pan-Canadian Oncology Drug Review

Stakeholder Feedback on a pCODR Request for Advice

(Manufacturer)

Bosutinib (Bosulif) for Chronic Myeloid Leukemia

August 1, 2019

3 Stakeholder Feedback on a pCODR Request for Advice

Name of the drug indication(s): **BOSULIF (bosutinib) is indicated for the treatment of chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior TKI therapy.**

**pCODR may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

3.1 Information to inform the Request for Advice

a) Please indicate your affiliation:

__X__ Submitter/Manufacturer ____ Patient Advocacy Group ____ Registered Clinician(s)

Please include name of your organization (or individual names for registered clinicians)
Pfizer Canada ULC

b) Please provide comments on the Request for Advice question(s).

Question: Is there evidence of clinical benefit sufficient to extend reimbursement eligibility of bosutinib "for the treatment of chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior TKI therapy" without limiting it further to those "for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate"?

Evidence for clinical benefit of bosutinib in the treatment of CML patients who are resistant or intolerant to prior TKI therapy (second-line CML) is supported by the 8-year update of Study 200, well-established long-term safety profile, a Matching-Adjusted Indirect Treatment Comparison (MAIC) comparing bosutinib to other TKIs used in second line and by clinical guidelines.

Study 200

The safety and efficacy of bosutinib in patients with Ph+ leukemias who are resistant or intolerant to prior TKI therapy have been evaluated in an open-label, single-arm, phase 1/2 (Study 200) with now 8 years of follow-up.[1] This study included 288 patients who are in second line CML, 115 patients in third line CML, 3 patients in fourth line CML and 143 patients in the accelerated phase (AP) or blast phase (BP).[1-4]

In previously treated patients with CP CML, bosutinib has long-term data demonstrating

high rates of MCyR, PFS, and OS and low rates of AP/BP transformation.

The efficacy and safety of patients in second line have been reported at 2-year, 4-year, 5-year and 8-year follow-up.[1,4-7] In total, 284 patients have been followed for 96.5 months (195 patients who are imatinib-resistant and 89 patients who are imatinib-intolerant). The median follow-up was 53.7 months (range 0.5-133.1) and the median duration of treatment was 25.6 months (range 0.2-133.1). The median time from CML diagnosis was 3.7 years.[1]

Cytogenetic response

The primary efficacy endpoint was cytogenetic responses and results are presented in Table 1 for Year 2, Year 5 and Year 8:

Table 1. Cytogenetic response in second-line chronic phase (CP) CML patients[1,8]

	Imatinib-resistant (n=195)			Imatinib-intolerant (n=89)			Total (N=284)		
Follow-up duration	Year 2	Year 5	Year 8	Year 2	Year 5	Year 8	Year 2	Year 5	Year 8
Evaluable patients,† n	182			80			262		
MCyR, n (%)	102 (56.0)	107 (58.8)	110 (60.4)	49 (61.3)	49 (61.3)	48 (60.0)	151 (57.6)	156 (59.5)	158 (60.3)
CCyR, n (%)	79 (43.4)	88 (48.4)	89 (48.9)	41 (51.3)	42 (52.5)	41 (51.3)	120 (45.8)	130 (49.6)	130 (49.6)

* Includes responses newly attained or maintained from baseline.
† Received ≥1 dose of bosutinib and had a valid baseline cytogenetic assessment.
CCyR=complete cytogenetic response; CHR=complete hematologic response; CML=chronic myeloid leukemia; CP=chronic phase; MCyR=major cytogenetic response

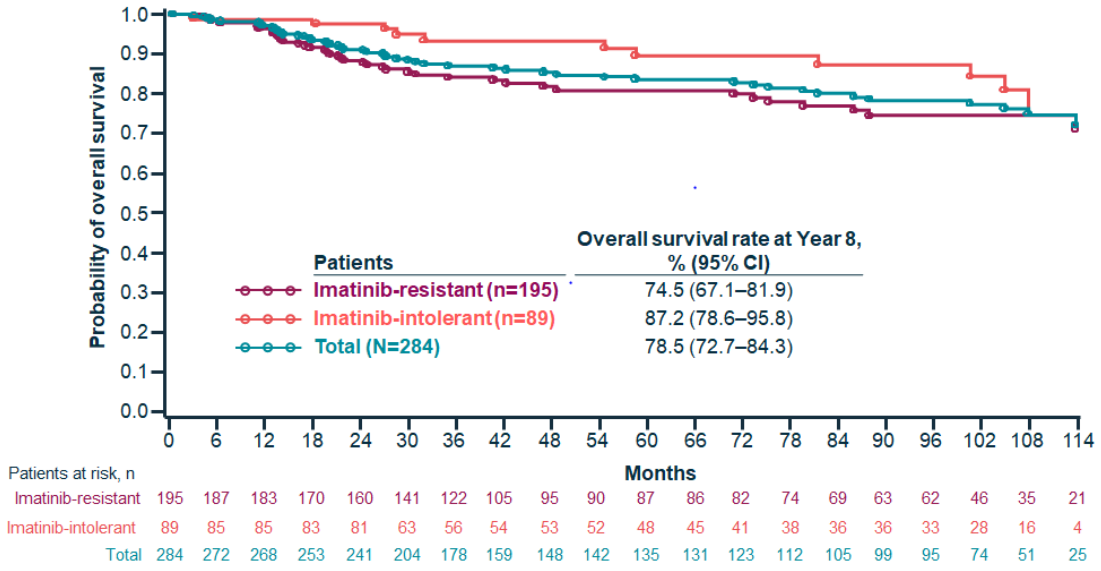
As presented in Table 1, the cytogenetic response remained consistent between Year 2, Year 5 and Year 8. There was no major difference between the imatinib-resistant and imatinib-intolerant group.

The probability of maintaining MCyR and CCyR at Year 8 was 64.5% (95% CI: 55.0%-72.5%) and 60.8% (95% CI: 50.4%-69.7%) respectively. These results are slightly decreased when compared vs previous updates. At Year 5, the probability of maintaining MCyR and CCyR was 71.1% (95% CI: 62.6%-78.0%) and 69.3% (95% CI: 59.7%-77.0%) respectively. At Year 2, the probability of maintaining MCyR and CCyR was 76.4% (95% CI: 68.5%-82.5%) and 77.8% (95% CI: 69.2%-84.2%) respectively.[1,8]

Overall survival

The overall survival (OS) was also evaluated in Study 200. The 8-year survival rate was 78.5% (95% CI: 72.7%-84.3%).

Figure 1. OS curve (8-year update)[1]

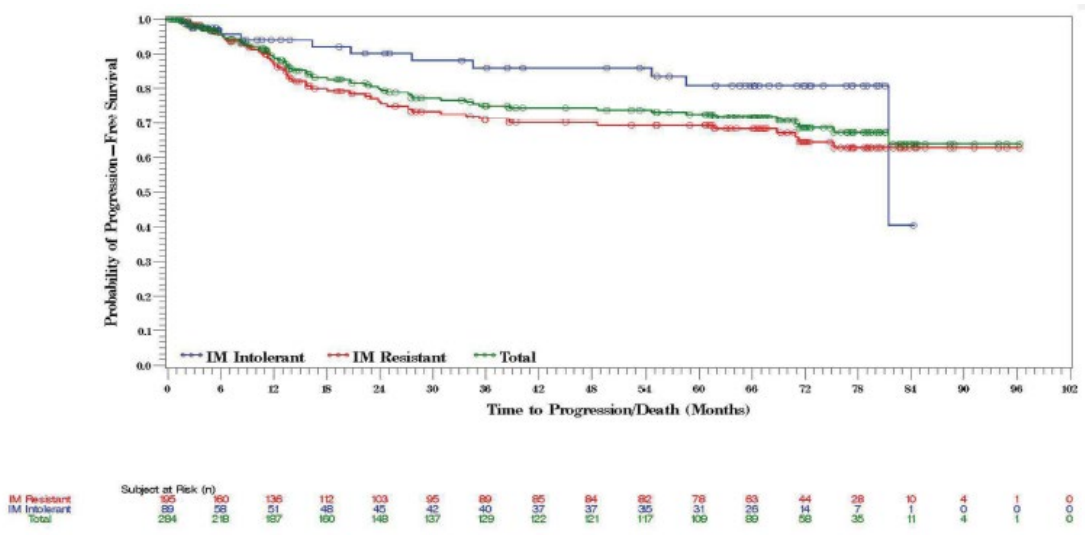


The OS rate has decreased slightly overtime. The OS rate was 91.2% (95% CI: 87.1%-94.0%) and 83.5% (95% CI: 78.1%-87.7%) at the 2-year and 5-year updates.[8]

Progression-free survival

The estimates of Progression-free survival (PFS) at 5 years was 73%; 69% for the imatinib-resistant patients and 81% for the imatinib-intolerant patients .[9]

Figure 2. PFS curves (5-year update)



At 2 years, the PFS rate was 79%, including 73% of imatinib-resistant and 95% of imatinib-intolerant patients.[4]

AP/BP transformation

Bosutinib as second-line therapy leads to low rates of transformation to advanced-phase CML and have slightly increased over time. At the 2-year update, the cumulative incidence

of transformation to AP/BP CML was 4.6% (95% CI: 2.7%-7.8%). At the 5-year update, the percentage of transformation to AP/BP was 4.9% (95% CI: 3%-8.2%). At the 8-year update, there were no new transformations to AP/BP CML.

Long-term safety

Bosutinib has a distinct, long-term safety profile that is well-established. Bosutinib is generally well-tolerated and most adverse events (AEs) were managed with standard therapies or by dose interruptions. Relative to other second-/third-generation TKIs, bosutinib generally appears to be associated with less severe AEs (eg, low incidence of cardiac, vascular occlusive, and pleural effusion events, some of which require costly management and may be associated with increased morbidity).

The most common AE associated with bosutinib is diarrhea (82%), which is mild for the majority of patients, occurs early in the course of treatment, resolves quickly, and has little to no impact on HRQOL.[9]

The manageability of diarrhea is underscored by the low discontinuation rate attributed to diarrhea (6 of 570 patients; 1%), low rate of treatment interruptions (14% of affected patients), and the high number of patients (97%) who were successfully rechallenged after treatment interruption.[9]

Bosutinib is associated with a low incidence of cardiac events, pleural and pericardial effusion, and QT prolongation.[9]

- The overall incidences of cardiac and vascular all-grade toxicities were low (9.5% and 6.8%, respectively) and remained low after long-term treatment (≥48 months of therapy).[10]

In a large meta-analysis of 10 trials (>3000 patients), no significant difference in risk of vascular occlusive events was found in patients treated with bosutinib (odds ratio [OR], 2.77; 95% CI, 0.39 to 19.77) relative to imatinib while an increased risk of vascular occlusive events was found for other new-generation TKIs, dasatinib (OR 3.86; 95% CI, 1.33 to 11.18), nilotinib (OR 3.42; 95% CI, 2.07 to 5.63), and ponatinib (OR 3.47; 95% CI, 1.23 to 9.78) vs imatinib.[11]

In the updated safety analyses based on a minimum 4-year follow-up, AEs were generally consistent with the safety profile reported in the primary analysis at 12 months.[9]

Matching-Adjusted Indirect Treatment Comparison: Bosutinib vs. Other Second-Line TKIs

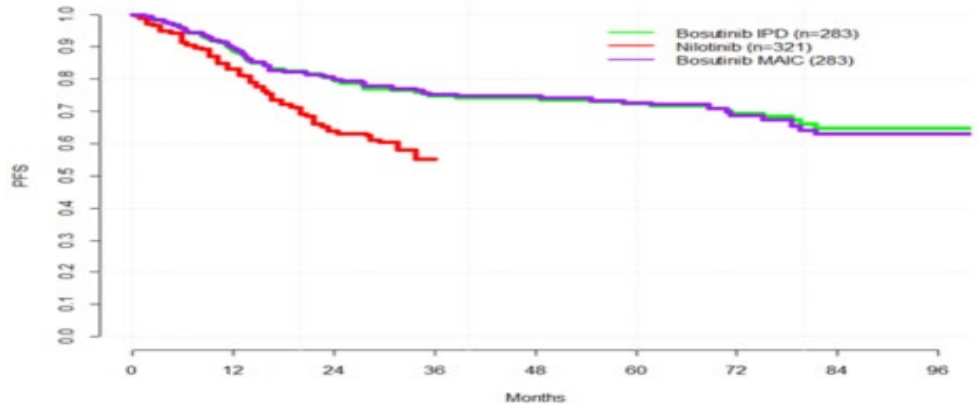
Due to the lack of available head-to-head data for TKIs in the second-line or later CP CML setting and the relative heterogeneity of patient populations and disease characteristics between second-line TKI clinical trials, a matching-adjusted indirect comparison (MAIC) was conducted. The goal of the MAIC analysis was to compare the efficacy of the long-term endpoints (PFS and OS) in CP CML patients treated with bosutinib vs. other second-line TKIs.[12]

<u>OS and PFS: Bosutinib vs. Nilotinib</u>

The OS comparison of bosutinib vs. nilotinib resulted in a non-significant hazard ratio of 1.4

(p=0.109). The PFS comparison of bosutinib vs. nilotinib resulted in a statistically significant hazard ratio of 2.0 in favor of bosutinib (p<0.01).[12]

Figure 3. MAIC of PFS: Bosutinib vs. Nilotinib

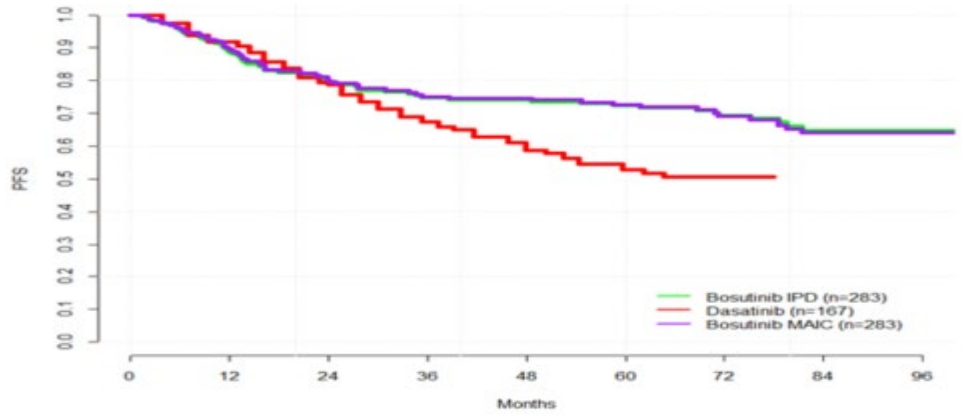


IPD = individual patient data; MAIC = matching-adjusted indirect comparison; PFS = progression-free survival

OS and PFS: Bosutinib vs. Dasatinib

The OS comparison of bosutinib vs. dasatinib resulted in a non-significant hazard ratio of 1.3 (p=0.30). The PFS comparison of bosutinib vs. dasatinib resulted in a statistically significant hazard ratio of 1.6 in favor of bosutinib (p<0.01). For PFS and OS, there was strong evidence of the proportionality assumption being violated and an additional test, the restricted mean survival time (RMST), was performed. The RMST had a statistically significant coefficient, to the advantage of bosutinib. The relative RMST were 1.123 (p=0.02) for PFS and 1.025 (p=0.41) for OS.[12]

Figure 4. MAIC of PFS: Bosutinib vs. Dasatinib



IPD = individual patient data; MAIC = matching-adjusted indirect comparison; PFS = progression-free survival

Overall, after MAICs were performed to adjust for cross-trial differences in baseline characteristics, bosutinib showed a significantly greater PFS than nilotinib. In addition, based on relative RMST analyses, bosutinib also appeared to have a greater PFS than dasatinib. OS results numerically favored bosutinib over nilotinib and dasatinib. Results of this MAIC suggest that, qualitatively, bosutinib is at least equally effective in the second-

line setting as nilotinib or dasatinib for the treatment of patients with CP CML.[12]

Guidelines

The use of bosutinib in second-line CML patients is supported by many guidelines including the National Comprehensive Cancer Network (NCCN), European LeukemiaNet (ELN) and the European Society for Medical Oncology (ESMO) guidelines.

NCCN guidelines

NCCN guidelines (2019) recommend imatinib, bosutinib, nilotinib or dasatinib as first-line treatment of CP CML. Patients with failure to a first-line TKI should be treated with bosutinib, nilotinib and dasatinib as an alternate second-generation TKI in the second-line setting.[13] The NCCN guidelines suggest considering patient comorbidities and drug toxicities when it comes to consider one TKI over another.

For switching to second-line TKI treatment based on failure to achieve treatment milestones, the mutational profile of the patient should be considered as shown in Table 2.

Table 2. Treatment Options Based on BCR-ABL1 Mutation Profile[13]

Mutation	Treatment Recommendation[m]
Y253H, E255K/V, or F359V/C/I	Dasatinib
F317L/V/I/C, T315A, or V299L	Nilotinib
E255K/V, F317L/V/I/C, F359V/C/I, T315A, or Y253H	Bosutinib
T315I	Ponatinib,[n] Omacetaxine,[o] allogeneic HCT (CML-6), or clinical trial

ELN and ESMO guidelines

The ELN guidelines (2013) and the ESMO guidelines (2017) also recommend the use of Bosutinib in second-line.[14-16]

References:

1. Brümmendorf TH, Gambacorti-Passerini C, Kim D-W, et al. Second-Line Bosutinib in Patients with Chronic Phase Chronic Myeloid Leukemia (CP CML) Resistant or Intolerant to Prior Imatinib: An 8-Year Update. Am Soc Hematology; 2017.
2. Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. *Blood.* 2012;119(15):3403-3412.
3. Gambacorti-Passerini C, Kantarjian HM, Kim DW, et al. Long-term efficacy and safety of bosutinib in patients with advanced leukemia following resistance/intolerance to imatinib and other tyrosine kinase inhibitors. *American journal of hematology.* 2015;90(9):755-768.
4. Cortes JE, Kantarjian HM, Brümmendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome–positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. *Blood.* 2011;118(17):4567-4576.
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6. Brümmendorf TH, Cortes JE, Khoury HJ, et al. Factors influencing long-term efficacy and tolerability of bosutinib in chronic phase chronic myeloid leukaemia resistant or intolerant to imatinib. *British journal of haematology*. 2016;172(1):97-110.
7. Brümmendorf TH, Cortes JE, Khoury HJ, et al. Bosutinib As Second-Line Therapy in Patients (Pts) with Chronic Phase Chronic Myeloid Leukemia (CP CML) Resistant or Intolerant to Prior Imatinib: 60-Month Update of a Phase 1/2 Study. Am Soc Hematology; 2014.
8. Gambacorti-Passerini C, Cortes JE, Lipton JH, et al. Safety and efficacy of second-line bosutinib for chronic phase chronic myeloid leukemia over a five-year period: final results of a phase I/II study. *Haematologica*. 2018;103(8):1298-1307.
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10. Cortes JE, Jean Khoury H, Kantarjian H, et al. Long-term evaluation of cardiac and vascular toxicity in patients with Philadelphia chromosome-positive leukemias treated with bosutinib. *American journal of hematology*. 2016;91(6):606-616.
11. Douxfils J, Haguet H, Mullier F, Chatelain C, Graux C, Dogné J-M. Association between BCR-ABL tyrosine kinase inhibitors for chronic myeloid leukemia and cardiovascular events, major molecular response, and overall survival: a systematic review and meta-analysis. *JAMA oncology*. 2016;2(5):625-632.
12. Muresan B, Mamolo C, Cappelleri JC, et al. Matching-adjusted indirect treatment comparison of bosutinib, dasatinib, nilotinib and ponatinib on survival for second line chronic phase chronic myeloid leukemia patients. Am Soc Hematology; 2016.
13. National Comprehensive Cancer Institute. *Chronic Myeloid Leukemia*. 2019.
14. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood*. 2013;122(6):872-884.
15. Baccarani M, Castagnetti F, Gugliotta G, Rosti G. A review of the European LeukemiaNet recommendations for the management of CML. *Ann Hematol*. 2015;94(2):141-147.
16. Hochhaus A, Saussele S, Rosti G, et al. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2017;28(suppl_4):iv41-iv51.

1 About Completing This Template

CADTH's pan-Canadian Oncology Drug Review program invites eligible stakeholders to provide feedback on the Request for Advice made by the pCODR Advisory Committee (PAC) or by the Provincial Advisory Group (PAG).

A Request for Advice is a written request made by PAC or by PAG, to the pCODR Expert Review Committee (pERC) for advice on specific therapeutic, clinical or pharmacoeconomic issues, or regarding a pERC Recommendation, which may result in a new Recommendation. The Request for Advice will be regarding a previous pERC Final Recommendation.

Stakeholders, including the submitter/manufacturer(s) of the drug(s) in question, patient advocacy groups and registered clinician(s) who provided input on the original submission in question are invited to comment or provide information using this template to help inform the question(s) or issue(s) raised by PAC or PAG ten (10) business days from the date of posting on the CADTH website.

When considering a Request for Advice, pERC may address the request by providing one of the following:

a) a revised pERC recommendation that would supersede a previous pERC Final Recommendation

b) a pERC Record of Advice document containing additional context and/or clarifications regarding a pERC Final Recommendation.

In either case, the pERC Record of Advice or revised pERC recommendation and supporting report will be posted ten (10) Business Days following the pERC Meeting on the pCODR section of the CADTH website.

2 Instructions for Providing Feedback on a pCODR Request for Advice

a) Only stakeholders who provided input on the original submission in question are invited to comment or provide information on the Request for Advice.

b) The template for providing *Stakeholder Comments on a pCODR Request for Advice* can be downloaded from the CADTH website. (See https://www.cadth.ca/pcodr/guidelines-procedures-and-templates for a description of the pCODR process and supporting materials and templates.)

c) At this time, the template must be completed in English. The comments should not exceed six (6) pages in length, using a minimum 11 point font on 8 ½" by 11" paper. If comments submitted exceed six pages, only the first six pages will be forwarded to the pERC.

d) Comments should be presented clearly and succinctly in point form, whenever possible. Comments must relate to the question at issue and the information provided must be made fully disclosable.

e) References to support comments may be provided separately.

f) The comments must be submitted via a Microsoft Word document to the pCODR program by the posted deadline date.

g) If you have any questions about the request for advice process, please e-mail info@pcodr.ca