Number needed to treat and cost per response achieved among patients with relapsed/refractory chronic-phase chronic myeloid leukemia managed with ponatinib or asciminib

Elias Jabbour, MD,[1] Fei Huang, MPH, PhD,[2] Michael J. Zoratti, MSc, PhD,[3] Megan Rutherford, MSc,[3] Hoora Moradian, PhD, MBA, BEng,[3] Melanie Young, PharmD, BCPS,[2] Mehul Dalal, PhD,[2] Hagop Kantarjian, MD,[1] Lucio N. Gordan, MD[4]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Takeda Development Centers America, Lexington, MA, USA; [3]Cytel Inc., Waltham, MA, USA; [4]Florida Cancer Specialists Research Institute, Gainesville, FL, USA

Introduction

- In patients with relapsed and refractory (R/R) chronic-phase chronic myeloid leukemia (CP-CML), there are limited effective treatment options
  - Ponatinib is the only pan-inhibitory tyrosine kinase inhibitor (TKI) designed to potently inhibit native BCR::ABL1 and all single-mutation variants, including T315I. It is also a treatment option for patients with CP-CML and resistance or intolerance (R/I) to ≥2 prior TKIs and for patients with accelerated-phase CML/blast-phase CML where no other TKI is indicated[1,2]
  - Asciminib is a BCR::ABL1 inhibitor Specifically Targeting the ABL Myristoyl Pocket (STAMP) and is a treatment option for patients with CP-CML and with a T315I mutation or for patients with CP-CML and R/I to ≥2 prior TKIs[3]
- Both ponatinib and asciminib are third-line treatment options in patients with CP-CML and are the only TKIs indicated for patients with the T315I mutation in the US
- Ponatinib demonstrated deep, long-lasting responses with beneficial overall survival outcomes greater than 5 years in 2 pivotal trials (OPTIC and PACE)[2,4]; asciminib has shown MMR benefit over bosutinib in the pivotal ASCEMBL trial with 24 to 48-week data[5,6]
- In the absence of head-to-head trials comparing ponatinib with asciminib, we analyzed responses from published studies and translated them into anticipated costs for payers
  - Number needed to treat (NNT) represents the expected number of patients who need to be treated with a therapy to achieve 1 patient with favorable response; it is a simple and intuitive statistical method that shows that when a less effective therapy is used, more patients need to be treated with that therapy to achieve 1 positive outcome[7,8]
  - We used 1 instance of complete cytogenetic response (CCyR) as our targeted response for NNT calculation as this is a common surrogate endpoint for long-term survival outcomes in patients with CML[9]

Objective

- To estimate the NNT and cost per response (CpR) to obtain 1 CCyR for ponatinib and asciminib by using published studies in patients with R/R CP-CML

Methods

- A systematic literature review (SLR) was conducted by searching Ovid MEDLINE, Embase, and Cochrane Database of Systematic Reviews and Central Register of Controlled Trials databases to identify clinical studies, dated between 01 January 2006 and 26 October 2021, reporting CCyR for patients with CP-CML treated with ponatinib or asciminib whose disease was R/I to at least 1 second-generation TKI or who had T315I mutation
- Updated data from the trials already captured in the SLR were also included when available after the SLR cutoff date
- Given the heterogeneity in later-line patient populations, the analysis was completed by assessing R/I patients without baseline CCyR response or who had the T315I mutation at time of treatment initiation for outcomes of interest
- Unadjusted pooled probabilities of CCyR were estimated with a Bayesian meta-analysis and used to calculate noncomparative estimates with a 95% credible interval (CrI) of the NNT to observe an additional response
  - NNT is determined by the reciprocal of the probability of achieving a response, NNT = $1/P_{Response}$[8]
- The CpR applies the cost of drug acquisition to the NNT to estimate the drug expenditure required to achieve 1 additional CCyR
- Wholesale acquisition cost (WAC) from RED BOOK (2022) was used to estimate the cost per additional response based on daily dose over 12 months **(Table 1)**

Table 1: Dosing and pricing assumptions based on the 2022 WAC (USD)

Drug	CP-CML Population	Dose, mg/d	Daily cost	Annual cost
Ponatinib	All *BCR::ABL1* mutations	45 mg	$596.10	$217,576.50
Asciminib	*BCR::ABL1* non-T315I mutations	40 mg×2	$596.67	$217,784.55
	BCR::ABL1 T315I mutations	40 mg×10	$2,983.35	$1,088,922.75

Results

- Of the 3680 publications identified for all TKIs in patients with CP-CML, 116 publications (from databases and conferences) describing 35 studies were included
  - Of these, 9 studies (6 ponatinib and 3 asciminib) among R/I patients with no baseline CCyR or T315I were included for analysis
  - Of the 6 ponatinib studies, 1 study was excluded because it only contributed 2 eligible patients
- The percentage of patients with resistance ranged from 76% to 100% for ponatinib and from 35% to 61% for asciminib **(Table 2)**
- 46%–75% of ponatinib-treated patients and 40%–44% of asciminib-treated patients achieved CCyR during the follow-up time **(Table 3)**
- The pooled estimate of posttreatment CCyR for patients without baseline response was 0.48 (95% CrI: 0.43–0.53) for ponatinib and 0.42 (95% CrI: 0.34–0.49) for asciminib **(Table 3)**
- The pooled estimate of CCyR for patients with the T315I mutation was 0.65 (95% CrI: 0.56–0.74) for ponatinib and 0.44 (95% CrI: 0.24–0.64) for asciminib **(Table 3)**
- To achieve 1 CCyR among R/I patients without baseline CCyR the NNT was 2.1 (95% CrI: 1.9–2.3) patients for ponatinib and 2.4 (95% CrI: 2.0–2.9) patients for asciminib **(Figure 1)**
- The estimated 12-month CpR was lower at $476,784 ($431,499–$533,171) for ponatinib and $518,896 ($441,230–$631,620) for asciminib **(Figure 2)**
- Among patients with the T315I mutation, the NNT was 1.5 (1.3–1.8) patients for ponatinib and 2.3 (1.6–4.0) patients for asciminib **(Figure 3)**
- In the T315I subgroup, the estimated 12-month CpR achieved was lower at $351,517 ($308,452–$408,942) for ponatinib compared with $2,485,315 ($1,706,030–$4,411,298) for asciminib, wherein CrIs did not overlap **(Figure 4)**
  - The cost difference between the 2 drugs was much greater in the T315I mutation group because of the lower response rate and higher dose requirement for asciminib
- Using the NNT estimates of patients without baseline response and assuming these estimates stayed the same, increasing the percentage of patients with the T315I mutation led to gradual increase in the CpR of asciminib because of the higher drug cost of asciminib for the T315I mutation treatment; meanwhile, the CpR of ponatinib did not change **(Figure 5)**

Table 2: Characteristics among included studies in patients with CML

Study	Cortes 2012[10] N=43	PACE 2018[4] N=270	OPTIC 2021[2] N=94	Tojo 2017[11] N=17	Milojkovic 2014[12] N=51	Hughes 2019[13,a] N=141	ASCEMBL 2021[5,6] N=157	Pérez-Lamas 2021[14] N=49
Design	Phase 1 dose escalation trial	Phase 2 open-label, single-agent trial	Phase 2 open-label, dose-optimization trial	Phase 1/2 open-label, single-arm trial	Observational study	Phase 1 dose-escalation trial	Phase 3 randomized trial	Retrospective, observational study
Intervention	Ponatinib	Ponatinib	Ponatinib	Ponatinib	Ponatinib	Asciminib	Asciminib	Asciminib
Age, median (range), y	55 (27–85)	60 (18–94)	46 (19–81)	62 (20–78)	62 (20–78)	56 (25–88) for non-T315I; 54 (23–76) for T315I	52 (24–83)	65 (37–91)
Male, n (%)	21 (49)	144 (53)	50 (53)	11 (65)	NA	76 (54)	82 (52)	23 (47)
Resistant at baseline,[b] n (%)	43 (100)	267 (99)	92 (98)	13 (76)	NA	63 (45)	95 (61)	17[c] (36)
Baseline CCyR, n (%)	NA	0	0	0	NA	56 (40)	15 (10)	22[c] (47)
T315I mutation, n (%)	12 (28)	64 (24)	25 (27)	3 (18)	6 (12)	28 (20)	0	3 (6)
Any mutation, n (%)	27 (63)	—[d]	41 (44)	5 (29)	—	40 (28)	20 (13)	15 (31)

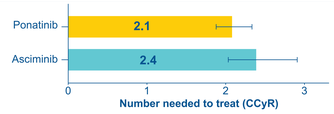
[a] In Hughes et al, the age at baseline was reported separately for patients with or without T315I mutation. The resistant patients might contain up to 9 patients with accelerated-phase CML
[b] Resistant at baseline also included patients who are both resistant and intolerant to prior TKI
[c] Percent calculation based on N=47 because 2 patients were excluded for short follow-up time
[d] The study only reported patients with T315I mutation
NA, not available

Table 3: Patients achieve CCyR over follow-up time

Study	Cortes 2012[10]	PACE 2018[4]	OPTIC 2021[2]	Tojo 2017[11]	Milojkovic 2014[12]	Hughes 2019[13]	ASCEMBL 2021[6]	Pérez-Lamas 2021[14]
Intervention	Ponatinib					Asciminib		
No baseline response								
Timepoint, wk	—	52	52	52	—	—	48	51
N	—	267	93	17	—	—	142	25
n (%)	—	123 (46)	48 (52)	10 (59)	—	—	60 (42)	10 (40)
Pooled est., % (95 CrI)	0.48 (0.43–0.53)					0.42 (0.34–0.49)		
T315I mutation								
Timepoint, wk	73	52	156	—	39	37	—	—
N	12	64	25	—	6	25	—	—
n (%)	9 (75)	42 (66)	15 (60)	—	3 (50)	11 (44)	—	—
Pooled est., % (95 CrI)	0.65 (0.56–0.74)					0.44 (0.24–0.64)		

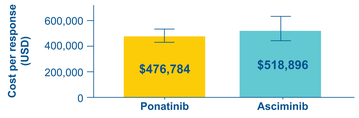
The Breccia M, et al (Ann Hematol. 2018;97(9):1577–80) study for ponatinib was excluded due to low sample size
All patients were in the third-line setting or beyond

Figure 1: NNT to achieve CCyR in R/I patients with no baseline response[a]



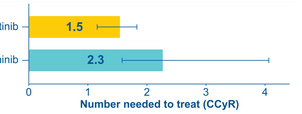
[a] The lower the NNT, the better the clinical effectiveness
Note: Whiskers illustrate the 95% CrI error bars for the NNT

Figure 2: 12-month CpR in 2022 to obtain CCyR in R/I patients with no baseline



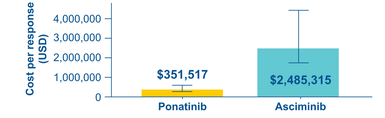
Note: Whiskers illustrate the 95% CrI error bars for the CpR

Figure 3: NNT to achieve CCyR in R/I patients with the T315I mutation[a]



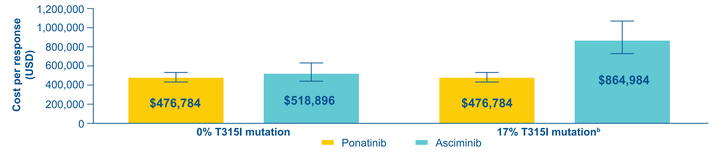
[a] The lower the NNT, the better the clinical effectiveness
Note: Whiskers illustrate the 95% CrI error bars for the NNT

Figure 4: 12-month CpR to obtain CCyR in R/I patients with the T315I mutation



Note: Whiskers illustrate the 95% CrI error bars for the CpR

Figure 5: Simulated CP-CML patient population CpR versus percentage of T315I mutation[a]



[a] The dose of asciminib for patients with T315I mutation is higher than the dose for patients without T315I mutation, leading to higher cost of asciminib for T315I mutation patients
[b] In the Branford S, et al study of 18 patients who developed resistance to imatinib, 3 patients (17%) had a T315I mutation[15]
Note: Whiskers illustrate the 95% CrI error bars for the CpR

Limitations

- Given the recent approval of asciminib by the US Food and Drug Administration (29 October 2021), we relied heavily on conference abstracts for post-approval data[16]
- Naive comparisons from studies with patients with heterogeneous baseline disease characteristics, such as resistance and intolerance, limit our ability to draw estimates of relative effect between interventions **(Table 2)**
- Further population-adjusted analysis with patient-level data may help to balance the background difference between the studies

Conclusions

- In the third-line setting and beyond, patients with CP-CML who were treated with ponatinib showed better NNT and CpR compared with those treated with asciminib, despite a higher percentage of TKI-resistant patients in the ponatinib group (76%–100%) than in the asciminib group (35%–61%); these results may inform decision-making among formulary and value assessment committees
- For patients with T315I mutations, the CpR over 1 year for asciminib ($2,485,315) could be 7-fold higher than the CpR over 1 year for ponatinib ($351,517)
- Because a higher dose of asciminib is required to treat patients with CP-CML with T315I mutations, the CpR for asciminib increased with higher T315I mutation incidence, whereas the CpR for ponatinib was not dependent on T315I mutation status

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Email for questions or comments: Elias Jabbour, ejabbour@mdanderson.org