Ponatinib vs Asciminib as Post–Second-generation Tyrosine Kinase Inhibitor Therapy for Chronic-phase Chronic Myeloid Leukemia: A Matching-adjusted Indirect Comparison

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Background

- Ponatinib is a BCR::ABL1 tyrosine kinase inhibitor (TKI) that potently inhibits native BCR::ABL1 and all reported single-resistance mutations, including T315I[1]
- Asciminib is an ABL myristoyl pocket (STAMP) inhibitor that targets the kinase activity of BCR::ABL1, including ABL1 kinase domain mutations such as T315I[2]
- Ponatinib and asciminib are both approved for third-line therapy in chronic-phase chronic myeloid leukemia (CP-CML) and are the only drugs approved for patients with a T315I mutation in the United States[3,4,a]
- There are currently no head-to-head trial data comparing ponatinib with asciminib in CP-CML
- We conducted a matching-adjusted indirect comparison (MAIC) analysis to compare the efficacy of ponatinib versus asciminib in patients with relapsed and refractory CP-CML who failed ≥1 prior second-generation TKI or with a T315I mutation

[a]Asciminib is not specifically indicated for patients with Philadelphia chromosome-positive CP-CML with the T315I mutation in Europe[3]

Methods

- A systematic literature search of medical literature databases (including MEDLINE, EMBASE, and the EBM Reviews Collection) was conducted to identify clinical trials investigating ponatinib or asciminib in patients with resistant or intolerant CP-CML who failed ≥1 second-generation TKI or had a T315I mutation
  - English language publications from January 1, 2006, to October 26, 2021, were identified
  - Studies reporting complete cytogenic response (CCyR), major molecular response (MMR), or *BCR::ABL1* transcript level on the international scale (*BCR::ABL1*^{IS}) ≤1% for patients with CP-CML treated with TKIs whose disease was resistant or who were intolerant to ≥1 second-generation TKI or who had T315I mutation
- MAIC analysis with individual patient-level data with ponatinib was used to balance baseline characteristics
  - Key prognostic factors and effect modifiers originally identified for population adjustment included age, sex, race, Eastern Cooperative Oncology Group (ECOG) performance status, number of prior TKI treatments, baseline *BCR::ABL1*^{IS} transcript levels, and resistance or intolerance to prior TKIs
  - However, as no common treatment arms were identified across ponatinib and asciminib trials, an unanchored MAIC was used, with adjustment of treatment effect modifiers and prognostic factors
    - The aim was to correct imbalances in as many factors as possible while maximizing effective sample size (defined as the number of unweighted patients that would yield the same level of uncertainty in the estimates as the weighted cohorts)
- Cumulative rates of *BCR::ABL1*^{IS} ≤1% and MMR (*BCR::ABL1*^{IS} ≤0.1%) were compared between ponatinib and asciminib in patients without a baseline response (*BCR::ABL1*^{IS} ≤1%)
  - Response data were assessed at 12 months to ensure data maturity, and a sensitivity analysis was conducted at 6 months

Results

- Four publications were selected for the MAIC to compare ponatinib and asciminib among resistant or intolerant patients with no baseline response and patients with T315I mutation for assessment of *BCR::ABL1*^{IS} ≤1% and MMR **(Figure 1; Table 1)**
  - Ponatinib: Phase 2 OPTIC (NCT02467270)[6] and PACE (NCT01207440)[1,7] trials
  - Asciminib: Phase 3 ASCEMBL (NCT03106779)[2,9] trial and a phase 1 randomized trial (NCT02081378)[8]

Figure 1: PRISMA flow diagram of studies included in MAIC analysis

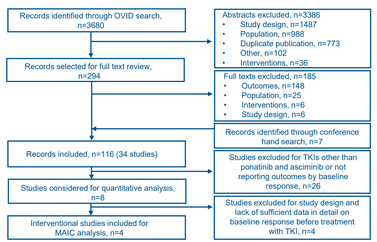


Table 1: Study summary and patient characteristics of included studies

Study	Study design	Intervention	N	Age, yr, median (range)	Exposure to prior regimens (resistance/ intolerance)	T315I mutation	CCyR at study entry	Study follow-up or treatment duration, mo (range)
Phase 1 asciminib[8]	Open-label, phase 1, dose-escalation trial	Asciminib: 10–200 mg PO BID 80–200 mg PO QD	141	Non-T315I: 56 (25–88) T315I: 54 (23–76)	Resistance or intolerance to ≥2 prior TKIs	Included (n=28)	Included	Non-T315I: Median follow-up: 72 (0.1–167) T315I: Median follow-up: 37 (0.7–167)
ASCEMBL[2,9]	Open-label, phase 3 RCT	Asciminib: 40 mg PO BID	157	52 (24–83)	Resistant or intolerance to ≥2 prior TKIs or intolerance to the previous TKI therapy at time of screening	Excluded	Included	Median follow-up: 27.6 Median duration of treatment: 23.7 (0.0–46.3)
OPTIC[6]	Open-label, phase 2, single-arm trial	Ponatinib: 45 mg PO QD and dose reduction to 15 mg PO QD upon achievement of ≤1% *BCR::ABL1*^{IS}	94	47 (19–81)	Resistance or intolerance to ≥2 prior TKIs	Included (n=25)	Excluded	Median follow-up: 32 (1–57) Median duration of treatment: 19.6 (0.1–51.3)
PACE[1,7]	Phase 2, single-arm trial	Ponatinib: 45 mg PO QD	270	58 (18–94)	Resistance or intolerance to dasatinib or nilotinib	Included (n=64)	Excluded	Median follow-up: 56.8 (0.1–73.1) Median duration of treatment: 32.1 (0.1–73.0)

BID, twice daily; PO, orally; QD, once daily; RCT, randomized clinical trial

- To ensure model convergence, a backward approach was employed until the most influential variables were retained based on their impact on achieving MMR and their role in addressing the heterogeneity of treatment effects **(Table 2)**
  - The variable "resistant to prior TKI" could not be included in the MAIC model, as there was not a sufficient number of intolerant patients in the ponatinib trials
  - The effective sample size of ponatinib patients decreased from 359 to 304.97 after matching
  - For patients with T315I mutation, the MAIC analysis was conducted in the phase 1 asciminib, OPTIC, and PACE trials
  - After matching, the covariates used for adjustment were balanced between cohorts

Table 2: Baseline characteristics of asciminib trials versus MAIC-unadjusted and MAIC-adjusted ponatinib trials

	Phase 1 asciminib	ASCEMBL asciminib	ASCEMBL and phase 1 asciminib[a]	OPTIC and PACE ponatinib-unadjusted	OPTIC and PACE matching-adjusted[b]
Sample size, N	141	157	298	359	Effective sample size[c]: 304.97 OPTIC: 81.65 PACE: 223.32
Mean age, yr (SD)	55.5[d]	51.0 (13.5)	52.6 (13.5)	55.2 (15.6)	52.6 (13.5)
Sex, male, %	54.5	52.2	53.0	53.2	53.0
Race, White, %	UNK	75.2	75.2	79.9	75.2
ECOG performance status 1 or 2, %	27.3	19.1	22.8	28.1	22.8
Mean prior TKIs (SD)	2.7[e]	2.5 (0.7)	2.6 (0.7)	2.6 (0.7)	2.6 (0.7)
Resistant to prior TKI, %	NR	60.5	NA	84.4	Not adjusted
***BCR::ABL1*^{IS} level >10%, %**	43.3	61.8	55.2	76.6	55.2

NR, not reported; NA, not applicable; SD, standard deviation; UNK, unknown
[a]The weighted results from phase 1 and ASCEMBL trials were used as the reference of the MAIC analysis; [b]MAIC analysis was conducted by using patient-level data from OPTIC and PACE trials that were matched against the combined results of phase 1 asciminib and ASCEMBL trials in all of the patient characteristics listed in the table; [c]Effective sample size: calculated as the square of the summed weights divided by the sum of the squared weights; [d]Only median age was available in phase 1 asciminib; [e]Prior TKI number in the phase 1 asciminib trial was estimated based on the published categorical data

- The cumulative efficacy outcomes by 12 months in each study before MAIC adjustment are listed in **Table 3**

Table 3: Original trial-reported *BCR::ABL1*^{IS} ≤1% and MMR among patients with CP-CML without baseline response

	Phase 1	ASCEMBL	PACE	OPTIC
Intervention	Asciminib	Asciminib	Ponatinib	Ponatinib
Sample size, N	87	142	253	90
6 months, % (95% CI)				
***BCR::ABL1*^{IS} ≤1%**	37.93 (27.74–48.13)	41.54 (33.44–49.65)	42.29 (32.02–52.43)	41.11 (35.04–47.17)
MMR	12.64 (5.66–19.63)	24.84 (17.56–31.74)	25.30 (16.54–34.57)	13.33 (9.24–17.64)
12-months, % (95% CI)				
***BCR::ABL1*^{IS} ≤1%**	39.08 (28.83–49.33)	50.70 (42.48–58.93)	45.85 (35.27–55.84)	52.22 (46.02–58.33)
MMR	19.54 (11.21–27.87)	33.12 (25.36–40.84)	31.62 (21.55–40.68)	18.89 (14.14–23.80)

- In patients with the T315I mutation and without baseline response, ponatinib outperformed asciminib for both efficacy endpoints evaluated by 6 and 12 months **(Table 4)**
  - Rate differences for *BCR::ABL*^{IS} and MMR were up to 43.54% and 47.37% higher for ponatinib, respectively

Table 4: Comparison of *BCR::ABL1*^{IS} ≤1% and MMR among patients with CP-CML with T315I mutation following MAIC adjustment

	Phase 1	PACE + OPTIC pre-MAIC	PACE + OPTIC MAIC-adjusted	Rate difference MAIC-adjusted[a]
Intervention	Asciminib	Ponatinib	Ponatinib	Ponatinib vs asciminib
Sample size, N	24	81	Effective sample size: 53.43	
6 months, % (95% CI)				
***BCR::ABL1*^{IS} ≤1%**	25.00 (7.68–42.32)	58.02 (47.28–68.77)	66.26 (53.58–78.94)	41.26 (19.79–62.73)
MMR	12.50 (0.00–25.73)	37.04 (26.52–47.55)	46.21 (32.84–59.58)	33.71 (14.90–52.52)
12 months, % (95% CI)				
***BCR::ABL1*^{IS} ≤1%**	25.00 (7.68–42.32)	64.20 (53.76–74.64)	68.54 (56.08–80.99)	43.54 (22.20–64.87)
MMR	12.50 (0.00–25.73)	49.38 (38.49–60.27)	59.87 (46.72–73.01)	47.37 (28.72–66.02)

*The difference is statistically significant when 95% CI does not contain zero

Question

To conduct a MAIC analysis to compare the efficacy of ponatinib vs asciminib in patients with relapsed and refractory CP-CML who failed ≥1 prior second-generation TKI or with a T315I mutation

Results

- Following MAIC adjustment, ponatinib consistently outperformed asciminib for the efficacy endpoints of *BCR::ABL1*^{IS} ≤1% and MMR by both 6 and 12 months

Comparison of *BCR::ABL1*^{IS} ≤1% and MMR among patients with CP-CML without baseline response following MAIC adjustment

	ASCEMBL + phase 1	PACE + OPTIC unadjusted	PACE + OPTIC MAIC-adjusted	Rate difference MAIC-adjusted[a,b]
Intervention	Asciminib	Ponatinib	Ponatinib	Ponatinib vs asciminib
Sample size, N	229	343	Effective sample size: 304.97	
6 months, % (95% CI)				
***BCR::ABL1*^{IS} ≤1%**	40.17 (33.82–46.52)	41.98 (36.76–47.21)	49.90 (44.29–55.51)	9.73 (1.25–18.20)
MMR	20.49 (15.43–25.56)	22.16 (17.76–26.55)	28.12 (23.07–33.16)	7.62 (0.48–14.77)
12 months, % (95% CI)				
***BCR::ABL1*^{IS} ≤1%**	46.29 (39.83–52.75)	47.52 (42.24–52.81)	55.61 (50.04–61.19)	9.33 (0.79–17.86)
MMR	28.28 (22.63–33.93)	28.28 (23.51–33.05)	35.11 (29.76–40.47)	6.84 (−0.95–14.62)

CI, confidence interval
[a]The difference is statistically significant when 95% CI does not contain zero; [b]A positive difference favors ponatinib, while a negative difference favors asciminib

Key Takeaway

- After adjustment for key baseline characteristics, *BCR::ABL1*^{IS} ≤1% and MMR rates by 6 and 12 months were statistically higher with ponatinib than asciminib in patients with relapsed and refractory CP-CML without a baseline response in most comparisons
- Rate differences for *BCR::ABL1*^{IS} ≤1% and MMR were up to 9.73% and 7.62% higher for ponatinib, respectively

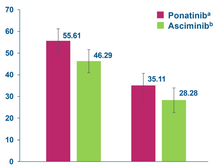
- After MAIC adjustment, *BCR::ABL1*^{IS} ≤1% and MMR response was slightly but not significantly more favorable for ponatinib treatment in patients without the T315I mutation in most comparisons **(Table 5)**

Table 5: Comparison of *BCR::ABL1*^{IS} ≤1% and MMR among patients with CP-CML without T315I mutation following MAIC adjustment

	ASCEMBL + phase 1	PACE + OPTIC pre-MAIC	PACE + OPTIC MAIC-adjusted	Rate difference MAIC-adjusted[a]
Intervention	Asciminib	Ponatinib	Ponatinib	Ponatinib vs asciminib
Sample size, N	205	262	Effective sample size: 218.65	
6 months, % (95% CI)				
***BCR::ABL1*^{IS} ≤1%**	41.95 (35.20–48.71)	37.02 (31.18–42.87)	46.90 (40.29–53.52)	4.95 (−4.50–14.41)
MMR	21.36 (15.95–26.78)	17.56 (12.95–22.16)	23.84 (18.20–29.49)	2.48 (−5.35–10.31)
12 months, % (95% CI)				
***BCR::ABL1*^{IS} ≤1%**	48.78 (41.94–55.62)	42.37 (36.38–48.35)	53.55 (46.94–60.16)	4.77 (−4.74–14.29)
MMR	30.00 (23.94–36.06)	21.76 (16.76–26.75)	28.51 (22.52–34.49)	−1.49 (−10.01–7.02)

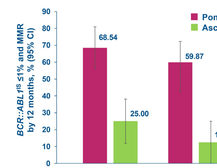
*The difference is statistically significant when 95% CI does not contain zero

Figure 2: *BCR::ABL1*^{IS} ≤1% and MMR by 12 months among patients with CP-CML without baseline response following MAIC adjustment



[a]PACE + OPTIC MAIC adjusted; N=304.97 (effective sample size)
[b]ASCEMBL + Phase 1; N=229

Figure 3: *BCR::ABL1*^{IS} ≤1% and MMR by 12 months among patients with CP-CML with T315I mutation following MAIC adjustment



[a]PACE + OPTIC MAIC adjusted; N=53.43 (effective sample size)
[b]Phase 1; N=24

Limitations

- Limitations of the MAIC model include the following:
  - The model did not include resistant and intolerant patients, owing to the ponatinib trials enrolling much more resistant patients and not having sufficient intolerant patients to match the intolerant patients in the asciminib trials
  - The analysis is limited by baseline characteristics available for all included studies
  - The comparison between ponatinib and asciminib is limited by the availability of the published data, as the data from the asciminib trials were based on the aggregated data in the public domain
  - Results should be interpreted with caution due to small sample size in some subgroups that may decrease reliability and increase the CI
  - The study focused on efficacy, and no assessment of safety was conducted

Conclusions

- In a MAIC analysis adjusted for patient characteristics across trials, ponatinib outperformed asciminib for *BCR::ABL1*^{IS} ≤1% and MMR by 6 and 12 months in resistant or intolerant patients with CP-CML without a baseline response for most comparisons
- In patients with T315I and without baseline response, those treated with ponatinib showed significantly greater *BCR::ABL1*^{IS} ≤1% and MMR response by 6 and 12 months
- In patients without the T315I mutation, the results trended in favor of ponatinib for most outcome comparisons

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Disclosures

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