MSR19

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A Matching-Adjusted Indirect Comparison of Asciminib versus Ponatinib, Nilotinib and Dasatinib in Chronic Phase Chronic Myeloid Leukemia Patients after ≥2 Tyrosine Kinase Inhibitors

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KEY FINDINGS & CONCLUSIONS

- An improved efficacy was observed with asciminib versus CP-CML treatments commonly used in ≥3L of therapy after adjusting for between-study differences within the scope of this MAIC.
- Asciminib exhibited favorable efficacy versus ponatinib (MMR, CCyR), nilotinib/dasatinib (CCyR) and dasatinib (MMR) based on MAIC results.
- These results align with the improved risk-benefit profile seen for asciminib versus bosutinib in the ASCEMBL trial. By 48 weeks, lower rates of discontinuation were observed with asciminib versus bosutinib (45.4% versus 88.7% due to any reason and 5.7% versus 23.7% due to adverse events), indicating its relative tolerability especially in the context of the high rate of prior TKI discontinuation due to intolerance (34.8%) among the ASCEMBL patient population.[3]
- The comparative evidence from this MAIC analysis can aid future decisions and research in defining a treatment path for patients in need of effective and safe innovative treatments, who fail ≥2 TKI therapies. These results will inform clinicians, health-policy-stakeholders, patients and other decision-makers about the comparative effectiveness of asciminib in ≥3L CP-CML.

This study is sponsored by Novartis Services Inc.
Poster presented at ISPOR-2022, held in-person and virtually on May 15-18, 2022.

INTRODUCTION

- Chronic myeloid leukemia (CML) is a rare cancer of the hematopoietic stem cells that begins in the bone marrow and is characterized by the reciprocal translocation between chromosomes 9 and 22.[1,2]
- While clinical guidelines are well established for first-line (1L) and second-line (2L) therapies, the choice of treatment beyond 2L varies from a patient to patient depending upon the individual situation related to comorbidities, prior adverse events, mutation profile, drug caused interaction and compliance issues.[1]
- Comparative analysis of chronic phase (CP) CML treatments in third- or later lines (≥3L) is challenging due to a high biological heterogeneity among the patients who fail multiple tyrosine kinase inhibitors (TKIs) and limited availability of head-to-head clinical studies.
- To fill this evidence gap and facilitate decision-making for an optimal treatment choice for ≥3L CP-CML patients, a matching-adjusted indirect comparison (MAIC) of asciminib efficacy versus most of the commonly used TKIs (ponatinib, nilotinib, and dasatinib) was performed.

METHODS

- The MAICs were preceded by a clinical systematic literature review (SLR) that ensured comprehensive inclusion of relevant data for the comparative analyses. Among the total studies included in the SLR, studies which provided baseline patient characteristics data of ≥3L CP-CML patients were considered eligible for the MAIC.
- Individual patient data (IPD) for asciminib was available from ASCEMBL trial (data cut-off: January 06, 2021; follow-up: ≥48 weeks). ASCEMBL is an open-label, randomized, phase-III trial for asciminib in CP-CML patients treated with ≥2 prior TKIs where the primary endpoint was the major molecular response (MMR) rate at week 24 for asciminib vs. bosutinib. The key secondary endpoint is the rate of MMR after 96 weeks (NCT03106779).[3]
- Published study-level aggregate data (AD) was used for comparator interventions .
- A MAIC model was developed based on the methodology described by Signorovitch *et al.*[4, 5] The study groups were matched and multiple MAICs were conducted comparing asciminib with ponatinib, nilotinib, and dasatinib, respectively.[6-9]
- The details of the MAIC methodology used for the current analysis are provided in the supplementary document.
- The cross-trial differences were accounted in the comparisons by matching the defined baseline variables available for the included studies namely sex, median age, race, partial cytogenetic response (PCyR) at baseline, prior TKIs, resistance/intolerance to prior TKIs, mutation status and Eastern Cooperative Oncology Group Performance Status (ECOG PS; 0,1). Efficacy outcomes, namely major molecular response (MMR), complete cytogenetic response (CCyR), and time to response (MMR and CCyR) were assessed in different MAICs.
- Asciminib MMR rates were compared versus ponatinib (by 6 and 12 months) and dasatinib (by 6 months). CCyR rates were compared versus ponatinib (by 6 and 12 months) and nilotinib/dasatinib (by 6 and 12 months).
- Time-to-response of MMR and CCyR for ponatinib was digitized using WebPlotDigitizer (v4.5) to retrieve relevant data points.

RESULTS

- The estimated sample size (ESS) was calculated after matching the key baseline characteristics reported in both ASCEMBL trial and the comparator studies (**Table 1**).

Table1. Overview of studies and outcomes analyzed in the MAIC

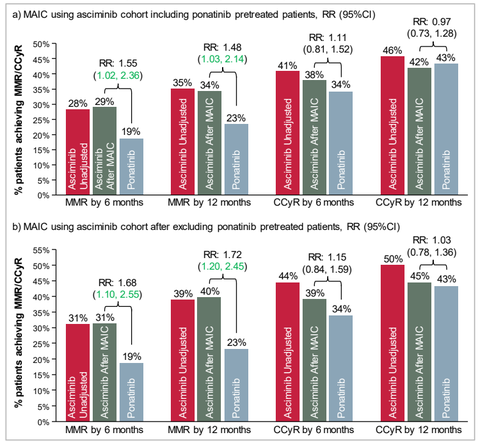
Trial/Study	Sample size (N, ESS) and clinical outcomes compared
Asciminib* vs Ponatinib (cohort A)	**MMR, CCyR**
PACE (Phase II, single-arm trial)	N=203
ASCEMBL – unadjusted	N=103
ASCEMBL – adjusted by matching	ESS=53
Asciminib vs Ponatinib (cohort A)**	**MMR, CCyR**
PACE (Phase II, single-arm trial)	N=203
ASCEMBL – unadjusted	N=90
ASCEMBL – adjusted by matching	ESS=38
Asciminib* vs Nilotinib/Dasatinib	**CCyR**
Ibrahim *et al*, 2010 (Prospective observational study)	N=26
ASCEMBL – unadjusted	N=103
ASCEMBL – adjusted by matching	ESS=35
Asciminib vs Dasatinib	**MMR**
Tan *et al*, 2019 (Retrospective chart review study)	N=24
ASCEMBL – unadjusted	N=157
ASCEMBL – adjusted by matching	ESS=23

*Since patients with CCyR at baseline were excluded in the PACE trial and Ibrahim et al, patients from ASCEMBL trial who either had CCyR at baseline (n=19) or if baseline CCyR data was missing (n=35) were similarly removed from the comparison to match the exclusion criteria. **excluding ponatinib pretreated patients.
Note: PACE cohort A (N=203) includes patients on ≥3L CP-CML therapy
Abbreviations: 3L, third line; CCyR, complete cytogenetic response; CP-CML, chronic phase-Chronic myeloid leukemia; ESS, effective sample size; MAIC, matching-adjusted indirect comparisons; MMR, major molecular response; TKIs, tyrosine kinase inhibitors

Asciminib vs Ponatinib

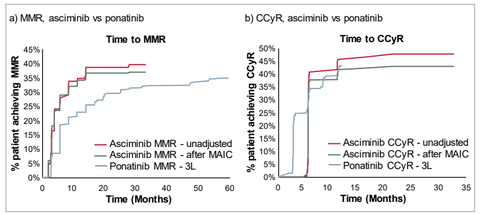
- An ESS of 53 patients was obtained for asciminib after cross-trial adjustments for matching ASCEMBL (N=103) and PACE (cohort-A: ≥3L CP-CML patients without T315I mutation; N=203).
- Compared to ponatinib, a significantly higher proportion of patients on asciminib achieved MMR by 6 and 12 months, respectively. CCyR rates were numerically higher with asciminib by 6 months and comparable to ponatinib by 12 months (**Figure 1 a**).
- Time to MMR by 6 months and 12 months and CCyR by 6 months, favored asciminib when compared with ponatinib (**Figure 2 a, b**).
- Additionally, a separate analysis was conducted after excluding the 13 ponatinib pre-treated patients from the asciminib arm (N=90) while comparing with ponatinib (cohort-A, N=203). After matching, an ESS of 38 patients was obtained for asciminib. A higher proportion of patients on asciminib achieved MMR by 6 and 12 months compared to ponatinib, while CCyR rates by 6 and 12 months were numerically higher in comparison with ponatinib patients (**Figure 1 b**). Favorable results were observed with asciminib regarding time taken to achieve MMR and CCyR when compared with ponatinib (**Figure 2 c, d**).

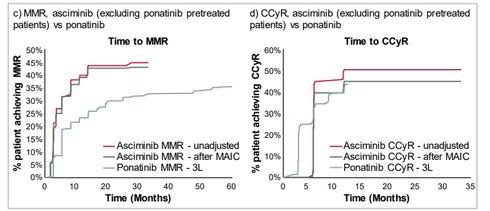
Figure 1. Comparison of cumulative molecular response by 6 and 12 months, asciminib (ASCEMBL) vs ponatinib (PACE cohort A).



Note: PACE cohort A (N=203) includes patients on ≥3L CP-CML therapy. Green color of 95%CI denotes statistically significant difference.
Abbreviations: 3L, third line; CCyR, complete cytogenetic response; CP-CML, chronic phase-Chronic myeloid leukemia; MAIC, matching-adjusted indirect comparisons; MMR, major molecular response; RR, risk ratio.

Figure 2. Cumulative response curves for time to MMR/CCyR of asciminib (ASCEMBL) versus ponatinib (PACE, cohort A)



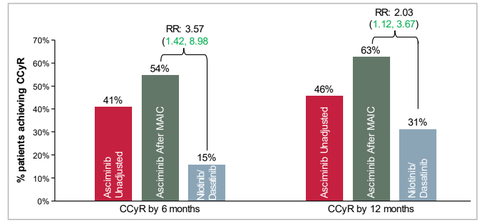


Note: PACE cohort A (N=203) includes patients on ≥3L CP-CML therapy.
Abbreviations: 3L, third-line; CCyR, complete cytogenetic response; MAIC, matching-adjusted indirect comparisons; MMR, major molecular response.

Asciminib vs Nilotinib/Dasatinib

- Between-study adjustments were performed before the analysis to match ASCEMBL (N=103) and Ibrahim *et al*, 2010 (N=26). An ESS of 35 patients was obtained for asciminib after matching.
- CCyR was significantly higher with asciminib versus nilotinib/dasatinib by 6 months and by 12 months, respectively (**Figure 3**).

Figure 3. Comparison of cumulative molecular response by 6 and 12 months, asciminib (ASCEMBL) vs nilotinib/dasatinib (Ibrahim *et al*, 2010), RR (95%CI)

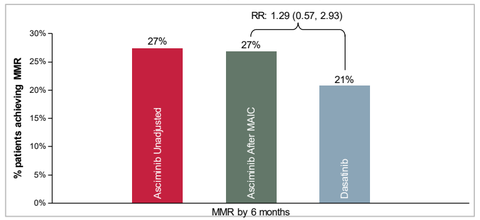


Note: Green color of 95%CI denotes statistically significant difference.
Abbreviations: CCyR, complete cytogenetic response; MAIC, matching-adjusted indirect comparisons; RR, risk ratio.

Asciminib vs Dasatinib

- Adjustment of between-trial differences to compare ASCEMBL (N=157) and Tan *et al*, 2019 (N=24) was performed, and an ESS of 23 patients was achieved for asciminib.
- MMR rates by 6 months were higher in the asciminib group versus dasatinib (**Figure 4**).

Figure 4. Comparison of cumulative molecular response by 6 months, asciminib (ASCEMBL) vs dasatinib (Tan *et al*, 2019)



Abbreviations: CCyR, complete cytogenetic response; MAIC, matching-adjusted indirect comparisons; RR, risk ratio.

Challenges and Limitations

- Paucity of data on CP-CML treatments for patients failing two or more TKIs impacts any attempt of comparative analysis. Indeed, limited published studies on off-label TKIs especially nilotinib and dasatinib, variable study designs across comparators, cross-trial differences in patients' baseline characteristics, and small sample size were challenges considered while attempting to perform indirect comparisons of efficacy of ≥3L CP-CML interventions. If applied, reported and interpreted correctly, MAIC is a valid technique for comparative effectiveness research.
- Though MAICs were designed to overcome these challenges by using IPD for asciminib and matching baseline parameters of AD for comparator studies to reduce the observed cross-trial differences, unobserved differences may still result in residual confounding. Furthermore, during MAIC the ESS for asciminib is notably reduced from the actual sample size of ASCEMBL trial, which may have an influence on the post-MAIC results of asciminib.
- For the current MAIC, studies were considered eligible for analysis if >75% of the study population was treated for ≥3L CP-CML, provided the baseline characteristics of this target patient group and had reported the efficacy outcomes of interest. Some of the studies that reported data in ≥3L patients, including BYOND and OPTIC, were not considered for the comparative analyses as they did not meet one or more of these selection criteria.
- Although comparing the tolerability profile of treatments in later lines of therapy is essential for a successful long-term management of this high-risk patient group, the MAIC methodology is unsuitable to compare the safety outcomes, as predictive factors for adverse events (AEs) are not yet established and varying definitions of AEs are used across studies.

Acknowledgements

Aurore Yocolly of Novartis Services Inc., East Hanover, USA, provided insights during the analyses and Madhavi Kanithi of Novartis Healthcare Pvt. Ltd., Hyderabad, India, provided graphic designing support.

Disclosures

Ehab Atallah: personal fees from Novartis, Bristol Myers Squibb, Takeda, and AbbVie. Vikalp Kumar Maheshwari and Lovneet Saini: employees of Novartis Healthcare Pvt. Ltd., Hyderabad, India. Michael J. Mauro: Sun Pharma / SPARC: Research Funding; Pfizer: Consultancy; Bristol Myers Squibb: Consultancy, Research Funding; Takeda: Consultancy, Carla Boquimpani: Pinth Pharma: Speakers Bureau; Novartis: Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; Jansen: Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. Delphine Réa: Novartis: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; Pfizer: Honoraria, Membership on an entity's Board of Directors or advisory committees. Andreas Hochhaus: Research Funding: Novartis, Bristol-Myers Squibb, Pfizer, Incyte. Yosuke Minami: Takeda: Honoraria; CMIC: Research Funding; Astellas: Honoraria; Ono: Research Funding; Pfizer Japan Inc.: Honoraria; Novartis Pharma KK: Honoraria; Bristol-Myers Squibb Company: Honoraria. Regina Corbin: employee and stockholder of Novartis Services Inc. East Hanover, NJ, USA.

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