Assessment of number needed to treat and cost per response in patients with relapsed/refractory chronic-phase chronic myeloid leukemia managed with ponatinib, asciminib, and bosutinib

CML-315

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Introduction

- In patients with relapsed and refractory (R/R) chronic-phase chronic myeloid leukemia (CP-CML), there are limited effective treatment options
  - Ponatinib (PON), the only approved pan-BCR::ABL1 inhibitor, is a third-generation tyrosine kinase inhibitor (TKI) designed to potently inhibit BCR::ABL1 with or without any single resistance mutation, 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 (ASC) is a BCR::ABL1 inhibitor specifically targeting the ABL myristoyl pocket 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]
  - Bosutinib (BOS) is a second-generation (2G) TKI indicated for patients with CP-CML and R/I to prior TKI treatment but is not indicated for patients with T315I mutations[4]
- Both PON and ASC are third-line treatment options in patients with CP-CML and are the only TKIs indicated for patients with the T315I mutation in the USA
- PON demonstrated deep, long-lasting responses with beneficial overall survival outcomes greater than 5 years in 2 pivotal trials (OPTIC and PACE);[2,5] ASC has shown a major molecular response benefit over BOS in the pivotal ASCEMBL trial with 24- to 96-week data[6,7]
- In the absence of head-to-head trials comparing PON with ASC or BOS, we analyzed response rates 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[8,9]
  - 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[10]

Objective

- To estimate the NNT and cost per response to obtain 1 CCyR for PON, ASC, and BOS 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 published between January 1, 2006, and October 26, 2021, reporting CCyR for patients with CP-CML treated with PON, ASC, or BOS whose disease was R/I to at least one 2G 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 until January 21, 2023
- Given the heterogeneity in later-line patient populations, the analysis was completed by assessing patients who are R/I and had CCyR during the >15-month follow-up (f/u) period or those 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 ($NNT=1/P_{Response}$)[9]
- The cost per response 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
PON	All *BCR::ABL1* mutations	45 mg	$596.10	$217,576.50
ASC	*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
BOS	*BCR::ABL1* non-T315I mutations	400 mg	$626.97	$228,844.05

Results

- Studies reporting CCyR with >15-month f/u for patients with R/I CP-CML after 2G TKI failure and patients with T315I with 12-month f/u were identified in the SLR
- Of 3680 identified publications, 8, 2, and 4 studies were eligible for PON, ASC, and BOS, respectively
- The pooled estimate of post-treatment CCyR for patients was 0.56 (95% CrI: 0.52–0.60) for PON, 0.45 (95% CrI: 0.37–0.53) for ASC, and 0.27 (95% CrI: 0.21–0.32) for BOS among patients with R/I CP-CML (**Table 2**)
- The pooled estimate of CCyR for patients with the T315I mutation was 0.65 (95% CrI: 0.56–0.74) for PON and 0.44 (95% CrI: 0.24–0.64) for ASC (**Table 3**)
- To achieve 1 CCyR among patients who are R/I, the NNT was 1.8 patients (95% CrI: 1.7–1.9) for PON, 2.2 patients (95% CrI: 1.9–2.7) for ASC, and 3.7 patients (95% CrI: 3.1–4.7) for BOS (**Figure 1**)
- The estimated 15-month cost per response was $508,634 (95% CrI: $474,453–$547,479) for PON, $605,099 (95% CrI: $513,755–$735,557.5) for ASC, and $980,535 (95% CrI: $811,146–$1,230,204) for BOS (**Figure 2**)
- Among patients with the T315I mutation, the NNT was 1.5 patients (95% CrI: 1.3–1.8) for PON and 2.3 patients (95% CrI: 1.6–4.0) for ASC (**Figure 3**)
- In the T315I subgroup, the estimated 12-month cost per response achieved was lower at $351,517 ($308,452–$408,942) for PON compared with $2,485,315 ($1,706,030–$4,411,298) for ASC, wherein CrIs did not overlap (**Figure 4**)
- BOS was excluded, as it is not active or indicated in patients with T315I

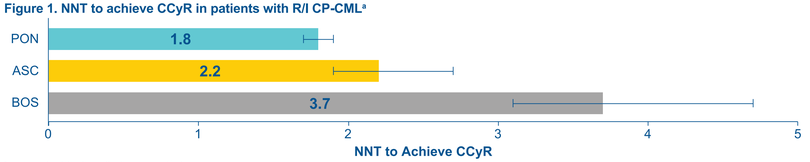
Table 2. Studies of patients with R/I CP-CML with >15-month f/u

Intervention	Study	Design	Time Point (weeks)	N	n	%	Pooled Estimate of CCyR (95% CrI)
PON	Cortes 2021 (OPTIC)[2]	Phase 2 trial	104	93	52	56	0.56 (0.52–0.60)
	Cortes 2018 (PACE)[5]	Phase 2 trial	260	267	144	54	
	Swaminathan 2018[11]	Observational study	260	71	41	58	
	Garcia-Gutierrez 2017[12]	Observational study	78	40	23	57	
	Garcia-Gutierrez 2016 (GELMC)[13]	Observational study	126	23	15	65	
	Jain 2013[14]	Observational study	97	47	26	55	
	Cortes 2012[15]	Phase 1 trial	73	43	27	63	
ASC	Rea 2021 (ASCEMBL)[6]	Phase 3 trial	96	142	64	45	0.45 (0.37–0.53)
BOS	Rea 2021 (ASCEMBL)[6]	Phase 3 trial	96	72	14	19	0.27 (0.21–0.32)
	Cortes 2019[16]	Observational study	547	34	8	24	
	Takahashi 2017[17]	Phase 1/2 trial	96	10	6	60	
	Khoury 2012[18]	Phase 1/2 trial	208	112	36	32	

Table 3. Studies of patients with CP-CML with a T315I mutation

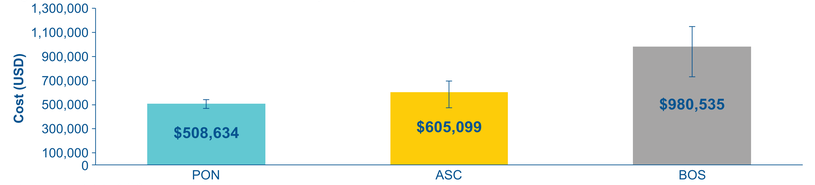
Intervention	Study	Design	Time Point (weeks)	N	n	%	Pooled Estimate of CCyR (95% CrI)
PON	Cortes 2021 (OPTIC)[2]	Phase 2 trial	52	25	15	60	0.65 (0.56–0.74)
	Cortes 2018 (PACE)[5]	Phase 2 trial	156	64	42	66	
	Milojkovic 2014[19]	Observational study	39	6	3	50	
	Cortes 2012[15]	Phase 1 trial	73	12	9	75	
ASC	Hughes 2019[20]	Phase 1 trial	37	25	11	44	0.44 (0.24–0.64)

Figure 1. NNT to achieve CCyR in patients with R/I CP-CML[a]



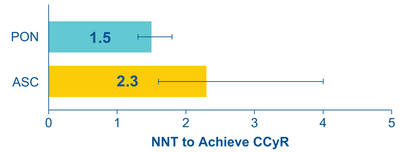
[a]The lower the NNT, the better the clinical effectiveness
Note: Whiskers illustrate the 95% CrI error bars for the NNT

Figure 2. 15-month cost per response to obtain CCyR in patients with R/I CP-CML



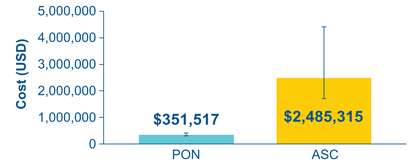
Note: Whiskers illustrate the 95% CrI error bars for the cost per response

Figure 3. NNT to achieve CCyR in patients who are R/I 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 cost per response to obtain CCyR in patients with R/I CP-CML with the T315I mutation



Note: Whiskers illustrate the 95% CrI error bars for the cost per response

Limitations

- Given the approval of ASC by the USA Food and Drug Administration on October 29, 2021, we relied heavily on conference abstracts for post-approval data[21]
- Naive comparisons from studies with patients with heterogeneous baseline disease characteristics, such as R/I, limit our ability to draw estimates of relative effect between interventions
- 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 PON showed significantly better long-term (>15 months) NNT and cost per response compared with BOS
- Additionally, PON showed favorable long-term (>15 months) NNT and cost per response compared with ASC, despite a higher percentage of TKI-resistant patients in the PON group than in the ASC group in the majority of the studies; these results may inform decision-making among formulary and value assessment committees
- For patients with T315I mutations, the cost per response over 1 year for ASC ($2,485,315) could be 7-fold higher than the cost per response over 1 year for PON ($351,517)
- The cost difference between PON and ASC was much greater in the T315I mutation group because of the lower response rate and higher dose requirement for ASC

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Acknowledgments

This study is sponsored by Takeda Development Center Americas, Inc. The authors acknowledge Kalpana Vijayan, PhD, of Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, USA, for medical writing support for the development of this presentation under the direction of the authors, which was funded by Takeda Pharmaceuticals, USA, Inc., and complied with the Good Publication Practice (GPP) guidelines (DeTora LM, et al. Ann Intern Med 2022;175:1298–1304)

Disclosures

EJ: Research grants from and advisory role for AbbVie, Adaptive Biotechnologies, Amgen, Bristol Myers Squibb, Genentech, Pfizer, and Takeda. **FH:** Employment with and ownership interest in Takeda. **MJZ:** Former employment with Cytel. **MR:** Employment with Cytel; consulting role for Takeda. **HM:** Employment with Cytel. **MY:** Former employment with Takeda. **MD:** Employment with and ownership interest in Takeda. **HK:** Honoraria from AbbVie, Amgen, ARIAD, Bristol Myers Squibb, ImmunoGen, Orsenix, Pfizer, Agios, Takeda, and Actinium; research funding (to institution) from AbbVie, Amgen, ARIAD, Bristol Myers Squibb, ImmunoGen, Pfizer, Novartis, Astex, Agios, Cyclacel, and Jazz Pharmaceuticals. **LNG:** Former president of and equity holder in Florida Cancer Specialists; board of directors for Community Oncology Alliance and Florida Society of Clinical Oncology; advisory role for Integra; equity holder in American Oncology Network; consulting for Integra, Tolmar, Janssen, and Illumina

Presented at the Eleventh Annual Meeting of the Society of Hematologic Oncology (SOHO), 6-9 September, 2023, Houston, TX, USA.

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