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MATCHING ADJUSTED INDIRECT COMPARISON OF ASCIMINIB VS FLUMATINIB AS FIRST-LINE TREATMENT FOR CHRONIC MYELOID LEUKEMIA IN CHINA

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KEY FINDINGS & CONCLUSIONS

- Asciminib demonstrated significantly higher odds of molecular response (EMR, MMR) vs flumatinib.
- Safety profile favored asciminib with a significantly lower risk of discontinuation due to AEs.
- ESS remained stable after weighting, supporting robustness of the MAIC.

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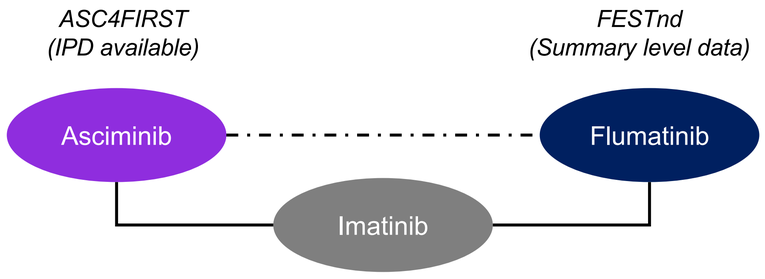
INTRODUCTION

- Asciminib, an inhibitor specifically targeting the ABL myristoyl pocket, has demonstrated superior efficacy and safety versus ATP-competitive tyrosine kinase inhibitors (TKIs) in newly diagnosed patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic-phase (Ph+ CML-CP) in the ASC4FIRST trial.
- Flumatinib remains a China-exclusive second-generation BCR::ABL TKI and has not been used as a comparator in the global, registration studies of asciminib.
- Since no direct comparative evidence between these agents is available, we conducted an anchored matching-adjusted indirect comparison (MAIC) using patient-level data from ASC4FIRST [2] and aggregate data from FESTnd [1] to estimate the relative efficacy and safety of asciminib versus flumatinib in newly diagnosed CML-CP patients in China.

METHODS

- An anchored MAIC [3] was performed using imatinib as the common comparator across the two trials (**Figure 1**). Individual patient data (IPD) from ASC4FIRST [2] were reweighed and matched to align with the baseline characteristics of FESTnd using entropy balancing.
- Based on insights from clinical experts and data from publications, the key variables included as clinically relevant prognostic factors and effect modifiers were age, sex, platelet count, and white blood cell count (WBC).
- Weighting and Balance: To match the baseline characteristics of FESTnd patients, weights were applied to ASC4FIRST patients to create a pseudo-comparable population from ASC4FIRST [1] . Effective Sample Size (ESS) was monitored to assess weight stability; for asciminib, ESS was 184.78 (7.6% reduction), indicating robust matching without extreme weights.

Figure 1. Evidence network of included studies



Abbreviations: IPD: Individual patient data
Note: Solid line represents direct comparison. Dotted line represents indirect comparison.

Outcomes and Analysis:

Outcomes

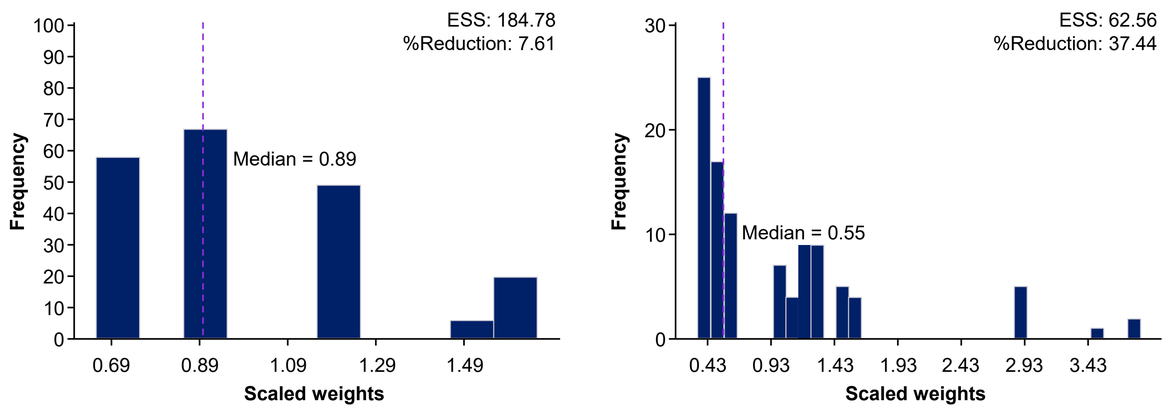
- **Efficacy**: Early molecular response (EMR) at 12 weeks and major molecular response (MMR) at 48 weeks summarized as odds ratios (OR) with 95% confidence intervals were estimated.
- **Safety**: Discontinuation due to adverse events (AEs) at 48 weeks summarized as relative risk ratio (RR) with 95% confidence intervals was estimated.

Effective Sample Size

- Distribution of weights assigned to individual patient records from the ASC4FIRST to align their baseline variable summary statistics with the aggregated summary statistics of patients from the FESTnd clinical trial is presented in **Figure 2**.
  - X-axis shows the range of weights assigned to each patient and y-axis shows the frequency i.e., number of patients who received each weight
  - For asciminib, after weighing, the ESS was 184.78, showing only 7.6% reduction from original sample, indicating stable weights and reliable matching (**Figure 2 (a)**).
  - The weights for imatinib patients showed greater variability, yielding an ESS of 62.56, a 37.4% reduction from the original sample (**Figure 2 (b)**).
- Weight distribution histograms confirmed balanced populations post-adjustment, and the ESS stability supported the robustness of the analysis.

Figure 2. Weight distribution histograms for analyzing ESS

(a) Asciminib (ASC4FIRST) vs Flumatinib (FESTnd) **(b) Imatinib (ASC4FIRST) vs Imatinib (FESTnd)**



Baseline Comparison Before and After Weight Adjustment

- **Table 1** presents the key baseline variables from the ASC4FIRST and FESTnd trials, both before and after weight adjustment in the IPD from the ASC4FIRST trial, to match the baseline variables of the FESTnd trial for conducting MAIC.

Table 1. Aggregated baseline summary after IPD weight adjustment for asciminib and imatinib from ASC4FIRST with flumatinib and imatinib from FESTnd.

Baseline Variables	ASC4FIRST Trial				FESTnd Trial	
	Before Matching		After Matching			
	Asciminib	Imatinib	Asciminib	Imatinib	Flumatinib	Imatinib
Sample size	200	100	184.78	62.56	196	197
AGE*	52.00	54.00	45.58	45.76	45.00	45.00
SEX**	0.66	0.63	0.64	0.60	0.64	0.60
PLATELET*	391.00	386.00	413.66	418.17	414.00	417.00
WBC*	25.00	35.30	24.25	20.27	24.00	20.00

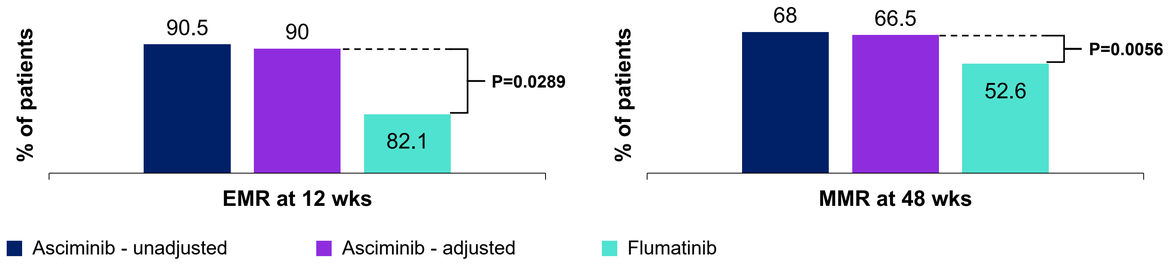
*median values; **proportion
Abbreviations: WBC: White blood cells

RESULTS

Efficacy Outcomes:

- Compared to flumatinib, asciminib achieved significantly better efficacy as it was 1.95 times more likely to achieve EMR at 12 weeks (95% CI 1.05-3.73; p=0.0289) (**Figure 3 and 4(a)**).
- After MAIC, asciminib demonstrated significantly superior efficacy compared to flumatinib, with patients being 1.79 times (95% CI 1.17-2.75; p=0.0056) more likely to achieve MMR at 48 weeks.

Figure 3. Summary of comparative analysis of efficacy outcomes

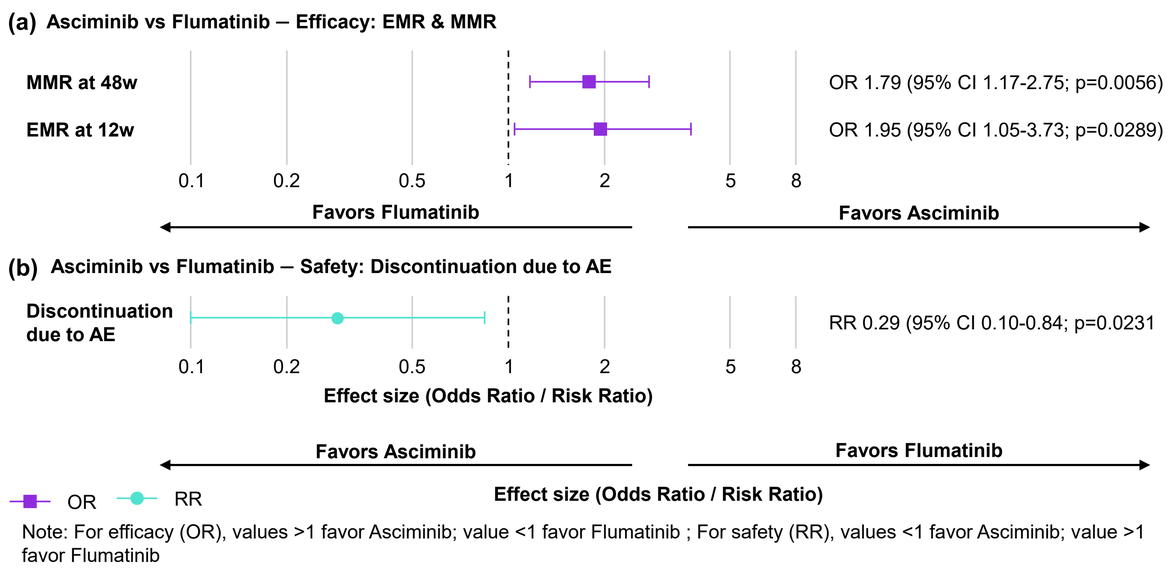


Abbreviations: EMR: Early molecular response; MMR: Major molecular response.

Safety Outcomes:

- Asciminib achieved favorable safety-results compared with flumatinib as seen in both unadjusted and adjusted rates of discontinuations due to AE (5.5%, 5.5% vs 10.2%, p=0.0231).
- The risk of discontinuation due to AEs was significantly less with asciminib, 71% lower than flumatinib (**Figure 4 (b)**).

Figure 4. Summary of comparative analysis of efficacy and safety outcomes outcomes



Note: For efficacy (OR), values >1 favor Asciminib; value <1 favor Flumatinib ; For safety (RR), values <1 favor Asciminib; value >1 favor Flumatinib

DISCUSSION

- By leveraging MAIC methodology, we addressed the absence of direct comparative evidence and adjusted for key baseline differences between trials for comparative analysis.
- The results of this MAIC demonstrate a consistently favorable efficacy and safety profile of asciminib versus TKIs like flumatinib.
- These results further support the positive risk/benefit profile of asciminib when used as a first-line treatment for CML-CP.

LIMITATIONS

- Given the limited data there are limitations of the cross-trial comparison, hence the anchored MAIC assumes conditional constancy of relative effects which can add to substantial bias in the interpretation.
- Despite careful considerations, residual confounding from unmeasured variables, including, but not limited to, geographic and demographic differences between ASC4FIRST (global) and FESTnd (China-only) may also influence this comparative analysis.

References

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Disclosures

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