Poster CML 311

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Matching-adjusted indirect comparisons of asciminib vs other tyrosine kinase inhibitors in third- or later-line chronic myeloid leukemia in chronic phase

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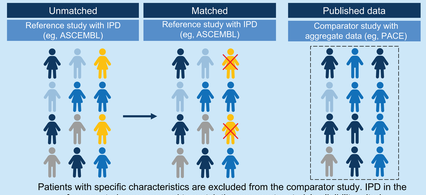
Introduction

- CML is a rare blood cancer characterized by the BCR::ABL1 fusion protein[1]
- The current standard of care for CML-CP is TKIs that target the ATP binding site of ABL1[2]
- Asciminib, the first BCR::ABL1 inhibitor to Specifically Target the ABL Myristoyl Pocket (STAMP), sustained superior efficacy and better safety and tolerability compared to bosutinib in the phase 3 ASCEMBL trial (NCT03106779) in the week 24, 48, and 96 analyses[3-5]
- With no head-to-head trials directly comparing asciminib to other TKIs beyond bosutinib, there is a need to further clarify treatment recommendations for patients with CML-CP after ≥2 prior TKIs
- Thus, MAICs were conducted to compare the efficacy of asciminib with competing TKIs in CML-CP after failure of ≥2 TKIs using week 96 follow-up data from ASCEMBL

Study design and methods

- According to methods by Signorovitch et al.[6,7], unanchored MAICs were conducted to adjust individual patient-level data for asciminib from the ASCEMBL trial (follow-up: ≥96 weeks) to published aggregate data for comparator TKIs (Figure 1)
  - Key comparator TKIs included ponatinib (PACE[8]: patients with ≥2 prior TKIs), nilotinib (Giles et al. 2010[9]; Ibrahim *et al*. 2010[10]), and dasatinib (Tan *et al*., 2019[11]; Rossi et al., 2013[12]; Ibrahim *et al*., 2010[10])
- The MAICs aimed to adjust for the following key prognostic factors: number of prior TKIs, resistance/intolerance to prior TKIs, cytogenetic response status, number of mutations, ECOG performance score, age, gender and race
- ESS was calculated to show the degree of overlap between the adjusted asciminib population and the comparator population.
  - A large reductions in ESS after adjustment indicates very little overlap between the asciminib and comparator populations
- MMR rates for asciminib were compared vs ponatinib (by 6 and 12 months) and dasatinib (by 6 months). CCyR rates for asciminib were compared vs ponatinib (by 6 and 12 months) and pooled nilotinib/dasatinib (by 6 and 12 months)
- Time-to-response curves for MMR and CCyR for asciminib vs ponatinib were digitized using WebPlotDigitizer (v4.5) to capture relevant data points
- An additional sensitivity analysis was conducted, where it considered the removal of 13 ponatinib pre-treated patients from the ASCEMBL trial

Figure 1. Process of matching based on eligibility criteria in MAICs



Patients with specific characteristics are excluded from the comparator study. IPD in the reference study are removed to match the comparator study's eligibility criteria

Results

- The ESS was calculated after matching and adjusting for select baseline characteristics reported both in the ASCEMBL trial and the comparator studies (**Table 1**)

Table 1. Overview of studies and outcomes in the MAIC

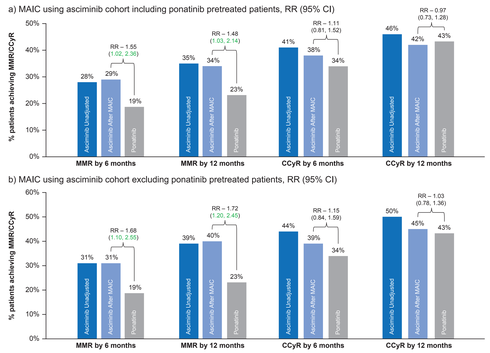
Trial/study	Sample size (N, ESS) and clinical outcomes compared
Asciminib* vs ponatinib (≥3L CML-CP)	**MMR, CCyR**
PACE (Phase II, single-arm trial)	N=203
ASCEMBL –unadjusted	N=103
ASCEMBL –post-MAIC	ESS=53
Asciminib vs ponatinib (≥3L CML-CP)**	**MMR, CCyR**
PACE (Phase II, single-arm trial)	N=203
ASCEMBL –unadjusted	N=90
ASCEMBL –post-MAIC	ESS=38
Asciminib vs dasatinib	**MMR**
Tan et al., 2019 (Retrospective chart review study)	N=24
ASCEMBL –unadjusted	N=157
ASCEMBL –post-MAIC	ESS=23
Asciminib* vs pooled nilotinib/dasatinib	**CCyR**
Ibrahim et al., 2010 (prospective observational study)	N=26
ASCEMBL –unadjusted	N=103
ASCEMBL –post-MAIC	ESS=35

*Given that patients with CCyR at baseline were excluded in the PACE trial and Ibrahim *et al*., 2010, patients from ASCEMBL who either had CCyR at baseline (n=19) or missing CCyR data at baseline (n=35) were removed to align with the exclusion criteria of these studies.
** This analysis removed 13 ponatinib pre-treated patients from ASCEMBL.

Asciminib vs ponatinib

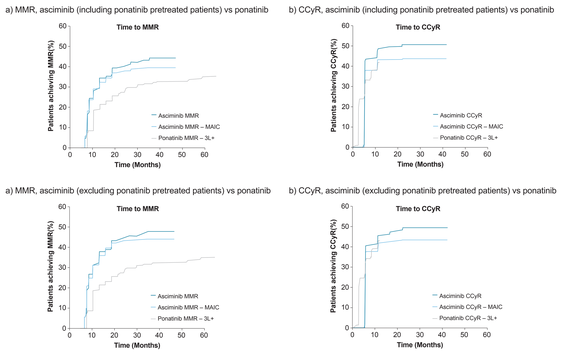
- An ESS of 53 patients was obtained for asciminib after matching and adjustment of ASCEMBL (N=103) according to PACE (≥3L CML-CP without T315I mutation; N=203)
- Compared to ponatinib, asciminib was associated with statistically significant improvements in MMR by 6 (relative risk [RR]: 1.55; 95% confidence interval [CI]: 1.02, 2.36) and 12 months (RR: 1.48; 95% CI: 1.03, 2.14) (**Figure 2**)
- There was no statistically significant difference for CCyR, by 6 months (RR: 1.11; 95% CI: 0.81, 1.52) or 12 months (RR: 0.97; 95% CI: 0.73, 1.28) for asciminib vs ponatinib. (**Figure 2**)
- Removal of ponatinib pre-treated patients (ESS=38) showed that asciminib had significant improvements in MMR by 6 (RR: 1.68; 95% CI: 1.10, 2.55]) and 12 months (RR: 1.72; 95% CI: 1.20, 2.45) and numerical improvements in CCyR by 6 (RR: 1.15; 95% CI: 0.84, 1.59) and 12 months (RR: 1.03; 95% CI: 0.78, 1.36) vs ponatinib (**Figure 2**)
- Post-adjustment asciminib had favorable results for times to MMR (by 6 and 12 months) and CCyR (by 6 months) vs ponatinib (**Figure 3**)
- Removal of patients pre-treated with ponatinib showed that post-adjustment asciminib had favorable results for times to MMR and CCyR by both 6- and 12-months vs ponatinib (**Figure 3**)

Figure 2. Comparison of cumulative MMR and CCyR by 6 and 12 months for asciminib (ASCEMBL) vs ponatinib (PACE: patients with ≥2 prior TKIs)



Note: 95% CIs highlighted in green indicate a statistically significant difference for the comparison between post-adjustment asciminib and comparator.

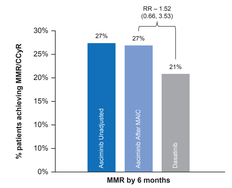
Figure 3. Cumulative response curves for time to MMR and CCyR for asciminib (ASCEMBL) vs ponatinib (PACE: patients with ≥2 prior TKIs)



Asciminib vs dasatinib

- An ESS of 23 patients was obtained for asciminib after matching and adjustment of ASCEMBL (N=157) according to Tan et al., 2019; N=24
- Compared to dasatinib, there were no statistically significant differences for asciminib in MMR by 6 months (RR 1.52; 95% CI: 0.66, 3.53)

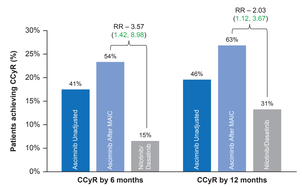
Figure 4. Comparison of MMR by 6 months for asciminib (ASCEMBL) vs dasatinib (Tan et al., 2019)



Asciminib vs pooled nilotinib/dasatinib

- An ESS of 35 patients was obtained for asciminib after matching and adjustment of ASCEMBL (N=103) according to Ibrahim et al., 2010; N=26
- Compared to pooled nilotinib/dasatinib, asciminib was associated with statistically significant improvements in CCyR by 6 (RR: 3.57; 95% CI: 1.42, 8.98) and 12 months (RR: 2.03; 95% CI: 1.12, 3.67)

Figure 5. Comparison of CCyR by 6 and 12 months for asciminib (ASCEMBL) vs pooled nilotinib/dasatinib (Ibrahim et al., 2010)



Note: 95% CIs highlighted in green indicate a statistically significant difference for the comparison between post-adjustment asciminib and comparator.

Challenges and limitations

- Given that data informing the comparators were limited to published aggregate data, comparator populations were balanced based on aggregate statistics rather than on the individual patients themselves. Thus, there may be residual heterogeneity at the patient level contributing to potential bias in the treatment effect estimates
- Although the analysis aimed to adjust for all identified important patient characteristics, the model did not converge when accounting for all these characteristics. Therefore, the present analyses aimed to balance the number of variables adjusted for while maintaining sufficient ESS
- Many comparator studies did not have sufficient overlap with ASCEMBL, resulting in a low ESS calculated for asciminib. However, most of the important patient characteristics impacting clinical outcomes were retained during the analysis
- Studies were eligible for inclusion in the MAICs if >75% of the study population were patients with CML-CP and ≥2 prior TKIs and if baseline characteristics and outcomes for this target patient group were available to minimize heterogeneity. Thus, some studies reporting on mixed study populations with patients with ≥2 prior TKIs, such as BYOND and OPTIC, could not be included in the analysis
- Comparisons with nilotinib and dasatinib were informed by three retrospective studies with small sample sizes (range: 24 to 39 patients)
- Although safety and tolerability are key factors in choice of treatment for patients with patients with CML-CP and ≥2 prior TKIs, MAICs are unsuitable for comparing these outcomes because predictive factors for AEs are not yet established, and AE definitions greatly vary across studies

Conclusions

Post-MAICs, asciminib continued to demonstrate improved efficacy vs other key TKIs in patients with CML-CP and ≥2 prior TKIs over long-term follow-up (≥96 weeks), especially among ponatinib-naïve patients receiving asciminib vs ponatinib

The results of these MAICs provide insights into the relative comparative effectiveness to address the paucity of head-to-head clinical trials evaluating asciminib against key comparators in patients with CML-CP and ≥2 prior TKIs. These results can be used to aid researchers, clinicians, and policymakers involved in healthcare decision-making

Moreover, such comparative analyses are vital in supporting the decisions of optimal treatment choice, which can help reduce the overall disease burden in patients with CML-CP who are resistant to multiple TKIs

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Poster presentation at: SOHO 2023 Eleventh Annual Meeting; September 6-9, 2023; Houston, TX, and virtual.

Abbreviations

ABL1, Abelson tyrosine kinase 1; **AE**; adverse event; **BCR**, breakpoint cluster region; **CML-CP**, chronic myeloid leukemia in chronic phase; **CCyR**, complete cytogenetic response; **ECOG**; Eastern Cooperative Oncology Group; **ESS**, estimated sample size; **IPD**, individual patient data; **IS**, International Scale; **MAIC**, matching-adjusted indirect comparison; **MMR**, major molecular response (*BCR::ABL1*^{IS} ≤0.1%); **TKI**, tyrosine kinase inhibitor.

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