difference in OS between patients who achieved MMR and those who did not.[6]

The superiority of second-generation TKIs is uncertain with respect to clinical outcomes, such as survival or quality of life. The National Comprehensive Cancer Network guidelines (version 1.2023) recommend second-generation TKIs as first-line therapy for patients with intermediate or high-risk Sokal or Euro scores. However, the reliance on Sokal and Euro scores for stratifying CML patients is problematic because these scores were developed from data on chemotherapy or interferon-alpha treatments and are not relevant in the TKI era. In the German CML Study IV there is no significant differences in cumulative incidence probabilities (CIPs) of death among different Sokol risk groups (Figure 3a in Pfirrmann et al.).[7]

In terms of efficacy, there is no evidence that the OS for second-generation TKIs is superior to imatinib. The ENESTnd study reported a 10-year OS of 88.3% for imatinib versus 90.3% for nilotinib ($p = .40$).[8] Similarly, the DASISION study found 5-year OS rates of 90.0% for imatinib and 91.0% for dasatinib ($p = .1192$).[9,10] Furthermore, while treatment-free remission (TFR) rates might be high with

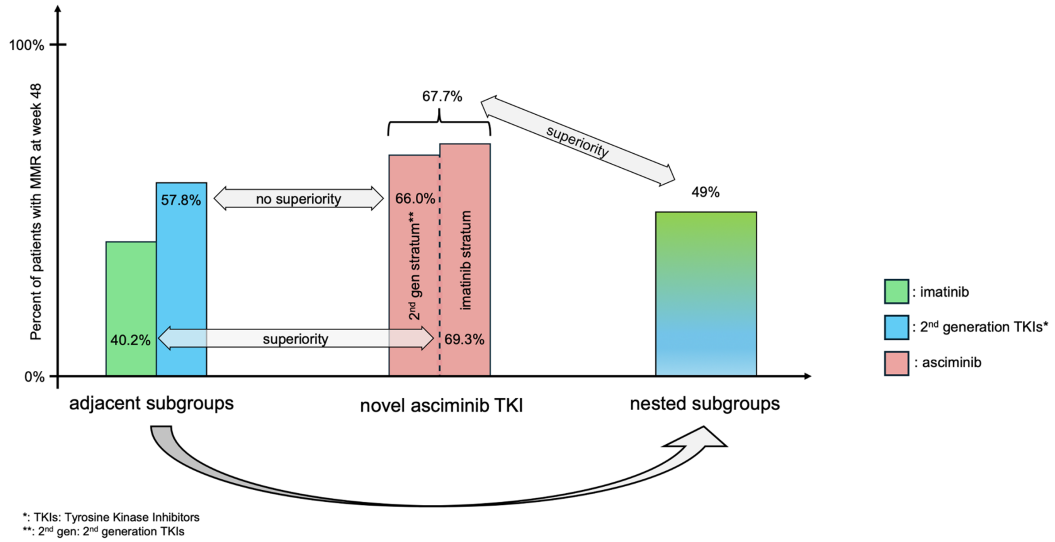

FIGURE 1 Comparison of major molecular response at Week 48 across separated and combined strata of patients in the ASC4FIRST trial.

second-generation TKIs, actual TFR rates from discontinuation trials are similar between imatinib, nilotinib, and dasatinib (approximately 50% for each).[9] Considering the significantly higher cost, increased toxicity, and adverse effects leading to possibly higher treatment interruptions,[8] we and others have argued that imatinib remains the preferred first-line treatment for all CML patients, regardless of their risk category.

While molecular milestones provide valuable insights, they should be interpreted within the broader context. This understanding is especially pertinent when evaluating new therapies that are poised to replace well-established treatments like imatinib.

The open-label nature of the ASC4FIRST trial introduces an additional concern. Participants might report side effects differently based on their knowledge of the treatment they are receiving, and researchers might unconsciously interpret data in a way that favors the investigational drug.

While open-label designs are sometimes necessary, especially in early-phase trials or when blinding is impractical, they also demand a critical evaluation of the reported outcomes. The ASC4FIRST trial's safety data, indicating fewer adverse events with asciminib compared with imatinib and second-generation TKIs, should be interpreted with caution. Without blinding, the potential for bias in adverse event reporting could be significant, and these findings should be corroborated with data from double-blind studies.

Double-blind trials, where neither the participants nor the researchers know who is receiving which treatment, are the gold standard for eliminating bias. They provide a more reliable assessment of both efficacy and safety, ensuring that the observed outcomes are attributable solely to the intervention. Therefore, future studies on asciminib should consider a double-blind design to validate the safety profile observed in the open-label ASC4FIRST trial.

The annual cost per patient for asciminib is nearly $300 000, while generic imatinib now can be obtained for less than $2000. The financial burden from choosing asciminib as the first-line therapy would be massive both for individual patients and health care systems.[11] Ideally, experts without financial ties to the company marketing asciminib are best capable of adjudicating the evidence.

The ASC4FIRST trial presents a view on the post-imatinib era, with promising data on asciminib as a new treatment for CML. However, the methodological concerns highlighted—nested group comparisons over adjacent groups, the validity of molecular milestones, and the open-label design—underscore we are nowhere close to moving on from imatinib. As the oncology community continues to explore new therapeutic options, it is imperative to ensure that study designs are robust and that endpoints are clinically meaningful. For the time being, we believe the era of imatinib is still here to stay.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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