CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

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Request for Advice

Bosutinib (Bosulif) for Chronic Myeloid Leukemia (CML)

Requestor:

pCODR Provincial Advisory Group (PAG)

Request for Advice 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"?

August 1, 2019

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Drug	Bosutinib (Bosulif)
Indication	Chronic Myeloid Leukemia
Manufacturer	Pfizer Canada Inc.

1. Executive Summary

1.1 Context for the Request for Advice

Bosutinib was recommended for reimbursement by pCODR in 2015 for "*treatment of patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) who have resistance or intolerance to prior TKI therapy, and for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate*." At that time, this reimbursement request aligned with the Health Canada Notice of Compliance with conditions (NOC/c) dated 06 March 2014.

The Health Canada Product Monograph was revised 10 December 2018, without conditions (i.e., Health Canada NOC) and 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*."

This indication no longer has the criterion of "*and for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate*". However, as of December 6, 2016, jurisdictions participating in the pCODR process funded bosutinib for CML based on the original submitted criteria (provinces of AB, MB, ON, NS, NB, and NL).

Health Canada specified that the Submitter provided the final phase 1/2 results of Study 200 along with supportive safety data. This information was required to meet the conditions in Health Canada's Notice of Compliance with conditions for bosutinib (Bosulif). As such, the restrictions of use of bosutinib in patients with CML for whom subsequent treatment with imatinib, nilotinib, and dasatinib is not clinically appropriate were removed.

PAG is seeking information on the removal of restricting the patient population to "for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate", and whether the pCODR recommendation for bosutinib for CML needs to be revised based on new data available since the final recommendation for bosutinib was issued in 2015.

pCODR Approach to the Request for Advice

A systematic review was undertaken to look for evidence to evaluate the effectiveness of bosutinib monotherapy for the treatment of chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) CML in adult patients with resistance or intolerance to prior TKI therapy.

The systematic review identified updated analyses for Study 200, match-adjusted indirect treatment comparisons (MAIC) and retrospective observational studies.

Stakeholder input was provided by Pfizer Canada Inc., the manufacturer of bosutinib, and the Chronic Myelogenous Leukemia (CML) Society of Canada, who had provided input on the original pCODR review of Bosutinib (Bosulif) for CML.

Results of the systematic review along with the stakeholder input were provided to the Clinical Guidance Panel to provide their interpretation and guidance to PAG's Request For Advice.

Refer to Appendix 3 for methodology.

1.2 Summary of Findings

Based on the results of the systematic review, there is weak comparative evidence to suggest bosutinib is a reasonable alternative to dasatinib, nilotinib, or ponatinib in patients with chronic, accelerated, or blast phase Ph+ CML who have resistance or intolerance to prior TKI therapy. Patient populations identified by the systematic review were not specific or limited further to those "for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate". The systematic review identified two matched adjusted indirect comparisons (bosutinib vs. dasatinib vs. nilotinib; bosutinib vs. ponatinib), three clinical studies (phase I/II Study 200 and Study NCT00811070; phase IV BYOND study), and four observational studies.

1.3 Clinical Guidance Panel's Interpretation and Conclusion on Request for Advice

Based on the systematic review and input from the patient advocacy group, the Clinical Guidance Panel (CGP) concluded that there is sufficient evidence of clinical benefit 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".

The CGP noted that there is no comparative randomized phase III study of bosutinib versus the other TKIs (imatinib, nilotinib, dasatinib and ponatinib) and that it is highly unlikely that a direct comparison of these agents against bosutinib after failure of two or more TKIs will be conducted in the future.

In making this conclusion, the CGP considered that:

- Data on sequencing of TKIs are limited and not informed by controlled clinical trials; decisions beyond first line therapy are also significantly influenced by the agents available for front-line therapy, clinical judgment, CML mutation status and patient comorbidities.
- Patients with CML can anticipate lifelong therapy in the majority of cases. Current TKIs including bosutinib have side effects that can affect adherence to treatment and require careful monitoring and management.
- While a significant number of patients discontinued bosutinib due to treatment-related adverse events, this did not seem to vary according to prior therapy, and seemed comparable to discontinuation rates seen with the use of imatinib, dasatinib, and nilotinib in previous trials of those agents.
- Bosutinib toxicities consist mainly of gastrointestinal effects (nausea, vomiting, diarrhea) and myelosuppression which may be successfully managed with dose interruptions and limited degree of dose reductions without an apparent loss of benefit.
- The data presented do not answer the question of whether bosutinib is better than dasatinib or nilotinib, and does not address the questions of cross-reactivity between TKIs.
- Bosutinib is not likely to be the therapy of first choice in all patients who have experienced disease progression on imatinib, but would be appropriate in instances where a second generation agent may be ineffective or inappropriate because of a known mutation or anticipated cross-intolerance, or due to an underlying comorbidity that may be exacerbated by a second generation agent (e.g. nilotinib: diabetes or peripheral vascular disease; dasatinib: asthma or prior/existing pleural effusion).
- Data on use of bosutinib in accelerated or blast phase CML are limited, but the prognosis of this patient population is very poor and the results with older aggressive induction chemotherapies are unsatisfactory. The results reported with bosutinib indicate that it may be of value for patients who have received one or two prior TKIs.
- There are insufficient data to determine the benefit of bosutinib in patients who have been treated with all three TKIs previously. In a matched adjusted indirect comparison, ponatinib appeared to have a higher rate of CCyR than bosutinib, but these comparisons have significant methodologic limitations due to unknown heterogeneity between the study populations and differences in how outcomes were assessed (e.g. PFS definitions differed between the second-line CML MAIC). The CGP however felt that it was extremely unlikely that a direct comparison of bosutinib to ponatinib or supportive care after failure of 2 or 3 prior TKIs will be conducted in the future. A comparison to supportive care only is unlikely to be acceptable to clinicians or patients with advanced CML

2. Background

Description of the Condition

Chronic Myeloid Leukemia (CML) is a clonal bone marrow stem cell disorder resulting in the unregulated growth of granulocyte precursor cells and production of excessive neutrophils, eosinophils and basophils in the bone marrow. With more routine blood counts being done as part of physicals, most patients are asymptomatic when diagnosed. Those presenting with symptoms typically present with fatigue, anemia, a high white blood cell (WBC) and platelet count, often with an enlarged spleen.

Blood and bone marrow cells in patients with CML usually contain a characteristic chromosomal abnormality resulting from a balanced translocation between chromosomes 9 and 22 (the Philadelphia chromosome, Ph+). The gene product of this BCR-ABL translocation is a tyrosine kinase that is constitutively active, resulting in the continuous activation of other cell cycle regulatory proteins and unrestrained bone marrow proliferation. This kinase is now the key therapeutic target in the treatment of CML, and the presence of cells bearing the t(9;22) translocation in the blood and bone marrow form the basis of response monitoring in this disorder.

CML accounts for approximately 10-15% of cases of leukemia diagnosed in Canada. The median age at diagnosis of CML is 65 years, with an incidence in North America of 1-2/100,000/year; it is estimated that 5890 cases were be diagnosed in the United States in 2014, and CML will be responsible for approximately 800 deaths.[1] There were 675 cases of CML diagnosed in Canada and 119 deaths in 2013, the most recent year for which there are incidence data.[2] Ph+ CML is very rare in children. In addition to age, significant radiation exposure (such as in atomic bomb survivors or nuclear reactor incidents) is a risk factor for the development of CML.

The majority of patients (>95%) with CML are in chronic phase (CP) at diagnosis. Older treatment results from chemotherapy using busulfan or hydroxyurea provided palliation of symptoms and improvements in blood counts and splenomegaly, but this was followed by progression to accelerated and blast phases which were invariably fatal. Overall survival prior to the use of modern treatment was approximately 3 to 5 years. Allogeneic stem cell transplantation from a sibling or matched unrelated donor resulted in cure of 70-80% of patient treated in CP, but this treatment was limited to younger patients and those with available donors, and applicable to less than 25% of the population. Hence, previously CML was a fatal disease for 80-90% of patients prior to the introduction of specific inhibitors of the BCR-ABL kinase, described below. For those who were not candidates for allotransplant, or for whom a donor could not be found, interferon alpha was effective in producing hematologic and occasional cytogenetic responses, but side effects limited its use to those <50 years of age.[3]

Accepted Clinical Practice

The use of oral tyrosine kinase inhibitors targeting the BCR-ABL kinase represents the standard of care for patients with newly diagnosed CP CML. Imatinib was the first drug in this class to be approved, and recent reports of improvements in population-based CML outcomes largely reflect the use of this agent.[4] Long-term follow-up of patients on the original trial comparing imatinib to interferon-cytarabine therapy shows that at 5 years, 87% of patients have had a complete cytogenetic response (no evidence of the Ph+ chromosome in the bone marrow), and only 6% have progressed to accelerated or blast phase.[5] The starting dose of imatinib is 400mg daily; comparisons of this dose to high-dose imatinib (800mg/day) showed similar rates of complete cytogenetic and major molecular response at 1 year, with fewer side effects.[6]

With additional follow up of patients treated with TKIs for CP CML, response criteria have been refined, and are summarized in table 3:[7]

Table 3: Response criteria for Chronic Phase CMP patients[7]

Time from start of therapy	Optimal Response	Treatment Failure
3 months	BCR-ABL <10% Ph+ <35% (partial cytogenetic response, PCyR)	No complete hematologic response (CHR) Ph+ >95%
6 months	BCR-ABL <1% Ph+ 0 (complete cytogenetic response, CCyR)	BCR-ABL >1% and / or Ph+ > 35%
12 months	BCR-ABL < 0.1% (major molecular response, MMR)	BCR-ABL >1% and / or Ph+ > 0
During follow-up	BCR-ABL < 0.1% (MMR)	Loss of CHR Loss of CCyR Loss of MMR mutations

Roughly 1/3 of patients treated with imatinib will discontinue therapy, due either to intolerance from side effects (diarrhea, fatigue, edema) or loss of previous molecular, cytogenetic or hematologic response because of emergence of drug resistance. A large number of mutations have been described in the BCR-ABL kinase domain that lead to drug resistance, and alternative therapies that are active in patients with resistance mutations are needed. The second generation TKIs, dasatinib and nilotinib, have a much smaller spectrum of resistance mutations, but neither are able to overcome the T315I mutation. Both of these agents produce similar rates of MMR and have similar progression-free and overall survival when used as second-line therapies.

Dasatinib and nilotinib have been compared to imatinib as initial therapy for CP CML. Nilotinib 300 mg twice daily was compared to imatinib 400 mg once daily and resulted in a significantly higher rate of CCyR after 1 and 2 years (80% vs 65%, and 87% vs 77%), a significantly higher rate of MMR after 1 year (50% vs 27%) and 3 years (73% vs 53%).[8] In a second trial, patients with newly diagnosed CP CML were randomized to dasatinib 100 mg daily vs imatinib 400 mg daily. Dasatinib resulted in a significantly higher rate of CCyR after 1 year compared to imatinib (83% vs 72%) and a significantly higher rate of MMR after 1 year (46% vs 23%) and 3 years (68% vs 55%).[9] In both of these trials, the second generation TKI also resulted in a higher proportion of patient with "deeper" molecular responses (>4.5 log reduction in BCR-ABL transcripts) compare to imatinib, a degree of response that has been associated with improved survival. Because the follow-up was short for both of these studies, however, overall survival was similar.

Current treatment recommendations of the European Leukemia Network are that imatinib, nilotinib or dasatinib are all appropriate for initial therapy for CP CML.[7] In Canada, imatinib is approved for initial therapy

in all provinces; funding for dasatinib and nilotinib varies from province to province, resulting in a heterogeneous approach to primary therapy across the country. Regular monitoring, using the above criteria to inform testing for resistance mutations or the presence of acquired cytogenetic abnormalities (e.g. loss of chromosome 7, 7q- and others), is recommended and treatment, with a second generation TKI initiated in the event of treatment failure. In addition to the presence of a mutation that may predict for reduced efficacy of a second-line agent, patients may have co-morbidities that may predict for drug-related adverse events, and make the use of dasatinib or nilotinib inappropriate. These underlying conditions include a history of pericardial or pleural effusion, or underlying cardiac disease or arterial hypertension when considering dasatinib; or pre-existing peripheral arterial occlusive disease or risk factors (smoking, diabetes, hypertension) in the case of nilotinib. In the current environment, when faced with failure or intolerance of one TKI, these conditions may only be relative contraindications; however agents that are active without the risk of exacerbating significant co-morbidities are very much needed in the treatment of CML.

Evidence-Based Considerations for a Funding Population

Bosutinib (SKI-606) is an oral, dual Src/Abl TKI with more potent inhibitory activity against Bcr-Abl than imatinib in CML cell lines. Bosutinib does not significantly inhibit c-kit or PDGF-R, which may be responsible for the side effects observed with other second generation TKIs. Phase II evaluation of bosutinib was undertaken in patients who have had previous therapy with imatinib alone, and had received either dasatinib or nilotinib as second-line therapy but had discontinued this therapy because of lack of benefit or intolerance.[10] Intolerance to imatinib, dasatinib, or nilotinib was defined as an inability to take the drug because of drug related grade 4 hematologic toxicity lasting more than 7 days, drug-related grade 3 or 4 nonhematologic toxicity, persistent grade 2 toxicity not responding to dose reduction and medical management, or loss of previously attained response on lower-dose therapy with an inabilityto receive a higher dose because of drug-related toxicity at higher doses. Mutation analysis showed that bosutinib was active in patients with a number of kinase mutations, including those known to result in resistance to dasatinib and nilotinib. Toxicity from bosutinib included myelosupression and mild elevations in liver transaminases. The Kaplan-Meier probability of retaining MCyR at 2 years was high among patients with nilotinib resistance (86%) and dasatinib intolerance (76%) but lower among those with dasatinib resistance (34%).

There are also mature data from a large phase II trial(Study 200) of bosutinib in treatment of patients with imatinib resistance or intolerance. After a median follow-up of 54 months, and median treatment duration of 26 months (longest duration 96 months), the cumulative response rates (new or maintained from baseline) were: MMR 46% and CcyR 58% at 2 years, and MMR 60% and CcyR 58% at 5 years. 169 patients had discontinued bosutinib at 5 years: of the 38 patients who stopped study treatment after 2 years, 11 did so for progressive disease. Of those who discontinued treatment because of toxicity, 85% did so during the first 2 years. New-onset toxicity after the first year was uncommon. Of the 85 patients with a specific adverse event cited as the reason for imatinib discontinuation (intolerance), 52 (61%) experienced the same AE with bosutinib, but only 14 had cross intolerance (stopped bosutinib for the same toxicity as imatinib). Therefore, bosutinib represents a potentially attractive new therapy for patients who have experienced treatment failure after imatinib as primary therapy, and nilotinib or dasatinib as second-line treatment, with an acceptable toxicity profile. Based on the high MCyR rate in patients who were intolerant to imatinib or experienced treatment failure, bosutinib is an important option for those patients with comorbidities predicting adverse events with the use of nilotinib or dasatinib, making the choice of the latter second-generation agents inappropriate.

Other Patient Populations in Whom the Drug May Be Used

Two trials have been reported comparing bosutinib to imatinib in previously untreated patients with chronic phase CML. The BELA trial randomized patients to bosutinib 500mg daily (n=250) or imatinib 400mg daily (n=252).[11] Rates of complete cytogenetic response (the primary study endpoint) were similar for bosutinib and imatinib at 12 months (70% vs 68%) and at 24 months (79% vs 80%, respectively); however, major molecular response rates were higher for bosutinib at 12 (41% vs 27%, p <.001) and 24 months (59% vs 49%, p value not stated). Rates of treatment discontinuation due to toxicity was more common in patients receiving bosutinib (25%) than those treated with imatinib (9%). There was no difference in event free or overall survival between treatment arms.

More recently, a second randomized trial was reported evaluating a lower dose of bosutinib 400 mg daily (n = 268) compared to imatinib 400 mg daily (n =268).[12] At a median follow-up of 15 months, there was a higher MMR at 12 months in patients receiving bosutinib (47.2%) compared to imatinib (36.9%, p=.02) and higher CCyR (77.2% vs 66.4%, p=.0075). discontinuation of therapy occurred in 22% of patients receiving bosutinib compared to 27% of imatinib-treated patients; discontinuation of therapy due to toxicity occurred in 12.7% of those on bosutinib compared to 8.7% of imatinib-treated patients. Patients treated with bosutinib experienced more grade 3 diarrhea (7.8% vs 0.8%) and more frequent grade 3 elevation of ALT (23.1 vs 2.3%) and AST (11.9 vs 3.0%); cardiac events and pleural effusions were rare. Treatment failure led to discontinuation in 2.2% of patients on bosutinib and 7.5% of patients on imatinib.

These trials suggest that bosutinib may have advantages in the front line setting over imatinib in terms of MMR and CCyR, with a different safety profile.

3. Stakeholder Input

Stakeholder Input was provided by two groups. Pfizer Canada Inc., the manufacturer of bosutinib (Bosulif) and The Chronic Myelogenous Leukemia (CML) Society of Canada, who had submitted patient input for the bosutinib (Bosulif) pCODR review. The information pertaining to the request for advice is provided below as it was provided by the stakeholder.

3.1 Manufacturer Input on RFA from Pfizer Canada Inc.

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.[13] 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).[10,13-15]

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.[10,13,16,17] 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.[13]

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[13,18]

	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)

	Imatinib-resistant (n=195)			Imatinib-intolerant (n=89)			Total (N=284)		
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

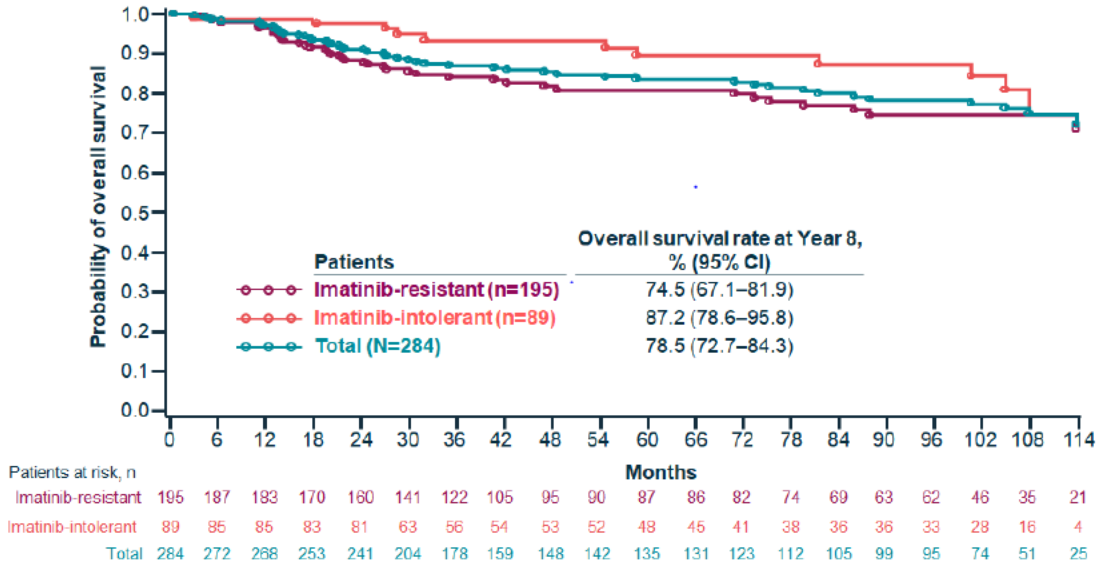
As presented in Table 1, the cytogenetic response remained consistent between Year 2, Year 5 and Year 8. There was no major difference between the imatinib-resistant and imatinib-intolerant group.

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.[13,18]

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)[13]

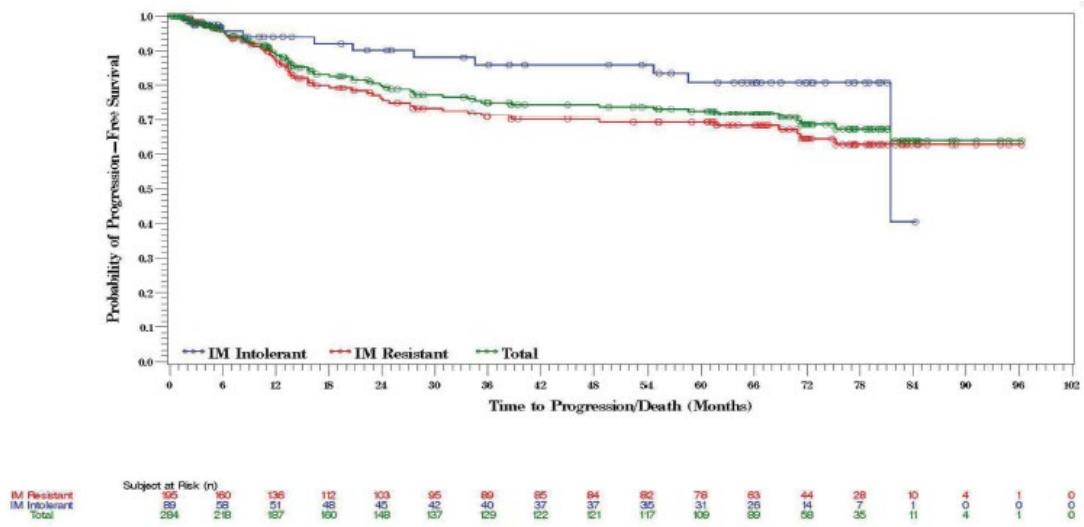


The OS rate has decreased slightly overtime. The OS rate was 91.2% (95% CI: 87.1%-94.0%) and 83.5% (95% CI: 78.1%-87.7%) at the 2-year and 5-year updates.[18]

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.[19]

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.[10]

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.[19]

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.[19]

Bosutinib is associated with a low incidence of cardiac events, pleural and pericardial effusion, and QT prolongation.[19]

- 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).[20]

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.[21]

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.[19]

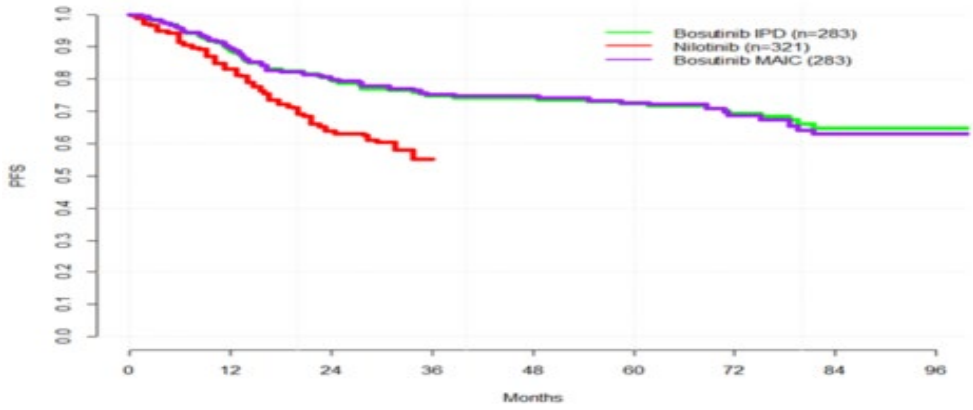
Matching-Adjusted Indirect Treatment Comparison: Bosutinib vs. Other Second-Line TKIs

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.[22]

OS and PFS: Bosutinib vs. Nilotinib

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).[22]

FIGURE 3. MAIC OF PFS: BOSUTINIB VS. NILOTINIB

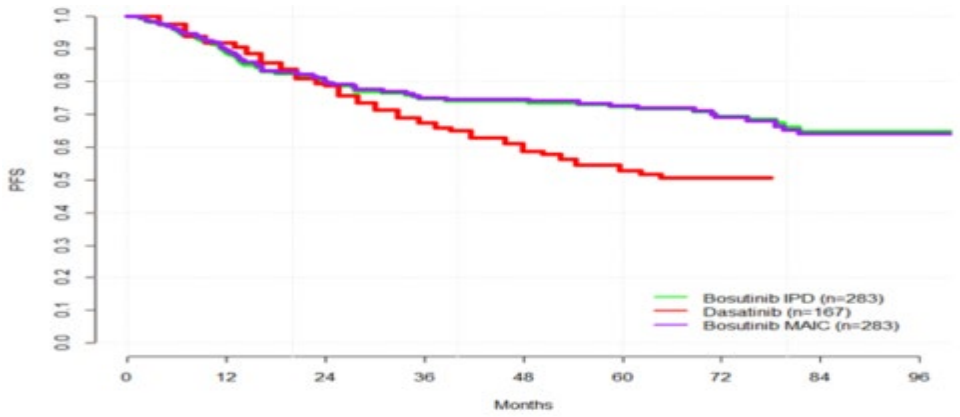


IPD = individual patient data; MAIC = matching-adjusted indirect comparison; PFS = progression-free survival

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.[22]

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.[22]

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.[23] 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[23]

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.[7,24,25]

3.2 Patient Advocacy Group Stakeholder Feedback on RFA from The Chronic Myelogenous Leukemia (CML) Society of Canada

We interviewed several patients who are currently being treated with Bosutinib in Canada, who had been treated with other TKI's and were either resistant or intolerant to the other TKI's currently available for treatment of chronic phase (CP) CML.

The majority of patients reported being started on imatinib/Gleevec at diagnosis of CP CML. Initial response to therapy was good, in the majority of the cases. Although one patient reported that there was little clinical response to imatinib with highly intolerable side effects almost immediately at the start. In the other patients, who reported a good response initially to imatinib and a reasonable ability to tolerate side effects, it was a build up of side effects that eventually led to an overall intolerability of the drug, which triggered the switch to another TKI. One patient reported being started on dasatinib/ sprycel at diagnosis. They reported this drug worked very well for about 3 years. Unfortunately the patient developed severe pleural effusions during the 4th year of treatment which necessitated a TKI change.

The majority of the patients switched to dasatinib (Sprycel) as an alternative, with the exception of the one patient who started nilotinib (Tasigna). The patient on nilotinib reported that unfortunately nilotinib triggered severe reactions and was only able to stay on this treatment for 6 weeks. This patient later went on to Gleevec.

The patients who reported being treated with dasatinib as a 2 nd line treatment, all reported good clinical responses and excellent tolerability. However, in all cases, after a few years of treatment, serious complications of pericarditis, pleural effusions, necessitated another TKI change.

With the exception of the one patient mentioned earlier, all of the patients we interviewed reported to us that they are very reluctant to try nilotinib given the black box warning. The patients told us that un less they were given the option of a thorough cardio oncology work up, they would not consider trying that drug. We should point out that the majority of the patients we interviewed for this report were below the age of 40 and were diagnosed in their early thirties. We realize that we naturally attracted this age group because our outreach was mainly conducted on-line, through patient chat groups and through appealing to current CML patients being treated with bosutinib via our Facebook page. None-the-less, this patient group is very concerned with QoL, being able to work and provide for their young family, while making treatment choices that may help them preserve their health over the long term treatment.

All of the patients we interviewed and have provided history for here are currently being treated with bosutinib. All of the patients reported to us, as of the time of their interview with us, they are

experiencing good clinical results and better tolerability then what they had experienced with their prior TKI therapy. All patients reported going through a few weeks of adjustment to bosutinib which included severe diarrhoea, which was well managed, but has improved significantly.

As a side note, particularly in the younger patient population, these patients do not consider that they have four TKI's to chose from. Interestingly, some of the patients we interviewed hinted to us that they may have chosen to move away from imatinib as they were concerned about being forced to try a generic version, which they have been told is not equivalent or safe as the branded. So, it may have been a combination of the build up of side effects along with the anxiety of having to move to a generic drug that escalated the need for a switch in TKI. We are very concerned about this and would be very concerned if this becomes a trend in general. It is important that we recognize this fact and manage it better. As of January 1, 2020 dasatinib will become generic. Patient education on generics will be very important as it will further reduce 'perceived choices' in TKI treatment for a sub set of this patient population.

The CML Society of Canada will certainly need the help of the community and CADTH to better educate this important patient population.

4. Systematic Review

4.1 Objectives

To evaluate the effectiveness of bosutinib monotherapy for the treatment of chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) CML in adult patients with resistance or intolerance to prior TKI therapy.

4.2 Methods

4.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol for the request for advice was developed jointly by the Clinical Guidance Panel and the pCODR Team. Studies were chosen for inclusion in the review based on the criteria in the table below.

Table 3: Selection Criteria

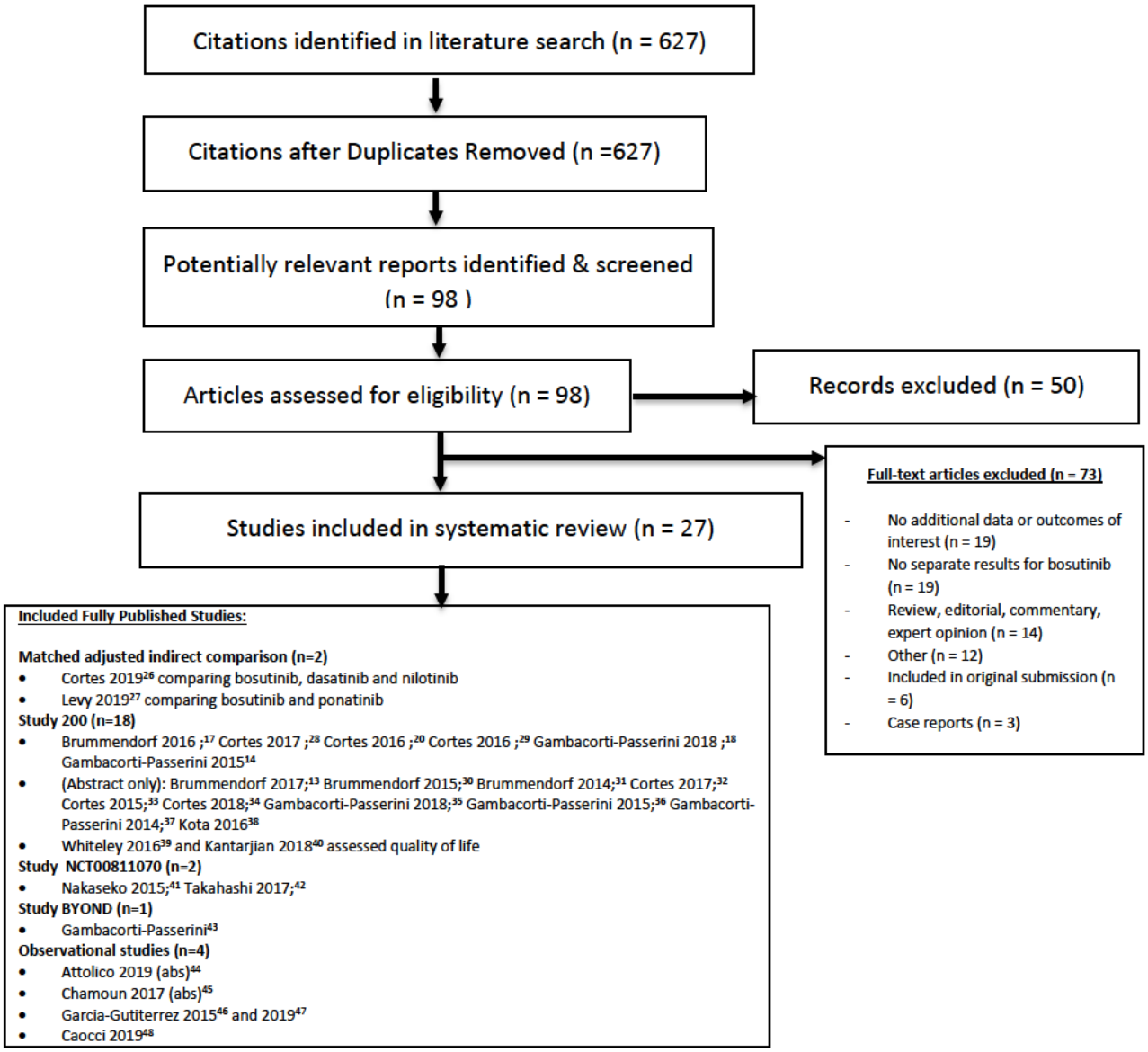
Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCT In the absence of RCT data, published: • clinical trials investigating the efficacy of bosutinib • Non-randomized clinical trials • Observational studies • Indirect treatment comparisons Exclusions: • Case Reports Reports of trials with only a dose-escalation design	Patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) CML with resistance or intolerance to prior TKI therapy	Bosutinib monotherapy (500 mg QD)	Best Supportive Care or no comparator in the case of single arm studies Dasatinib Nilotinib Ponatinib	OS PFS Hematologic Response Cytogenic Response Molecular Response Quality of Life Grade 3 or 4 Adverse events WDAE
Notes: CML= Chronic Myeloid Leukemia; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; QD=Once daily; Ph+ = Philadelphia chromosome-positive; QOL=quality of life; RCT=randomized controlled trial; TKI= tyrosine kinase inhibitor.				

4.3 Results

4.3.1 Literature Search Results

Of the 98 potentially relevant reports identified, 27 studies were included in the pCODR systematic review and 73 studies were excluded. Most studies were excluded because there were no additional data or outcomes of interest; no separate results for bosutinib, or they were review, editorial, commentary, or expert opinion pieces. Of the included studies, two were full publications of matched adjusted indirect comparisons, Study 200 was represented in 18 publications (8 full publications and 10 abstracts), Study NCT00811070 in two full publications, Study BYOND in one abstract, and four observational studies (two full publications and two abstracts).

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



4.3.2 Summary of Included Studies

Eighteen publications on the phase I/II Study 200 investigating the efficacy of bosutinib were included, six of which were fully published and twelve were abstract only publications. This systematic review included results from Study 200 from the latest cut-off dates available (and where applicable, full publications). Data from earlier cut-off points or abstracts were similar and confirmed the results observed in final analyses/full publications. Two full-text publications on the phase I/II study in Japanese patients with any-phase Ph+ CML. One abstract on phase IV BYOND study of bosutinib in pretreated CP CML patients.

Four publications for match adjusted indirect treatment comparisons were included, two of which were fully published and two were abstracts of the fully published studies.

In addition, four observational studies were included, two of which were fully published studies for fourth line treatment of patients with CML with bosutinib.

4.3.2.1 Detailed Trial Characteristics

The table below highlights key study characteristics between all included studies.

Table 4: Summary of Study Characteristics of the Included Studies

Study Design	Population/Inclusion Criteria	Intervention and Comparator	Outcomes
Matched adjusted indirect treatment comparisons			
Cortes JE et al, 2019[26] Match adjusted indirect treatment comparison comparing bosutinib, dasatinib and nilotinib for CP-CML. Cox-proportional hazard ratio regressions were used for odds ratios and restricted mean survival (RMST)	Second-line CP-CML patients, only trials with three of more years of follow-up were included	Bosutinib 500mg/d Dasatinib 100mg/d Nitonib 400mg twice daily	OS PFS MCyR by 24 months
Levy MY et al, 2019[27] Match adjusted indirect treatment comparison comparing ponatinib and bosutinib using benefit risk profiles and adjusting for trial patient characteristics Published data from bosutinib trial and individual patient level data from ponatinib pivotal trial were used.	Third line CP-CML patients, 4 year follow-up data used from Study 200 for bosutinib; most recent individual level data on file for ponatinib	Bosutinib 500mg/d (as per Study 200) Ponatinib 45mg/d (as per PACE trial)	OS PFS MCyR Duration of Cytogenetiic response PFS Treatment duration Treatment discontinuation
Clinical trials investigating the efficacy of bosutinib			

Study Design	Population/Inclusion Criteria	Intervention and Comparator	Outcomes
Study 200[6]			
Gambacorti-Passerini C et al, 2018[18] Final results of Study 200 from at least 5 years from the time the last patient was enrolled. Methods previously described.	Imatinib-resistant or imatinib-intolerant CP CML	Bosutinib 500 mg/d	MCyR CCyR MMR PFS OS Time to on-treatment transformation to AP/BP CML AEs TEAEs
Kantarjian et al, 2018[40] Patient-reported HRQOL was assessed with the EuroQol 5-Dimensions Questionnaire (EQ-5D) and the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu). Descriptive statistics were obtained for the scale scores and mean change from baseline score at each timepoint. Had 264 weeks or more of follow-up.	A total of 403 patients composed the safety population (i.e., they had received 1 or more doses of bosutinib), 284 and 119 patients were in the CP2L and CP3L cohorts, respectively. Bosutinib-treated patients with Ph+CML and resistant or intolerance to 1 (CP2L, n=284) or more (CP3L, n=119) TKIs	Bosutinib 500 mg/d	EQ-5D and Fact-Leu assessments at baseline, weeks 4, 8, 12, every 12 weeks thereafter, and at treatment completion. HrQoL was also assessed in a post hoc assessment of a subset of patients with chronic diarrhea to determine how this AE affects patient HrQoL
Cortes et al, 2017[28] The objectives were to assess the extent and time course of renal dysfunction, to identify predictors of Grade ≥3b eGFR in bosutinib-treated patients, and to evaluate reversibility of treatment-emergent eGFR decline. Additionally, the effect of Grade ≥3b eGFR on the efficacy of bosutinib across treatment lines was evaluated. Time from the last patient's first dose to data cut-off was ≥48 months.	Patients with Ph+ leukemias receiving first-line bosutinib (n=248) or imatinib (n=251), or second-line or later bosutinib (n=570).	Bosutinib 500 mg/d	Incidence of renal adverse events and estimated glomerular filtration rate
Brummendorf T et al, 2016[17]	Adults with imatinib (IM)-resistant (IMR; n = 196) / IM-intolerant (IM-I; n = 90) chronic phase (CP) CML	Bosutinib 500 mg/d	Demographic and baseline patient characteristics as

Study Design	Population/Inclusion Criteria	Intervention and Comparator	Outcomes
Retrospective, exploratory analysis assessed effects of baseline patient characteristics on long-term efficacy and safety and assessed response durability, ≥48 months after the last patients' first visit.			predictors of MCyR or CCyR by 3 months, PFS, OS, time to first grade 3/4 diarrhea or liver-related AEs
Cortes JE et al, 2016[20] A retrospective analysis of two large clinical trials (phase 3 BELA and phase 1/2 Study 200). Follow-up time was ≥48 months (both studies).	Second-/third-/fourth-line bosutinib for Ph+ leukemia resistant/ intolerant to prior TKIs (N=570). First-line bosutinib (n=248) versus imatinib (n=251) in chronic phase chronic myeloid leukemia	Bosutinib 500 mg/d	Vascular/cardiac toxicities associated with long-term bosutinib treatment based on TEAEs and changes in QTc intervals and ejection Fraction.
Cortes et al, 2016[29] Long-term (≥48 months) efficacy and safety of third-/fourth-line bosutinib in adults with chronic phase (CP) CML. Also exploratory analyses assessing baseline predictors of long term outcomes.	Third- and fourth-line bosutinib therapy in an ongoing phase 1/2 trial in patients with CP CML resistant/intolerant to imatinib plus dasatinib and/or nilotinib.	Bosutinib 500 mg/d	Multivariable analyses evaluated baseline characteristics as predictors of MCyR, CCyR, PFS, OS, time to first diarrhea AE (grade 3/4) or liver-related AEs (any grade and grade 3/4)
Whiteley et al, 2016[39] Patient-reported HRQoL assessments completed at baseline; weeks 4, 8, and 12; every 12 weeks thereafter; and at treatment completion. Used FACT-Leu, general health status using 5-item EuroQoL (EQ-5D) instrument and a VAS. 96-week follow-up duration.	76 accelerated-phase (AP) and 64 blast-phase (BP) patients resistant/intolerant to prior imatinib with or without prior exposure to other TKIs	Bosutinib 500 mg/d	EQ-5D Utility scores, VAS scores FACT-Leu scores and MIDs from baseline
Gambacorti-Passerini C et al, 2015[14] The data include a long-term follow-up to ≥4 years after the last patients' first visit.	AP or BP CML or Ph+ ALL (n=167) Who were resistant/intolerant to prior imatinib and were allowed to have received prior dasatinib and/or nilotinib	Bosutinib 500 mg/d	Durability of response and long-term safety
Study NCT00811070			
Phase 1/2 study in Japanese Subjects with Philadelphia Positive Leukemia[41,42]	63 patients with CP or ADV CML who were resistant/refractory or intolerant to prior TKI treatment	Bosutinib 500 mg/d (Phase II)	Long-term efficacy and safety: CCyR,

Study Design	Population/Inclusion Criteria	Intervention and Comparator	Outcomes
Median bosutinib follow-up of 132 weeks (range 3–372)[42].			MCyR, CMR, MMR, PFS, OS Additional: cCHR, cOHR, TTF
Study BYOND			
Phase 4 study of bosutinib for pretreated CP CML[43] Median follow-up of 30.4 months	163 patients, 156 patients had Ph+ CP CML (46, 61, and 49 after 1, 2, and 3 prior TKIs, respectively)	Bosutinib (500 mg/d)	Primary endpoint of cumulative confirmed major cytogenetic response (MCyR) by 1 year
Observational Studies			
Attolico et al, 2018[44] Retrospective analysis of efficacy and real life bosutinib administration from 22 Italian Hematological Institutions. Median follow-up of 26 months (range 3-49).	85 CP CML patients R/I to other TKIs	31 patients (36%) started at the full standard dose of 500 mg[%]	MMR, DMR, CHR, PCyR, CCyR, AEs
Chamoun et al, 2017[45] Analysed outcome of patients at a single institution with 2nd generation TKI in the 2nd line following failure of frontline TKI. Median follow-up from diagnosis of 96 months (range 4-283).	621 patients with CML following failure of frontline TKI; 572 patients received second-line TKI	Dasatinib (n=338, 54%) Nilotinib (n=194, 31%) Bosutinib (n=40, 6%) Dosing: NR	MCyR, PCyR, CCyR, MMR, transformation to AP/BP, OS, TFS, EFS
Garcia-Gutierrez V et al, 2019[47] *Retrospective Cohort Analysis of patients with CP-CML who have failed imatinib, dasatinib and nilotinib* *Patients treated between Nov 2011 and Jan 2016*	62 CML fourth-line patients treated with bosutinib between Nov 2011 and Jan 2016. Bosutinib prescribed after intolerance or failure to previous TKIs (imatinib, dasatinib and nilotinib). Chronic Phase (CP), Blast Phase (BP) and Accelerated Phase (AP) evaluated according to European LeukemiaNet (ELN) 2013 recommendations	500mg QD for patients resistant or intolerant to prior therapy	Event Free Survival (EFS) Progression Free Survival (PFS)
Caocci et al, 2019[48]	Adult patients with CML who were initiated on 2nd and 3rd generation TKIs between 2012 and 2017 at 17 Italian centers. All patients had previous history of arterial occlusive events (AOEs), including myocardial infarction, angina, stroke, peripheral	Bosutinib** Dasatinib Ponatinib Nilotinib	AOEs

Study Design	Population/Inclusion Criteria	Intervention and Comparator	Outcomes
	artery disease, and ischemic cerebrovascular events		

[%] Initial dose was 100 mg in 4/85 patients (5%), 200 mg in 24 (28%), 300 mg in 18 (22%), 400 in 8 (9%)

** TKI dosage strengths not reported

a) Studies

For Study 200, data from full-publications with the latest follow-up period are presented in this review with updated data from abstracts where applicable.

For Study NCT00811070, data from two full-publications were included with 8 year follow-up.[42]

For Study BYOND, data from one abstract was presented in this review.[43]

Two Match Adjusted Indirect Comparisons (MAIC) were included. The MAIC conducted by Levy et al.[27], looked at the comparison of boustinib and ponatinib in the third treatment of CML and the MAIC conducted by Cortes et al.,[26] looked at the comparison of all second line CP CML treatment options, including nilotinib and dasatinib.

Two institutional observation studies[44,45] were included on real-world bosutinib use in Italy (n=85, 22 Italian Hematological Institutions) and one location not reported (n=621, 1 institution). In addition, one Spanish retrospective cohort for the use of bosutinib in fourth line was included; two individual fully published studies from the Spanish compassionate access program are reported.[46,47]

In addition, one cohort of Italian CML patients treated with second or third generation TKI outside clinical trials, with a previous history of a cardiovascular event, reported on arterial occlusive events (AOEs).[48]

b) Populations

The population of Study 200 was previously described in the pCODR original submission and are presented in Table 5. Other publications on Study 200 included the following subgroups of the entire population[28,32,34,35,38] of patients with either CP CML or ADV (AP/BP CML or Ph+ALL): CP-CML,[18,20,40] CP2L,[13,17,30,31,33] CP3L,[29,37] AP and BP CML.[14,36,39]

Table 5: Baseline Patient Characteristics Across Studies

Included Publications	Phase	# of patients	Median age (range)	Male, n (%)	ECOG PS	Median time since CML diagnosis, y (range)	# of Prior Lines of Therapy	Prior therapy	Follow-Up Time, months (range); Treatment Duration	Analysis Date
MAIC										
Levy et al., 2019**[27]	CP3L	n=119 for bosutinib n=97 for ponatinib n=70 for ponatinib matched population	>56.0 years Bosutinib (50.0%) Ponatinib (53.6%) Ponatinib adjusted (50.0%)	Bosutinib=44.5% Ponatinib = 51.5% Ponatinib matched adjusted = 44.5%	ECOG PS of 1- Bosutinib = 27.7% Ponatinib =29.9% Ponatinib matched =27.7%	>6.6 years Bosutinib - 50% Ponatinib - 42.3% Ponatinib matched - 50%	Bosutinib = 113 in 3L and 3 in fourth line Ponatinib = 97 in 3L	Imatinib Dasatinib Nilotinib	Bosutinib - 4 year follow up; median treatment duration: 38.4 (0.2-58.1) months Ponatinib = 2.25 years additional to PACE; median treatment duration: 8.6 (0.2-87.7) months	Bosutinib - 4 year follow-up Ponatinib - Aug 3, 2015
Cortes et al., 2019[26]	CP2L	Dasatinib - 670 Nilotinib - 321 Bosutinib - 288	Dasatinib - 56 Nilotinib - 58 Bosutinib - 53	Dasatinib - 50% Nilotinib - NR Bosutinib - 52%	NR	NR	NR	NR	Dasatinib - 6 year Nilotinib - 4 years Bosutinib- 8 year	NR
Study 200										
Gambacorti-Passerini C et al, 2018[18]	CP2L	284 IM-R (n=195); IM-I (n=89)	53 (18-91)	149 (52)	0: 76% 1: 23% 1: <1%	3.7 (0.1-15.1)	1: 65% 2: 35% 3: 0% 4: 0%	SCT: 3% Interferon: 35%	54.8 (0.6-96.3); 25.6 (0.2-96.3)	October 2 2015, at year 5. 115 (40%) patients were receiving treatment

Included Publications	Phase	# of patients	Median age (range)	Male, n (%)	ECOG PS	Median time since CML diagnosis, y (range)	# of Prior Lines of Therapy	Prior therapy	Follow-Up Time, months (range); Treatment Duration	Analysis Date
Cortes et al, 2016[29]*	CP3-4L	119 IM+D-R (n=38) IM+D-I (n=50) IM+N-R (n=26) IM+N±D (n=5)	56 (20-79)	56 (20-79)	0: 71% 1: 28% Missing: 1%	6.6 (0.6-18.3)	2: 44% 3: 55% 2: 2%	IM+D: 77% IM+N: 26% IM+D+N: 3% Interferon: 55% SCT: 8%	32.7 (0.3-93.3); 8.6 (20.2-87.7)	May 23, 2014, 4-year update. The time from the last patient's first dose to data cut-off was 50.2 months. 29 (24%) patients were still receiving bosutinib at the 4-year follow-up.
Gambacorti-Passerini C et al, 2015[14]	AP CML	79	51 (18-83)	44 (56)	0: 57% 1: 41% 2: 3%	5.6 (1.1-22.1)	1 (l): 37% 2: 32% ≥3: 32%	IM: 100% D: 32% N: 19% Interferon: 52% SCT: 9%	28.4 (0.3-88.6); 10.2 (0.1-88.6)	May 23, 2014 based on an unlocked database for this interim manuscript, 14 (18%) AP CML, 2 (3%) BP CML, and 1 (4%) ALL patient was still receiving bosutinib at 4 years
	BP CML	64	47 (19-82)	42 (66)	0: 34% 1: 45% 2: 20%	3.3 (0.4-14.5)	1 (l): 47% 2: 27% ≥3: 27%	IM: 100% D: 34% N:17% Interferon: 31% SCT: 6%	10.4 (0.4-79.9); 2.8 (0.03-55.9)	
	ALL	24	59 (24-84)	12 (50)	0: 38% 1: 42% 2: 21%	1.0 (0.1-20.0)	1 (l): 63% 2: 33% ≥3: 4%	IM: 100% D: 33% N: 4% Interferon: 4% SCT: 13%	3.6 (0.4-89.2); 0.97 (0.3-89.2)	
Study NCT00811070										

Included Publications	Phase	# of patients	Median age (range)	Male, n (%)	ECOG PS	Median time since CML diagnosis, y (range)	# of Prior Lines of Therapy	Prior therapy	Follow-Up Time, months (range); Treatment Duration	Analysis Date
Takahashi 2017[42&]	CP2L	45	55 (20–78)	26 (58)	0: 89% 1: 11%	NR	NR	IM: 100% D: 0 N: 0	240 weeks (3–372); 240 weeks (1–372)	8 years, final data (August 7, 2015) 29 patients (46%) continued treatment until study completion and 34 patients (54%) discontinue study treatment.
	CP3L	10	49 (34–69)	6 (6)	0: 90% 1: 10%	NR	NR	IM: 100% D: 80% N: 20%	126 weeks (105–160); 126 weeks (13–160)	
	ADV	8	64 (55–78)	7 (88)	0: 75% 1: 25%	NR	NR	IM: 100% D: 13% N: 0	66 weeks (17–179); 10 weeks (1–179)	
Study BYOND										
Gambacorti-Passerini et al, 2019[43,49%]	CP	163	61	NR (51.9)	NR	NR	1: 30% 2: 39% 3: 31%	Prior treatment with ≥1 TKI (I, D, and/or N)	30.4 months (NR); NR	One year after last enrolled patient, 56.4% of patients were still on treatment.
Observational Studies										
Attolico et al, 2018[44]	CP	85^	60 (18-90)	NR	NR	44 (10-204)	<3: 28% ≥3: 72%	NR	26 months (3-49), NR	75/85 (88%) were alive and 54/75 (72%) were still in treatment.

Included Publications	Phase	# of patients	Median age (range)	Male, n (%)	ECOG PS	Median time since CML diagnosis, y (range)	# of Prior Lines of Therapy	Prior therapy	Follow-Up Time, months (range); Treatment Duration	Analysis Date
Chamoun et al, 2017[45]	CP2L	621[$]	47 (12-86)	49%	NR	32 (0-206)	NR	1L TKI: 516 Interferon or chemotherapy: 105	NR	Median follow-up from diagnosis of 96 months (range 4-283)
Garcia-Gutierrez et al, 2019[47]	CP4L	62	NR	NR	NR	105.4 months (9.2-163.2)	NR	NR	Median follow-up: 14.3 (0.5-36.1) Median duration of bosutinib: 9.12 (6.5-18.37)	Nov 2011 - Jan 2016
Caocci et al, 2019[48]	NR	57	52 (45-87)	NR	NR	NR	>1: 41 >2: 16 >3: 4	NR	NR	60 months after initiating treatment with 2nd/3rd generation TKI

*Patients who received >1 treatment with IM, N, D, or interferon were counted once for the respective treatment. &Starting dose of bosutinib was 500 mg for CP3L/ADV; and 35 (78%) of CP2L. ^60 (71%) were resistant/refractory, 25 (29%) were intolerant to previous TKIs.
[$]572 received dasatinib, nilotinib, or bosutinib as second-line TKI (not including 49 patients treated with ponatinib, imatinib, or investigational TKI)). Patients switched to a 2nd generation TKI for resistance (n=337, 54%) or intolerance (n=279, 45%).
**baseline characteristics for the MAIC were taken from the ponatinib phase 2 trial, PACE and the bosutinib phase 1/ 2 trial, Study 200
[%]156 had Ph+ CP CL, of 163 patients who received bosutinib

c) Interventions

Bosutinib was administered orally at 500mg a day in Study 200, Study NCT00811070, and Study BYOND. As previously outlined in the pCODR original submission, for Study 200, inpatient dose escalation to 600mg/day was allowed for lack of efficiency (failure to achieve CHR by week 8 or CCyR by week 12).

In addition to Study 200, the MAIC used the PACE study for the comparison between ponatinib and bosutinib.[27] Ponatinib was dosed at 45mg/day. For the MAIC comparing bosutinib, dasatinib and nilotinib, dasatinib was dosed at 100mg once daily, and nilotinib at 400mg twice dail.y[26]

With respect to observational studies, Attolico et al, 2018[44] reported bosutinib use in 85 patients, the initial dose was 100 mg in 4/85 patients (5%), 200 mg in 24 (28%), 300 mg in 18 (22%), 400 in 8 (9%); 31 patients (36%) started at the full standard dose of 500 mg. Chamoun et al, 2017[45] and Caocci et al., 2019[48] did not report on dosing of bosutinib dasatinib, or nilotinib. The median dose reported for the Spanish compassionate access program from 2019 for bosutinib was 450 (150-550) mg.[47]

d) Patient Disposition

The MAIC conducted by Levy et al.,[27] reported patients in the PACE study were less likely to discontinue treatment compared with those receiving bosutinib. Reasons for treatment discontinuation included death, disease progression, or unsatisfactory response. It was noted that treatment failure (death, disease progression or unsatisfactory response) led to discontinuation in 42% of bosutinib and 9% of ponatinib patients and that adverse events let to discontinuation among 24% and 19% of bosutinib and ponatinib patients, respectively.

Over a five-year period, considered the final results of the phase I/II Study 200, for CP CML (n=284), patients discontinued treatment as they were enrolled in the extension study (n=83, 29%), due to adverse events (n=67, 24%), or due to progressive disease (n=51, 18%).[18]

For Study 200, treatment discontinuation at >5 years on treatment were relatively low and were due to disease progression (n=8, 1, and 1), TEAEs (n=7, 5, and 2), and death (n=6, 1, and 0) for CP2L, CP3L, and ADV patients, respectively.[35]

For Study NCT00811070 over 8 years, 46% of patients continued treatment until study completion and 54% discontinued study treatment.[42] Most patients discontinued due to AEs (25%) or disease progression (14%) with one patient experiencing death (2%).[42]

Attolico et al, 2018[44] reported that discontinuations were due to intolerance in 8/75 patients (11%), loss of response in 3 (4%), and resistance to therapy in 10 (13%). Chamoun et al, 2017[45] reported that 248 (43%) of patients switched to a third-line TKI, either due to resistance (n=110, 44%) or intolerance (n=128, 52%).

Additionally, results from the retrospective Spanish compassionate access program report that that the patients discontinued bosutinib for intolerance (16%), and lack of efficacy (9%).[47] In the 2015 publication, a total of 11 (36.7%) of patients discontinued treatment due

to disease progression (3.3%), death (3.3%), adverse events (10%), and allogenic stem cell transplantation/surgical procedure (6.7).[46]

e) Limitations/Sources of Bias

There are no randomized controlled trials evaluating the use of bosutinib versus dasatinib, nilotinib, or ponatinib; the present report summarizes data from phase I/II studies, observational studies, and match adjusted indirect treatment comparisons.

Based on the results of the systematic review, there is weak comparative evidence to suggest bosutinib is a reasonable alternative to dasatinib, nilotinib, or ponatinib in patients with chronic, accelerated, or blast phase Ph+ CML who have resistance or intolerance to prior TKI therapy. Patient populations identified by the systematic review were not specific or limited further to those "for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate". The systematic review identified two matched adjusted indirect comparisons (bosutinib vs. dasatinib vs. nilotinib; bosutinib vs. ponatinib), three clinical studies (phase I/II Study 200 and Study NCT00811070; phase IV BYOND study), and four observational studies.

Of note, the systematic review identified the results presented by the manufacturer for 8-year update of Study 200 and MAIC comparing bosutinib to other TKIs used in second line; these were summarized and critically appraised.

Below are key limitations of the included studies, separated by type of study included.

Further details can be located in Appendix 1.

Limitations of indirect treatment comparisons, as per Signorovitch et al, 2012:[50]

- *Levy et al., 2019.*[27] *Bosutinib (Study 200) and Ponatinib (PACE) in 3L CP CML*
  - For the results included, tests of statistical significance were not conducted and only descriptive results are reported.
  - Unadjusted comparisons were performed on the analysis of reasons for treatment discontinuation for bosutinib and ponatinib.
  - The MAIC was only able to adjust for baseline measures that were reported in both trials and could not correct for unreported differences between the enrolled populations.
  - Adjustment for specific sequences of prior TKIs, which included prior treatment with bosutinib in the ponatinib trial was not carried out.
  - Potential selection bias through the inclusion and exclusion criteria specific to the safety and efficacy profile of each TKI (e.g. documented history of T3151 mutation status for the bosutinib trial; significant or active cardiovascular disease for the ponatinib trial). Therefore, the result of the residual confounding is unknown and cannot be corrected for.
  - Patient level data from the bosutinib Study 200 was not available thus rigorous statistical significance tests could not be performed.

- *Cortes et al., 2019. Bosutinib, Dasatinib and Nilotinib in 2L CP CML*[26]

- Only observed differences between the trials could be corrected for and not unobserved differences
- Comparison population is not of national cohorts or registry data rather it is assumed the nilotinib/dasatinib population is the target population for comparison
- The definition of PFS differs between the three trials, therefore findings on statistically significant differences of PFS must be interpreted with caution

Limitations of clinical studies:

- Phase I/II Study 200:
  - As identified in the original pCODR submission,[51] the study was a single arm open label study phase 1/2 study and therefore no comparator. Since there is no comparative evidence for bosutinib, the efficacy of bosutinib versus current treatments is uncertain.
  - Pfizer, was the sponsor of the study and several of the publications also had a medical writer funded by Pfizer.
  - Quality of life was an exploratory endpoint. Results are presented as overall trends in data as there were no adjustments for multiplicity of testing. EQ-5D scores were also derived with the UK value set and applicability to the Canadian population is unknown. Smaller number of patients at later time points may suggest results are most applicable to those who stayed on treatment and did not discontinue treatment due to AE; these patients may represent those with more favourable treatment experience and would be expected to have better HrQoL.
  - Per protocol, follow-up was for 30 days after treatment discontinuation for most assessments and there was limited follow-up for survival for 2 years after treatment discontinuation. Long-term outcomes may be biased due to early discontinuation of patients due to unacceptable toxicity or inadequate response. However, reasons for treatment discontinuation were captured.
  - Multiple analyses with preliminary analysis 15 months after last enrollment, subsequent analyses at 24 and 48 months, and final results for the CP cohort at least 5 years from enrollment.
- Phase I/II Study NCT00811070:
  - The study was a single arm open label study phase 1/2 study and therefore no comparator. Since there is no comparative evidence for bosutinib, the efficacy of bosutinib versus current treatments is uncertain.
- Phase IV Study BYOND:
  - The study was a post-authorization commitment made by Pfizer to the EMA to provide additional safety and efficacy data. The primary endpoint of cumulative confirmed major cytogenetic response (MCyR) by 1 year was not powered. There is limited long term data up to one year after the last enrolled patient.

Limitations of observational studies:

- The main limitation of the Spanish Compassionate access retrospective study was that the study was retrospective in nature and that data may be susceptible to

selection bias. The population was also very heavily treated, showed age, comorbidities and previous exposure to TKIs much higher than patients in clinical trials.

- The main limitation of the Caocci et al.[48] cohort study on arterial occlusive events (AOEs) was that aggregated results were presented. Though the authors reported the sequential use of second and third generation TKIs as a predictive risk factor for recurrent AOEs, the cumulative incidence of recurrent AOE`s for all TKIs, irrespective of line of therapy or sequential use was reported.
- Limited reporting in abstract data.

Given the lack of information in all the included abstracts it is not possible to assess the important considerations above and conclude if the analyses were appropriately conducted.

4.3.3.2 Detailed Outcome Data and Summary of Outcomes

Table 6.1-6.5 below outlines the response (MCyR, CCyR, CHR), overall survival, and progression free survival data from the included studies.

Table 6.1 Match Adjusted Indirect Treatment Comparisons

Study	Levy et al., 2019[27] Bosutinib and Ponatinib		Cortes et al., 2019[26] Bosutinib, Dasatinib and Nilotinib	
Phase & Line	3L CP CML		2L CP CML	
	Bosutinib	Ponatinib	Bosutinib compared with Dasatinib	Bosutinib compared with Nilotinib
# of patients	119	70 matched 97 unmatched	283 bosutinib - 167 dasatinib	283 bosutinib 321 nilotinib
OS	78% (95%CI 68%-85%)	83% (95% CI 71%-90%) (adjusted) 79% (95% CI 69%-86%) (unadjusted)	HR: 0.82 (95% CI 0.54-1.26) p = 0.37	HR: 0.72 (95% CI 0.46-1.13) p = 0.16
PFS Rates	76%(95% CI 67%-83%)	69%(95% CI 55%-79%) (unadjusted) 68%(95% CI 57%-77%) (adjusted)	0.63 (95% CI 0.44 - 0.90) p = 0.01	0.54 (95% CI 0.38-0.76) p=0.0004
Cytogenetic Response, n (%) [95%CI]	25.9%	65.0% (unadjusted) 61.2% (adjusted)	0.78 (95% CI 0.53 - 1.16) Not statistically significant, CI includes 1	0.98 (95% CI 0.71 - 1.35) Not statistically significant, CI includes 1
Molecular Response, n (%) [95%CI]	33%	69.8% (unadjusted) 71.1% (adjusted)	NR	NR
Follow Up Months	4 years	4 years	Bosutinib: 8yrs Dasatinib: 6 years	Bosutinib: 8yrs Nilotinib: 4 years

Table 6.2 Clinical Studies for Chronic Phase (2nd-Line)

Study	Study 200			Study NCT00811070	Study BYOND		
Phase	CP 2L			CP2L	CP (phase not reported)		
Included Publications	pCODR Original Submission	Gambacorti-Passerini C et al.[18]	Gambacorti-Passerini C et al.[35]	Takahashi et al, 2017[42]	Gambacorti-Passerini et al, 2019[43]		
# of patients	288	284	284	45	163		
Cytogenetic Response, n (%) [95%CI]	Evaluable patients: 266 MCyR: 157 (59) [53-65] CCyR: 128 (48) [42-54]	Evaluable patients: 262 <u>Year 2</u> Cumulative MCyR: 151(58) [51.4-63.7] CCyR: 120 (46) [39.7-52.0] <u>Year 5</u> Cumulative MCyR: 156(60) [53.3-65.5] CCyR: 130 (50) [43.4-55.8]	Evaluable patients: 262 MCyR: 60% CCyR: 50%	CCyR at baseline: 11 (24) MCyR: 33 (73) [58–85] CCyR: 30 (67) [51–80]	Evaluable: 144 Cumulative confirmed MCyR by 1 year: 71.5% (63.4-78.7) Cumulative complete cytogenetic response rate anytime on treatment: 81.3% (73.9-87.3)		
Molecular Response, n (%) [95%CI]	Evaluable patients: 200 MCyR: 69 (35) [28-42] CCyR: 55 (28) [21-34]	Evaluable patients: 197 <u>Year 2</u> Cumulative MMR: 62(31) [25.1-38.5] <u>Year 5</u> Cumulative MMR: 82(42) [34.7-48.8]	NR	CMR at baseline: 1 (2) MMR: 24 (53) [38–68] CMR: 22 (49) [34–64]	<u>1 Prior TKI</u> Evaluable patients: 46 Cumulative rate any time on treatment MMR: 82.6 (68.6-92.2) MR: 69.6 (54.2-82.3)	<u>2 Prior TKI</u> Evaluable patients: 55 Cumulative rate any time on treatment MMR: 76.4 (63.0-86.8) MR: 61.8 (47.7-74.6)	<u>3 Prior TKI</u> Evaluable patients: 48 Cumulative rate any time on treatment MMR: 56.3 (41.2 - 70.5) MR: 39.6 (25.8 - 54.7)

Hematologic Response, n (%) [95%CI]	Evaluable patients: 287 CHR: 244 (85) [80-89]	NR	NR	CHR: 32 (71) [56–84]	NR	NR	NR
OS rates, % (95%CI)	2 year: 91% (95%CI: 87-94) Median OS: Not Reached	<u>Year 2</u> 91.2 (87-94.0) <u>Year 5</u> 83.5 (78.1-87.7)	79%	<u>Year 2</u> 98% (95% CI 93–100%) <u>Year 5</u> 98% (95% CI 93–100%)	<u>Year 1</u> 98.0%		
PFS rates	2 year: 81% (74-85) Median PFS: Not Reached	NR	NR	96 week: 91% (95% CI 81–100%) 240 week: 91% (81–100%)	NR	NR	NR
Follow-Up, months (range)	Minimum 24	Median 54.8 (0.6-96.3)	8 year follow-up	Median: 240 weeks (3-372) 8 year follow-up	Median: 30.4 months		

Table 6.3 Clinical studies for Chronic Phase (3rd-Line and beyond)

Study	**Study 200**			**Study NCT00811070**
Phase	**CP 3L-4L**	**CP 3L-4L**	**CP3L**	**CP3L**
Included Publications	pCODR Original Submission	Gambacorti-Passerini C et al.[18]	Gambacorti-Passerini C et al.[35]	Takahashi et al, 2017[42]
# of patients	118	45	119	10
Cytogenetic Response, n (%) [95%CI]	Evaluable patients: 108 MCyR: 35 (32) CCyR: 26 (24)	CCyR at baseline: 11 (24) MCyR: 33 (73) [58–85] CCyR: 30 (67) [51–80]	Evaluable patients: 112 MCyR: 41% CCyR: 32%	CCyR at baseline: 5 (50) MCyR: 7 (70) [35–93] CCyR: 6 (60) [26–88]
Molecular Response, n (%) [95%CI]	Evaluable patients: 105 MCyR: 16 (15) CCyR: 12 (11)	CMR at baseline: 1 (2) MMR: 24 (53) [38–68] CMR: 22 (49) [34–64]	NR	CMR at baseline: 3 (30) MMR: 4 (40) [12–74] CMR: 4 (40) [12–74]
Hematologic Response, n (%) [95%CI]	Evaluable patients: 116 CHR: 85 (73)	CHR: 32 (71) [56–84]	NR	CHR: 9 (90) [55–100]
OS rates, % (95%CI)	2 year: 83% Median OS: Not Reached		72%	Year 2: 100% (100–100%) Year 5: NR
PFS rates	2 year: 73%		NR	Year 2: 88% (95% CI 65–100%)

Study	Study 200			Study NCT00811070
Phase	CP 3L-4L	CP 3L-4L	CP3L	CP3L
	Median PFS: Not Reached			Year 5: NR
Follow-Up Time	28.5-month follow-up	Minimum follow-up of 48 months	7 year follow-up	8 year follow-up

Table 6.4 Clinical studies for Accelerated and Blast Phase

Study	Study 200						Study NCT00811070
Phase	AP	CP3L	AP	BP	AP	BP	ADV
Included Publications	pCODR Original Submission		Gambacorti-Passerini C et al.[14]		Gambacorti-Passerini C et al.[35]		Takehashi et al, 2017[42]
# of patients	76	64	79	64	ADV = 167		8
Cytogenetic Response, n (%) [95%CI]	MCyR: 35 (24-47)	MCyR: 30 (18-44)	Evaluable patients: 72 MCyR: 29 (40)e [29%-53%] CCyR: 22 (31)	Evaluable patients: 54 MCyR: 20 (37)f [24%-51%] 4 CCyR: 15 (28)	Valid baseline assessment: n=72 MCyR: 40% CCyR: 31%	Valid baseline assessment: n=54 MCyR: 37% CCyR: 28%	CCyR at baseline: 1 (13) MCyR: 4 (50) [16–84] CCyR: 3 (38) [9–76]
Molecular Response, n (%) [95%CI]	NR	NR	NR	NR	NR	NR	CMR at baseline: 0 MMR: 1 (13) [0.3–53] CMR: 1 (13) [0.3–53]
Hematologic Response, n (%) [95%CI]	CHR: 35 (24-47)	CHR: 28 (18-41)	Evaluable patients: 72 CHR by 4 years 41 (57) [45-69]	Evaluable patients: 60 CHR by 4 years 17 (28) [18-41]	NR	NR	CHR: 2 (25) [3–65]
OS rates, % (95%CI)	1 year: 76% (65-84)	1 year: 44% (31-56)	1-year: 78% (67%-86%) 4-year: 59% (46%-69%)	1-year: 42% (30%-54%) 4-year: 23% (10%-39%) Median OS: 10.9 (8.7-19.7)	59%	23%	Year 2: 50% (15–85%) Year 5: NR
PFS rates	1 year: 65% (52-75)	1 year: 14% (6.0-26)	NR	NR	NR	NR	Year 2: 33% (95% CI 0–69%) Year 5: NR
Follow-Up Time	May 20 2014	May 20 2014	≥4 year follow-up Treatment duration 10.2 (0.1-88.6)	≥4 year follow-up Treatment duration 2.8 (0.03-55.9)	7-year follow-up	7-year follow-up	8 year follow-up

e Included four patients with a partial cytogenetic response determined by using FISH instead of cytogenetic analysis.

f Included one patient with CCyR determined by using FISH instead of cytogenetic analysis.

Table 6.5 Retrospective Observational Studies

AOE = arterial occlusive events

Phase	CP	CP2L			CP4L	CML (phase not reported)			
Included Publication	Attolico et al, 2018[44]	Chamoun et al, 2017[45] (N=572)			Garcia Gutierrez 2019[47]	Caocci et al., 2019			
Treatment	BOS	DAS	NIL	BOS	BOS	BOS	DAS	NIL	PON
# of patients	n=85 Evaluable: 80	338 (54%)	194 (31%)	40 (6%)	n=62 Evaluable: 61	First line: 2 Second or Subsequent line: 10	First line: 12 Second or Subsequent line: 13	First line: 2 Second or Subsequent line: 8	First line: 0 Second or Subsequent line: 10
Cytogenetic Response, n (%) [95%CI]	PCyR: 6 (14%) CCyR: 10 (23%)	MCyR: 85% CCyR: 76%	MCyR: 76% CCyR: 70%	MCyR: 67% CCyR: 50%	MCyR: NR CCyR: 65%	NR	NR	NR	NR
Molecular Response, n (%) [95%CI]	DMR/MMR 37 (46%)	MMR: 72% $MR^{4.5}$: 55%	MMR: 65% $MR^{4.5}$: 46%	MMR: 55% $MR^{4.5}$: 39%	MMR: 41% $MR^{4.5}$:16%	NR	NR	NR	NR
Hematologic Response, n (%) [95%CI]	CHR: 4 (9%)	NR	NR	NR	CHR: 100%	Incidence of Recurrent AOE: 30.5 +/- 15.5%	Incidence of Recurrent AOE: 44 +/- 24.2%	Incidence of Recurrent AOE: 76.7 +/- 14.3%	Incidence of Recurrent AOE: 64 +/- 21%
Long-term Efficacy	NR	Median OS and TFS were not reached and median EFS was 121 months. No difference in OS, TFS and EFS was found when comparing dasatinib, nilotinib and bosutinib in all patients.			EFS: 68.3% Median EFS: 27.14 months (95% CI: 11.95-42.32) PFS: 85.2% Median PFS: NR	NR			
Follow-Up Time	26 months (3-49)	Median follow-up from diagnosis of 96 months (range 4-283).			14.3 (0.5-36.1)	60 months			

Summary of Efficacy Outcomes from MAIC

SECOND LINE CP CML

Bosutinib compared with dasatinib[26]

Comparing bosutinib with dasatinib in terms of OS resulted in a HR of 0.82 (95% CI 0.54-1.26), p = 0.37 (not statistically significant) in favor of bosutinib. For progression free survival (PFS), the HR

was 0.63 (95% CI 0.44-0.90), p<0.05 in favour of bosutinib. In terms of MCyR, no statistically significant difference was observed between dasatinib and bosutinib (OR of 0.78 (0.53-1.16)

Bosutinib compared with nilotinib[26]

Comparing bosutinib with nilotinib in terms of OS, the HR was 0.72 (95% CI 0.46-1.13) in favour of bosutinib, p = 0.16 (not statistically significant). In terms of PFS, when bosutinib was compared with nilotinib through the MAIC, the HR was 0.54 (95% CI 0.38-0.76) in favour of bosutinib, p <0.01. For MCyR, no statistically significant difference was observed (OR at 0.98 (0.71-1.35).

THIRD LINE CP CML[27]

Overall Survival

From Study 200, the KM estimated 4-year overall survival was 78% (95% CI 68%-85%) for bosutinib and the adjusted 4 year OS from the PACE study was 83% (95% CI 71% - 90%). Median survival durations could not be estimated for either bosutinib or ponatinib due to the low mortality rates in both trials.

Progression Free Survival

Based on the cumulative incidence of on treatment bosutinib, the 4-year PFS was 76% (95% CI 67%-83%), with 24% of patients on treatment at 4 years. The adjusted PFS for ponatinib was 69% (95% CI of 55%-79%).

Cytogenetic Response

Levy et al.[27], noted the probability over time of retaining CCyR among ponatinib and bosutinib. The KM estimate of maintaining CCyR at 4 years was 54% (95% CI 35%-70%) for bosutinib and 89% (95% CI 73%-96%) for match-adjusted ponatinib data.

Summary of Efficacy Outcomes from Clinical Trials

SECOND-LINE CHRONIC PHASE (CP2L)

Overall Survival

For Study 200, after 8 years from last patient enrolled, the OS rate was 79% (95%CI: 73-84) for the CP2L.[13,35] There was a decline in OS rate, where at year 2 the OS rate was 91.2% (95%CI: 87-94.0),[31] at year 5 the OS rate was 83.5 (95%CI: 78.1-87.7).[18,30]

For Study NCT00811070, at years 2 and 5 the OS rates were 98%.[42]

Progression Free Survival

There were no updated results for Study 200 for PFS rates for CP2L. As previously reported, based on 24 month follow-up, the PFS rate at 2 years was 81% and the median PFS had not been reached.

For Study NCT00811070, at years 2 and 5 the PFS rates were 91%.[42]

Cytogenic Response (Major and Complete)

For Study 200, CP2L cohort the newly attained or maintained MCyR was 59% and CCyR was 48%. Subsequent follow-up results reported similar results at minimum follow-ups of 48 months, 60 months, 96 months, 6 years and 7 years from last patient enrolled.[13,17,30,31,33,35] The majority of MCyR and CCyR had occurred in 2 years or less.[30] After 6 years of follow-up the median MCyR duration had not been reached.[33] Gambacorti-Passerini et al, (2018),[35] reported after 8 years of follow-up, for patients with a valid baseline assessment (n=262), MCyR was achieved by 60% and CCyR by 50% of patients.

For Study NCT00811070, CP2L cohort at baseline had a CCyR in 11 patients (24%), where MCyR was 73% and CCyR was 67%.[42]

Molecular Response

For Study 200, based on a median follow-up of 54.8 months (range 0.6-96.3), at year 5 for CP2L cohort, the cumulative MMR was 42% (n=82/197; 95%CI: 34.7-48.8).[18]

For Study NCT00811070, only 1 CP2L patient had a CMR at baseline, MMR was 53% and CMR was 49%.[42]

Hematologic Response

There were no updated results for Study 200 for CHR. As previously reported, based on 24 months of follow-up, the CHR was 85 (n=244/287; 95CI: 80-89) for the CP2L cohort.[18]

CHR occurred in 32 (71%) of patients in Study NCT00811070 CP2L cohort.[42]

THIRD-LINE AND BEYOND CHRONIC PHASE (CP3L)

Overall Survival

For Study 200, after 7 years from last patient enrolled, the OS rate was 72% for the CP3L[35]. There was a decline in OS rate, where at year 2 the OS rate was 84% and at year 4 it was 78% (95%CI: 68-85).[29,35,37]

For Study NCT00811070, at year 2 the OS rate was 100%.[42]

Progression Free Survival

There were no updated results for Study 200 for PFS rates for CP3L. As previously reported, based on 24 month follow-up, the PFS rate at 2 years was 73% and the median PFS had not been reached.

For Study NCT00811070, at year 2 the PFS rate was 88%.[42]

Cytogenic Response (Major and Complete)

For Study 200, CP3L cohort the newly attained or maintained MCyR was 32% and CCyR was 24% at 28.5 months of follow-up. Longer follow-up suggested MCyR was 40% and 32% at a minimum of 48 months of follow-up; at 7 years from last patient enrolled, the MCyR was 41% and CCyR was maintained at 32%.[29,35,37]

For Study NCT00811070, CP3L cohort at baseline had a CCyR in 5 patients (50%), where MCyR was 70% and CCyR was 60%.[42]

Molecular Response

There were no updated results for Study 200 for molecular response. As previously reported, based on 24 months of follow-up, the MCyR was 15% and CcyR was 11%

For Study NCT00811070, 3 (30%) CP3L patient had a CMR at baseline, MMR was 40% and CMR was 40%.[42]

Hematologic Response

For Study 200, based on updated results of a minimum of 48 months of follow-up, the newly attained or maintained CHR was 74% (95%CI: 65-81).[29]

CHR occurred in 9 (90%) of patients in Study NCT00811070 CP3L cohort.[42]

ADVANCED PHASE (AP/BP CMP, PH+ ALL)

Overall Survival

For Study 200, after 7 years from last patient enrolled, the OS rate was 59% for AP CML and 23% for BP CML.[35] There was a decline in OS rate, where at year 1 the OS rate was 78% and at year 4 was 59% for AP CML; at year 1 the OS rate was 42% and at year 4 the OS rate was 23% for BP CML.[14] At ≥4 years of follow-up, the median OS was 10.9 months for BP CML.[14]

For Study NCT00811070, at years 2 the OS rate were 50%.

Progression Free Survival

There were no updated results for Study 200 for PFS rates for AP/BP CL. As previously reported, based on 24 month follow-up, the PFS rate at 1 year was 65% and 14% for AP CML and BP CML, respectively.

For Study NCT00811070, at years 2 the OS rate were 33%.

Cytogenic Response (Major and Complete)

For Study 200, at both follow-up updates (≥4 years and 7 years), for AP CML the MCyR was 40% and CCyR was 31%.[35] Similar results were seen for BP CML, where at both follow-up updates (≥4 years and 7 years), the reported MCyR was 37% and CCyR was 28%.

For Study NCT00811070, ADV cohort at baseline had a CCyR in 1 patient (13%), where MCyR was 50% and CCyR was 38%.

Molecular Response

No included studies reported molecular response for the AP/BP CML cohorts.

Study NCT00811070, no ADV patients had a CMR at baseline, both MMR and CMR were 1%.

Hematologic Response

For Study 200, CHR by 4 years was 57% for AP CML and 28% for BP CL.[14]

CHR occurred in 2 (25%) of patients in Study NCT00811070 ADV cohort.

ONGOING CLINICAL STUDY OF BOSUTINIB FOR CP CML

Study BYOND[43] reported of 144 evaluable patients with a valid baseline assessment, cumulative confirmed MCyR by 1 year was 71.5% (95%CI: 63.4-78.7); cumulative complete cytogenetic response rate anytime on treatment was 81.3% (95% CI 73.9-87.3). Across all lines of therapy, cumulative molecular response rates were high.

Quality of Life[39,40]

For Study NCT00811070 and Study BYOND, patient-reported health-related quality of life (HrQoL) was not assessed.

For Study 200, HrQoL was reported in two publications (57, 90). EQ-5D and Fact-Leu assessments were completed at baseline, weeks 4, 8, 12; every 12 weeks thereafter, and at treatment completion. For patients with CP (CP2L and CP3L) and patients with AP/BP CL, there was 264 weeks and 96 weeks of follow-up duration, respectively.

Table 7. Quality of life from Study 200

Baseline values	*CP2L (n=284)*	CP3L (n=119)	AP (n=76)*	BP (n=64)^
Fact-Leu scale (mean SD)				
Individual domain scores				
PWB (scale: 0-28)	22.96	22.61	21.6 (6.8)	19.2 (6.6)
SWB (scale: 0-28)	21.17	21.09	20.9 (7.1)	21.2 (6.9)
EWB (scale: 0-28)	17.76	17.96	17.0 (5.3)	16.7 (4.8)
FWB (scale: 0-28)	19.09	19.31	18.2 (6.7)	15.5 (6.9)
Composite Scores				
FACT-G Total	81.04	80.81	77.7 (18.3)	72.6 (18.1)

Baseline values	*CP2L (n=284)*	CP3L (n=119)	AP (n=76)*	BP (n=64)^
FACT-Leu Total	133.22	132.50	127.5 (29.2)	117.3 (28.7)
FACT-TOI	94.28	93.75	89.6 (23.6)	79.3 (23.4)
Additional concerns	52.16	51.83	NR	NR
EQ-5D Questionnaire				
Utility (scale: 0-1)	0.83 (95%CI: 0.80-0.85)	0.80 (95%CI: 0.76-0.85)	0.78 (0.28)	0.66 (0.30)
VAS (scale: 0-100)	NR	NR	69.8 (23.7)	61.5 (26.1)

*n=60 for PWB, SWB, EWB, FWB, FACT-G; n=59 for EQ-5D Utility; n=58 for FACT-TOI; Fact-LEU Total; and n=56 for EQ-5D VAS
^n=57 for PWB, SWB; n=56 for EWB, FWB, FACT-G, and n=55 for FACT-TOI, FACT-Leu Total, EQ-5D Utility, and EQ-5D VAS

Quality of Life for Chronic Phase Patients[40]

EQ-5D

At baseline, 87% of EQ-5D assessments were collected; at treatment completion, 68% and 66% of EQ-5D assessments and 66% and 65% of FACT-Leu assessments were collected in the CP2L and CP3L cohorts, respectively. The EQ-5D scores remained relatively stable throughout the 384 weeks of bosutinib treatment in both cohorts, although there was a decline in number of patients in each cohort at later time points. Improvements from baseline were observed at weeks 36, 96, 192, and 360 in the CP2L cohort, however, MID was not determined or reported for EQ-5D scores. The mean EQ-5D VAS scores were 71.31 (95% CI: 68.32-74.29) and 72.56 (95% CI: 67.92-77.21) in the CP2L and CP3L cohorts, respectively. Similar results to the EQ-5D scores were observed, improvements were observed at weeks 8 to 96, 120, 144, and 168 to 264 in the CP2L cohort and at weeks 48 to 96, 120, 168, and 240 in the CP3L cohort.

Fact-Leu

Minimally important differences (MIDs) for each FACT-Leu scale have been identified: Physical Well-Being (2 or 3 points), Social/Family Well-being (has not been estimated), Emotional Well-Being (2 points), Functional Well-Being (2 or 3 points), FACT-G Total (3-7 points), FACT-TOI (5 or 6 points), and FACT-Leu Total (6-12 points). Baseline mean FACT-Leu score were similar between the CP2L and CP3L cohorts. MIDs denoting benefit were observed for the CP2L cohort at weeks 168, 216, and 264 for EWB; at weeks 168 and 216 for FACT-G Total and FACT-Leu Total. For CP2L, at week 168, an MID was observed for FACT-TOI as well. There was a decline in FWB at treatment completion of the CP2L cohort but this did not meet the MID. For CP3L, there was an MID denoting benefit only at week 264 for the change from baseline in the FACT-Leu Total score but not any other summary scale scores.

Fact-Leu in patients with chronic diarrhea

For patients with chronic diarrhea, 101 and 30 patients were in the CP2L and CP3L cohorts, respectively. Overall, baseline FACT-Leu general and summary scales were similar across cohorts and compared to the larger CP2L and CP3L cohorts. For CP2L, MIDs denoting benefit were observed at weeks 168, 216, and 264 for EWB; at weeks 168, 216, and 264 for FACT-G total, at weeks 168, 216, and 264 for FACT-Leu Total, and at weeks 168 and 265 for FACT-TOI. MIDs denoting benefit were observed for the CP2L cohort at weeks 168, 216, and 264 for EWB; at weeks 168 and 216 for FACT-G Total and FACT-Leu Total. For CP3L, MIDs denoting benefit were observed at week 168 for EWB; at weeks 60 and weeks 168 for FACT-G Total; and at week 168 for FACT-Leu total. For CP3L, MIDs denoting impaired HrQoL were observed at treatment completion for FWB (and week 264), FACT-G Total, and FACT-TOI.

Quality of Life for Accelerated and Blast Phase Patients[39]

Baseline assessments were complete for FACT-Leu and EQ-5D for 76.3% and 77.6% of patients in the AP cohort and for 85.9% and 87.5% of patients in the BP cohort, respectively. There were sharp declines in completion rates in the BP and AP CML cohorts ((FACT-Leu Total scores were 50.0% and 28% (week 24) and 16% and 3% (week 96); EQ-5D Utility scale were 51% and 25% (week 24) and 18% and 3% (week 96)).

EQ-5D

Health status as measured by EQ-5D utility scores were stable throughout treatment in AP CML patients; scores were significantly improved versus baseline at weeks 4, 8, 12, and 36 in BP CML patients. For mean VAS scores, there were significant improvements at weeks 8, 36, and 48 for AP CML patients; there were significant improvements at weeks 4, 8, 12, 24, 36, and 96 in BPCML patients.

FACT-Leu

Mena FACT-Leu Total scores met MIDs denoting benefit at weeks 24, 36 and 48 in both AP and BP cohorts; there were additional time points where MID were reached for BP (at weeks 4, 8, 12, and 96).

Summary of Efficacy Outcomes from Retrospective Studies

MCyR was 67% (50%CCyR) with bosutinib, 85% (76% CCyR) with dasatinib, and 76% with nilotinib (70% CCyR) in a single centre.[45] At a median follow-up from diagnosis of 96 months (range of 4 to 283), 39 (7%) patients transformed to either accelerated or blast phase while on second-line TKI. Median OS and transformation-free survival (TFS) were not reached and the median event-free survival (EFS) was 121 months. No difference in OS, TFS and EFS was found when comparing dasatinib, nilotinib and bosutinib in all pts (p=0.651, p=0.673, p=0.057).

In the abstract from patients in Italy, MMR/DMR was achieved by 37 of 80 (46%) evaluable patients; the best responses were CHR in 4 (9%) patients and PCyR in 6 (14%).[44] After a median follow-up of 26 months, 75 (88%) patients were alive and 54 (72%) were still in treatment.

The study conducted by Caocci et al.,[48] for the recurrence of arterial occlusive events reported the 60-month cumulative incidence rate of recurrent AOEs was 47.8±10.9%. Patients treated with nilotinib and ponatinib had a higher incidence rate of recurrent AOEs, 76.7±14.3% and 64±20.1% respectively, than those treated with dasatinib and bosutinib, 44±24.2% and 30.5±15.5% respectively (p=0.01)

Observational studies included did not report on HrQoL.

Summary of Harms outcomes from MAIC

The second line CP CML study from Cortes et al., 2019[26] did not report on harms outcomes as part of the match adjusted indirect treatment comparison between bosutinib, dasatinib and nilotinib. Though specific date on AEs was not provided as part of the Levy et al.[27], 2019 MAIC for ponatinib and bosutinib in 3L CP CML, it was noted that treatment failure (death, disease progression or unsatisfactory response) led to discontinuation in 42% of bosutinib patients, but only 9% of ponatinib patients. AEs led to discontinuation among 24% of bosutinib patients and 19% of ponatinib patients.

Summary of Harms Outcomes from Clinical Trials

For Study 200, newly occurring adverse events for years 1-4 were assessed by cohort of CP2L, CP3L, and ADV.[29,30,32] The most commonly reported adverse event with bosutinib was diarrhea in year 1 with 239 (84%) patients with CP2L, 82 (69%) with CP3L, 67 (85%) with AP, and 41 (64%) with BP. There were none or low newly occurring diarrhea AEs across all cohorts; rates of cardiac, vascular, and renal were low at year 1 and throughout to year 4.[29,30,32]

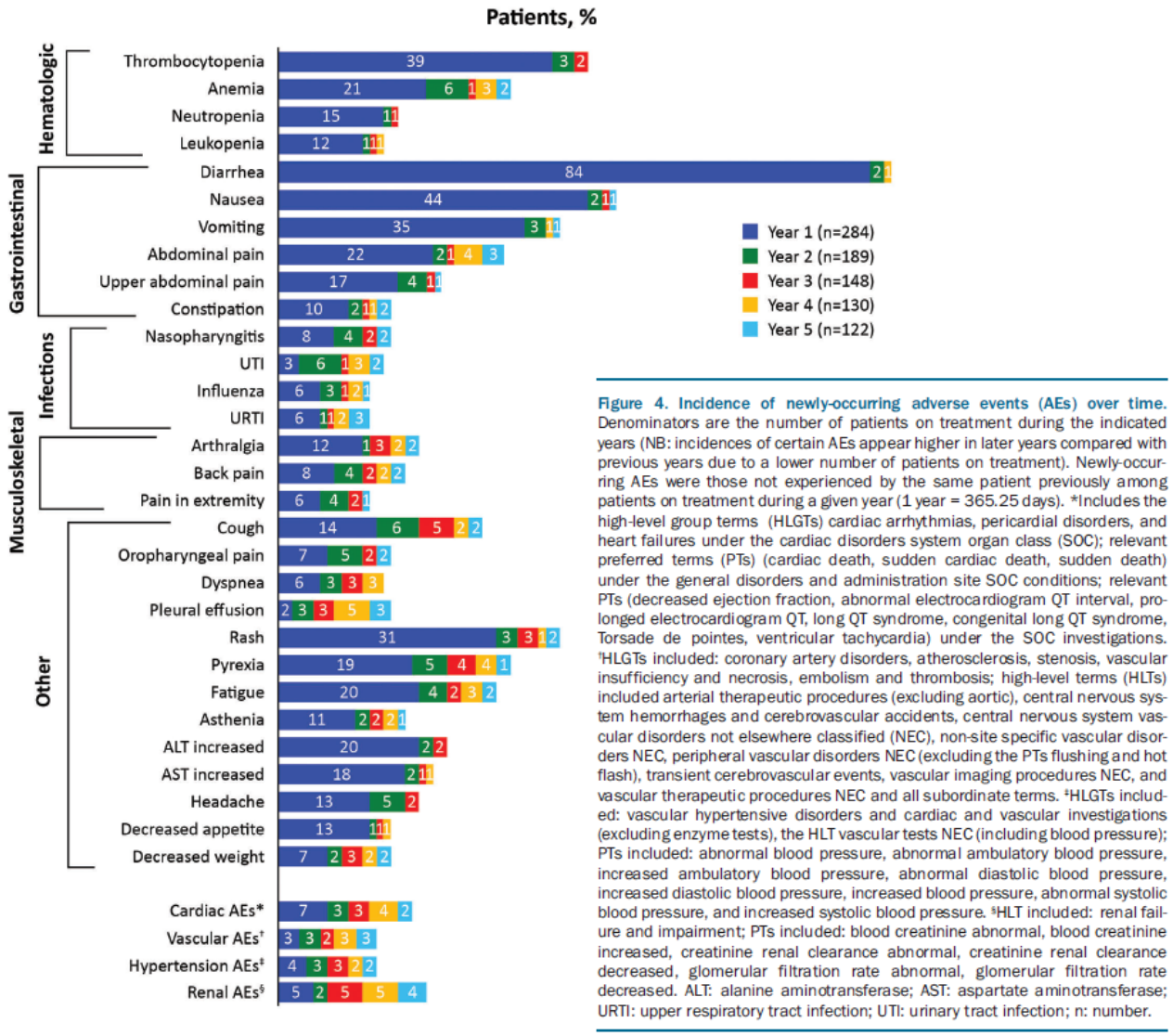


Figure 4. Incidence of newly-occurring adverse events (AEs) over time. Denominators are the number of patients on treatment during the indicated years (NB: incidences of certain AEs appear higher in later years compared with previous years due to a lower number of patients on treatment). Newly-occurring AEs were those not experienced by the same patient previously among patients on treatment during a given year (1 year = 365.25 days). *Includes the high-level group terms (HLGTs) cardiac arrhythmias, pericardial disorders, and heart failures under the cardiac disorders system organ class (SOC); relevant preferred terms (PTs) (cardiac death, sudden cardiac death, sudden death) under the general disorders and administration site SOC conditions; relevant PTs (decreased ejection fraction, abnormal electrocardiogram QT interval, prolonged electrocardiogram QT, long QT syndrome, congenital long QT syndrome, Torsade de pointes, ventricular tachycardia) under the SOC investigations. †HLGTs included: coronary artery disorders, atherosclerosis, stenosis, vascular insufficiency and necrosis, embolism and thrombosis; high-level terms (HLTs) included arterial therapeutic procedures (excluding aortic), central nervous system hemorrhages and cerebrovascular accidents, central nervous system vascular disorders not elsewhere classified (NEC), non-site specific vascular disorders NEC, peripheral vascular disorders NEC (excluding the PTs flushing and hot flash), transient cerebrovascular events, vascular imaging procedures NEC, and vascular therapeutic procedures NEC and all subordinate terms. ‡HLGTs included: vascular hypertensive disorders and cardiac and vascular investigations (excluding enzyme tests), the HLT vascular tests NEC (including blood pressure); PTs included: abnormal blood pressure, abnormal ambulatory blood pressure, increased ambulatory blood pressure, abnormal diastolic blood pressure, increased diastolic blood pressure, increased blood pressure, abnormal systolic blood pressure, and increased systolic blood pressure. §HLT included: renal failure and impairment; PTs included: blood creatinine abnormal, blood creatinine increased, creatinine renal clearance abnormal, creatinine renal clearance decreased, glomerular filtration rate abnormal, glomerular filtration rate decreased. ALT: alanine aminotransferase; AST: aspartate aminotransferase; URTI: upper respiratory tract infection; UTI: urinary tract infection; n: number.

Figure 2. Incidence of newly-occuring adverse events over years 1 to 5

Source: Gambacorti-Passerini 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 Aug;103:1298-1307. Copyright 2018 Ferrata Storti Foundation. Reprinted in accordance with CC BY-NC 4.0.[18]

Supplementary Table S2. Treatment Discontinuations by Year of Treatment*

Reasons for Discontinuation	Year 1 (n=284)	Year 2 (n=197)	Year 3 (n=153)	Year 4 (n=136)	Year 5 (n=123)	Total† (n=284)
Discontinued treatment,‡ n (%)	87 (31)	44 (22)	17 (11)	13 (10)	8 (7)	284 (100)
AE	47 (17)	10 (5)	2 (1)	4 (3)	1 (1)	67 (24)
PD	21 (7)	15 (8)	7 (5)	3 (2)	1 (1)	51 (18)
Patient request	9 (3)	5 (3)	2 (1)	2 (1)	1 (1)	24 (8)
Unsatisfactory response (efficacy)	5 (2)	9 (5)	4 (3)	1 (1)	2 (2)	23 (8)
Death	0	2 (1)	1 (1)	0	2 (2)	8 (3)
Investigator request	1 (<1)	0	1 (1)	1 (1)	0	8 (3)
Lost to follow-up	1 (<1)	1 (<1)	0	2 (1)	0	4 (1)
Symptomatic deterioration	1 (<1)	1 (<1)	0	0	0	2 (1)
Other	2 (1)	1 (<1)	0	0	1 (1)	96# (34)
Discontinuation due to any AE,§,‖ n						
Thrombocytopenia	14	2	0	0	1	17
Neutropenia	6	0	0	0	0	6
ALT increased	6	0	0	0	0	6
Diarrhea	3	1	0	0	0	4
Rash	3	0	0	0	0	3
AST increased	3	0	0	0	0	3
Anemia	3	0	0	0	0	3
Pneumonia	0	1	0	0	0	1
Intestinal obstruction	0	1	0	0	0	1
Abdominal adhesions	0	1	0	0	0	1
Cardiac failure	0	1	0	0	0	1
Lipase increased	0	1	0	0	0	1
White blood cell count increased	0	1	0	0	0	1
CAD	0	0	1	0	0	1
Scleroderma	0	0	1	0	0	1
Renal failure	0	0	1	0	0	1

Figure 3. Treatment discontinuation in Study 200 over years 1 to 5

Source: Gambacorti-Passerini et al., Long-term efficacy and safety of bosutinib in patients with advanced leukemia following resistance/intolerance to imatinib and other tyrosine kinase inhibitors, Am J Hematol. 2015 Sep;90(9):755-68. Copyright 2015 The Authors. Reprinted in accordance with CC BY-NC-ND 4.0.[14]

TABLE V. Incidence of Newly Occurring Serious AEs, any Causality Over Time[a]

	Year 1			Year 2			Year 3			Year 4		
	AP CML (n = 79)	BP CML (n = 64)	ALL (n = 24)	AP CML (n = 34)	BP CML (n = 5)	ALL (n = 1)	AP CML (n = 19)	BP CML (n = 3)	ALL (n = 1)	AP CML (n = 15)	BP CML (n = 2)	ALL (n = 1)
Any AE,[b] n (%)	36 (46)	37 (58)	18 (75)	10 (29)	1 (20)	0	3 (16)	1 (33)	0	5 (33)	0	0
Thrombocytopenia	6 (8)	1 (2)	3 (13)	0	0	0	0	0	0	0	0	0
General physical health deterioration	1 (1)	3 (5)	2 (8)	0	0	0	0	0	0	0	0	0
Anemia	5 (6)	1 (2)	0	0	0	0	0	0	0	0	0	0
Febrile neutropenia	1 (1)	4 (6)	4 (17)	0	0	0	0	0	0	0	0	0
Leukocytosis	1 (1)	2 (3)	2 (8)	0	0	0	0	0	0	0	0	0
Nausea	0	5 (8)	1 (4)	0	0	0	0	0	0	0	0	0
Vomiting	0	4 (6)	1 (4)	0	0	0	0	0	0	0	0	0
Disease progression	5 (6)	3 (5)	1 (4)	0	0	0	0	0	0	0	0	0
Pyrexia	4 (5)	6 (9)	1 (4)	0	0	0	0	0	0	0	0	0
Pneumonia	6 (8)	5 (8)	3 (13)	3 (9)	0	0	0	0	0	0	0	0
Headache	4 (5)	2 (3)	2 (8)	0	0	0	0	0	0	0	0	0
Pleural effusion	3 (4)	2 (3)	1 (4)	0	0	0	1 (5)	0	0	1 (7)	0	0
Respiratory failure	1 (1)	2 (3)	2 (8)	0	0	0	0	0	0	0	0	0

[a] Newly occurring serious AEs refers to those not experienced by the same patient in previous years for patients on-treatment during that specific year (1 year = 365.25 days).
[b] In ≥5 patients in the safety population (n = 167) in year 1, or in ≥2 patients in years 2, 3, or 4.
AE, adverse event; AP, accelerated phase; CML, chronic myeloid leukemia; BP, blast phase; ALL, acute lymphoblastic leukemia.

Figure 4. Incidence of newly occurring serious AEs in Study 200 over years 1 to 4
Source: Gambacorti-Passerini et al., Long-term efficacy and safety of bosutinib in patients with advanced leukemia following resistance/intolerance to imatinib and other tyrosine kinase inhibitors, Am J Hematol. 2015 Sep;90(9):755-68. Copyright 2015 The Authors. Reprinted in accordance with CC BY-NC-ND 4.0.[14]

For Study 200 and at the latest follow-up, treatment discontinuation at >5 years on treatment were relatively low and were due to disease progression (n=8, 1, and 1), TEAEs (n=7, 5, and 2), and death (n=6, 1, and 0) for CP2L, CP3L, and ADV patients, respectively.[35]

At ≥7 years of follow-up, rates of TEAEs, SAEs, bosutinib withdrawals, and drug-related TEAEs in cardiac, vascular, and hypertension clusters were generally similar across CP2L, CP3L, and ADV cohorts.[32]

In Study NCT00811070, most newly occurring AEs were experienced in the first year, AEs newly occurring after the first year in ≥4 patients were nasopharyngitis (n=13 after the first year), dental caries (n=9), gastroenteritis (n=5), gingivitis (n=5), dry skin (n=4), lymphopenia (n=4), pleural effusion (n=4), arthralgia (n=4), influenza (n=4), hyperlipidemia (n=4), hypertension (n=4), and pharyngitis (n=4).[42]

For Study NCT00811070, all patients experienced an AE (any grade) and grade 3/4 TEAEs occurred in 55 (87%) of patients.[42] The most frequently grade 3/4 TEAEs occurring in ≥10% of patients overall were: diarrhea in 8 (13%), rash in 7 (11%), lymphopenia in 16 (25%), increased alanine aminotransferase in 11 (17%), thrombocytopenia in 13 (21%), anemia in 8 (13%), increased aspartate aminotransferase in 6 (10%), leukopenia in 6 (10%), neutropenia in 13 (21%), and increased lipase in 12 (19%).

For Study BYOND,[43] 25% of patients treated with bosutinib discontinued treatment due to AEs and 5.1% due to insufficient response. The most common TEAEs were diarrhea in 87.8% and nausea in 41.0% of patients; grade 3/4 TEAEs in >10% of patients was diarrhea (16.7%) and increased ALT (14.7%).

Summary of Harms Outcomes from Observational Studies

Attolico et al, 2018[44] reported discontinuations from treatment were due to intolerance in 8 (11%), loss of response in 3 (4%), and resistance to therapy in 10 (13%) patients. Hematological toxicities of grade 3-4 were observed in 3 (3%) and of any grade in 14 patients (16%). Extra-hematological toxicity of grade 3-4 was observed in 14 (16%) patients.

Chamoun et al, 2017[45] did not report on harm outcomes.

Garcia-Gutierrez et al., 2019[47] reported on the toxicities of bosutinib; anemia (21%), thrombocytopenia (21%), diarrhea (39%) were the highest reported. In addition to neutropenia (10%), pleural/pericardial effusions (11%), cardiovascular events (5%), liver enzymes elevation (13%), acute pancreatitis (3%), and rash (8%).[47]

Caocci et al, 2019,[52] reported a higher incidence of recurrent AOEs in patients treated with a second or third generation TKI (5 year incidence = 47.8%) in comparison with the rate found in cardiovascular patients across European countries (10 year incidence = 20%). Sequential treatment with two or more second or third generation TKIs was also confirmed as a predictor risk factor for recurrent AOEs. Patients treated with nilotinib and ponatinib showed a higher incidence of recurrent AOEs (76.7 ± 14.3% and 64 ± 20.1%, respectively) than those treated with dasatinib and bosutinib (44 ± 24.2% and 30.5 ± 15.5% , respectively) p = 0.01. In multivariate analysis, treatment with a second or third generation TKI given as a second or subsequent line therapy showed a significant association with an increased incidence of recurrent AOR (p = 0.039).

Additional Outcomes Reported

Additional outcomes for patients included transformation to AP/BP CML, cross intolerance with bosutinib, prognostic and predictive factors for efficacy and safety outcomes, and renal outcomes (Table 8).

Table 8. Additional Outcomes Reported

Additional Reported Outcomes of Interest
Transformation to AP/BP CML For Study 200, on-treatment transformation to AP/BP CML at five years was reported at 4-5%[18,29-31] of all CP CML patients (7% for IM-R and 2% for IM-I),[13] 55% of patients discontinued without transformation, and 2 transformed to AP in years 3 to 5.[30,31] No BP transformation or new on-treatment transformations occurred after 2 years.[29] Similar rates were seen at years 4 when considering subgroup of patients <65 years (n=9, 4%) and ≥65 years (n=2, 3%).[18,30] For Study NCT00811070, 1 (2%) patient and 1 (17%) in CP2L and ADV experienced AP/BP transformation, respectively.[42] For Study BYOND, no patients progressed to accelerated/blast phase on treatment.[43] At a median follow-up from diagnosis of 96 months, Chamoun et al, 2017[45] reported, 39 (7%) of patients transformed to either accelerated (n=26, 5%) or to blast phase (n=13, 2%) while on 2nd-line TKI.
Cross-intolerance For Study 200 patients with CP CML, cross-intolerance with bosutinib (i.e., discontinued bosutinib due to the same AE that lead to discontinuation of prior imatinib) was reported between 16-24%.[17,18,29,34] The most common AEs were hematologic AEs; cross-intolerance in imatinib-intolerant patients was low for rash, diarrhea, edema/fluid retention, and myalgia as well as intolerance du to pleural effusion in dasatinib-intolerant patients.[34] No deaths on bosutinib due to the same AE that led to intolerance to any of the three prior TKIs occurred.[17,29,34]

Cross intolerance was reported in the Spanish Compassionate access program retrospective analysis.[47] Cross intolerance for the most common side effects with previous TKIs were anemia (39%), pleural effusions (28%), liver toxicity (33%), and vascular events (16%). For pleural effusions, 25/62 patients (40%) in the bosutinib cohort previously experienced plural effusions, all patients while on dasatinib and one patient with dasatinib and nilotinib. Twenty eight percent (7/25) of patients who experienced pleural effusions on dasatinib, also experienced it while on bosutinib.
Prognostic and predictive factors Based on Study 200, several factor were identified as predictive of MCyR, and CCyR by 3 and 6 months, including: prior IM cytometric response, baseline MCyR, prior interferon therapy, and <6 months duration from diagnosis to IM treatment initiation, and no interferon treatment before IM.[17] Baseline Ph+ ratio ≤35 vs. ≥95% was prognostic of MCyR and CCyR by 3 and 6 months as well as PD/death.[29,33] One publication reported that baseline bosutinib-sensitive BCR-ABL1 mutation was the only significant predictor of grade 3/4 diarrhea and there were no significant predictors identified for liver-related AEs.[17] Prognostic risk factors for vascular TEAEs were: age ≥65 years, a history of diabetes with first-line bosutinib, ECOG PS >0, and a history of vascular disorders in the second-line or later setting.[20] The prognostic risk factors for cardiac TEAEs with second-line or later bosutinib were: ≥65 years, ECOG PS > 0, a history of cardiac disorders, and history of hyperlipidemia/increased cholesterol.[20]
Renal Outcomes[28] In Study 200, renal AEs were reported in 73 patients (n=73/570, 13%) of patients receiving second-line or later bosutinib, follow-up duration was ≤30 days from treatment discontinuation. Overall, 139 (n=139/570, 24%) patients developed grade ≥3b eGFR, time to grade ≥3b eGFR was also shorter with second-line or later bosutinib compared with first-line bosutinib. Improved to ≥45 mL/min/1.73m^2 eGFR as of the last follow-up occurred in 53% of patients (n=74/139). Results suggest long-term bosutinib treatment is associated with apparently reversible decline in renal function similar to that observed with long-term imatinib treatment. Garcia-Guttierrez (2019), also reported that renal AEs were not reported in their study, which may be due to the short follow-up.
Efficacy and safety following bosutinib dose reduction[38] Of 570 CP2L/CP3L/ADV patients who received bosutinib, 257 (45%) experienced ≥1 dose reduction (236 patients to 400 mg/d and 95 to 300 mg/d). Patients achieved anew or maintained a previously achieved CCyR following dose reduction to 400 mg/d (achieved 29%, maintained 13%) and to 300 mg/d (achieved 14%, maintained 24%). TEAEs were generally similar in incidence, type and severity before and after dose reduction to 400 mg/d (diarrhea 84% versus 50%; nausea 45% versus 23%; vomiting 33% versus 21%) or to 300 mg/d (diarrhea 85% versus 31%; nausea 43% versus 14%; vomiting 34% versus 11%).

5. Discussion

5.1 Clinical Interpretation and Guidance

In order to address the Provincial Advisory Group's Request for Advice (RFA), the Clinical Guidance Panel updated the original interpretation and guidance sections of the pCODR 2015 review of bosutinib (Bosulif) for CML.[51] The update was based on the stakeholder input provided by the patient advocacy group and the systematic review evidence (Section 4).

As noted in the original pCODR submission for Bosutinib, approximately one-third of patients treated with imatinib for CP CML discontinue therapy because of disease progression (10%) or intolerance (25%). Adherence to treatment is acknowledged to be an important factor in optimizing outcomes in chronic phase CML. While emerging data suggest that some patients with durable complete molecular response to TKI therapy (> 4.5 log reduction in BCR-ABL transcripts, undetectable by PCR),[53] most patients can expect to be on lifelong therapy, and current treatments are associated with side effects that require dose reductions, treatment interruptions, medical management, or in some cases switching to an alternative TKI. However, intolerance and the resistance to second-line TKI's occurs as well. While allogeneic stem cell transplantation remains an option for patients with CML not responding adequately to TKI's, this treatment has very limited applicability (to recipient age <65, those with available donor) and still carries a risk of treatment-related mortality of 20-30% in the first year and results in 2 year EFS of 36% for those with kinase domain mutations.[18] Patients would prefer oral TKI therapy and the management of treatment-related side effects to the significant risks and long-term morbidity of allogeneic stem cell transplant. People living with CML are also concerned about the emergence of drug resistance while on TKI therapy, and bosutinib appears to provide an alternative for at least some cases of emerging drug resistance. The CGP acknowledged that these concerns and symptoms were also reported in patient group input, however, noting the patient population was younger.

The CGP noted that there is a phase III trial evaluating the use of bosutinib for the first line treatment of CML. Though, it is out of scope for the current RFA, the CGP commented that that adoption of bosutinib as first line therapy would be unlikely.

Evidence to support PAGs Request for Advice:

Bosutinib for Second line use:

At 24 months, 58% of patients who were imatinib resistant achieved major cytogenetic response and 46% complete cytogenetic response; at five years, MMR was achieved in 45% and CCyR in 48%. For imatinib intolerant patients the MCyR and CCR rates were 61% and 54% respectively after 24 months; MMR rate was 36% and CCyR 53% at five years.[18]

Bosutinib for Third and Fourth line use:

For patients resistant to imatinib and dasatinib, MCyR was seen in 31% of patients resistant to dasatinib, and 35% of patients resistant to imatinib and nilotinib. Importantly, amongst patients treated with two

prior TKIs who had documented kinase domain mutations conferring drug resistance, MCyR was seen in 26/39 and CCR in 11/35, including mutations conferring resistance to dasatinib or nilotinib. No major cytogenetic responses were observed following bosutinib in the seven patients with T3151 mutations.[15]

Bosutinib for Advanced Phase/Blast Phase use:

In this poor prognosis group, 40.3 % of accelerated phase patients and 37% of blast phase patients obtained a major cytogenetic response, an important outcome given their progression on prior TKI therapy. Progression free survival at 1 year for the accelerated phase patients was 65% and overall survival was 76%; for blast phase PFS and OS at 1 year were 14% and 44%. Notably, bosutinib was associated with an improvement in quality of life in both disease subgroups.

Safety

An extensive safety evaluation from the phase II SKI-200 has been reported, and the side effect profile of bosutinib appears to be similar to other TKI's used for the treatment of CML. The most frequent side effects were gastrointestinal (diarrhea, nausea and vomiting) and thrombocytopenia, but the majority of these events were grade 1 or 2 and resolved with successful re-initiation of therapy. The most significant grade 3 or 4 adverse events were diarrhea (10%) & thrombocytopenia (26%).[3] The CGP acknowledged that these concerns and symptoms were also reported in patient group input, however, noting the patient population was younger. Cross intolerance to bosutinib (defined as discontinuation of bosutinib for the same reason as the previous TKI) occurred in 11/50 patients who were dasatinib intolerant. For the 85 patients receiving second line therapy with bosutinib who had a specific AE leading to imatinib discontinuation, 14 patients had cross-intolerance to bosutinib.

Clinical Guidance Panel Interpretation of the Evidence on Effectiveness:

The CGP noted that based on the evidence for the RFA, bosutinib would appear to be an important addition to the treatment armamentarium for chronic myeloid leukemia. Cytogenetic response to second-line dasatinib has been associated with improved survival and has been used to inform regulatory approval.[10,54] The MMR and CCyR rates for bosutinib in the second line (post-imatinib failure or intolerance) appear to be in line with those achieved with dasatinib or nilotinib,[26] with a comparable rate of discontinuation for toxicity. The side effect profile of bosutinib differs from dasatinib, and imatinib, making this an attractive option for patients who are intolerant to previous TKI therapy. With regard to drug resistance, bosutinib appears to have activity in patients with mutations conferring the resistance to other TKIs, although new mutations did emerge on bosutinib therapy and no activity was seen in patients with T3151 mutations.[15]

In addition, the CGP noted that there is an ongoing Phase IV study demonstrated maximum response at any time, which is a different endpoint than MMR at 5 years.[43] The maximum response at any time data showed that bosutinib was effective and could induce MMR. The CGP also noted that bosutinib may be a better option after 1st line rather than after 3rd or 4th line of therapy. However, the CGP also noted that the population is not well-defined and the follow-up period is shorter than the SKI200 trial and the CGP can not comment on second-line results.

As noted in the original bosutinib submission,[51] the variability between provinces in funding of second-generation agents for first line therapy, the number of comorbidities that may be relative contraindications for the use of one of the currently available agents, and the unpredictable nature of emergence of drug resistance and treatment intolerance makes a general statement on sequencing of TKIs for CML difficult. Based on the data from the SKI200 trial, bosutinib would be appropriate for patients experiencing treatment failure following dasatinib or nilotinib. For patients who have experienced intolerance to a second-generation agent, the use of another second-generation agent is considered appropriate by the CGP, provided there would be no expected cross-intolerance. The most common reason for stopping bosutinib for cross intolerance in patients who has previously discontinued dasatinib was myelosuppression (grade 3-4 thrombocytopenia or neutropenia); only 2 of 19 patients who stopped dasatinib because of pleural effusion developed grade 3-4 effusions on bosutinib and in both cases the patients remained on therapy.[17] The most common side effects leading to cross-intolerance of imatinib and bosutinib were hematologic; however, most patients who discontinued imatinib for hematologic toxicity did not discontinue bosutinib for the same AE; similarly, only 1 of 7 patients who discontinued imatinib because of diarrhea stopped bosutinib for the same reason. Forecasting cross-intolerance between TKIs is a challenge, and data are insufficient for practitioners to allow choices of subsequent TKI that will avoid cross-intolerance with certainty.

Limitations of the evidence

The main limitation of the evidence supporting the use of bosutinib for second or third-line treatment of CP CML is a lack of a direct randomized comparison of alternative TKIs beyond first line treatment, or to other therapeutic alternatives, older agents such as hydroxyurea or interferon, or supportive care. The definitions of imatinib and dasatinib intolerance are necessarily somewhat subjective and the definition used in clinical trials may not be strictly adhered to in clinical practice, although most clinicians are experienced in managing TKI side effects, in light of the importance of treatment adherence to ultimate favorable outcome. In addition, a MAIC suggested ponatinib appeared to have a higher rate of CCyR than bosutinib, but these comparisons have significant methodologic limitations due to unknown heterogeneity between the study populations and differences in how outcomes were assessed (e.g. PFS definitions differed between the second-line CML MAIC).

5.2 Conclusions

Based on the evidence presented in the RFA, the Clinical Guidance Panel's overall conclusions remains that there is an overall clinical benefit to the use of bosutinib as second or third-line therapy in chronic phase CML for patients who are either resistant to or intolerant of a previous TKI. This recommendation is based on a single large phase II trial, with detailed analysis of toxicity experienced by patients who were resistant to or intolerant of imatinib and dasatinib. The Clinical Guidance Panel noted that there is limited head to head comparison data on bosutinib and other TKIs, and based on the available data, it is unknown whether bosutinib is better or worse than dasatinib or nilotinib and should be noted as an alternative second or third line treatment option for patients with CML.

In making this conclusion, the Clinical Guidance Panel considered that:

- Data on sequencing of TKIs are limited and not informed by controlled clinical trials; decisions beyond first line therapy are also significantly influenced by the agents available for front-line therapy, clinical judgment, CML mutation status and patient comorbidities.
- Patients with CML can anticipate lifelong therapy in the majority of cases. Current TKIs including bosutinib have side effects that can affect adherence to treatment and require careful monitoring and management.
- While a significant number of patients discontinued bosutinib due to treatment-related adverse events, this did not seem to vary according to prior therapy, and seemed comparable to discontinuation rates seen with the use of imatinib, dasatinib, and nilotinib in previous trials of those agents.
- Bosutinib toxicities consist mainly of gastrointestinal effects (nausea, vomiting, diarrhea) and myelosuppression which may be successfully managed with dose interruptions and limited degree of dose reductions without an apparent loss of benefit.
- The data presented do not answer the question of whether bosutinib is better than dasatinib or nilotinib, and does not address the questions of cross-reactivity between TKIs.
- Bosutinib is not likely to be the therapy of first choice in all patients who have experienced disease progression on imatinib, but would be appropriate in instances where a second generation agent may be ineffective or inappropriate because of a known mutation or anticipated cross-intolerance, or due to an underlying comorbidity that may be exacerbated by a second generation agent (eg nilotinib: diabetes or peripheral vascular disease; dasatinib: asthma or prior/existing pleural effusion).
- Data on use of bosutinib in accelerated or blast phase CML are limited, but the prognosis of this patient population is very poor and the results with older aggressive induction chemotherapies are unsatisfactory. The results reported with bosutinib indicate that it may be of value for patients who have received one or two prior TKIs.
- There are insufficient data to determine the benefit of bosutinib in patients who have been treated with all three TKIs previously. In a matched adjusted indirect comparison, ponatinib appeared to have a higher rate of CCyR than bosutinib, but these comparisons have significant methodologic limitations due to unknown heterogeneity between the study populations and differences in how outcomes were assessed (ex. PFS definitions differed between the second-line CML MAIC[26]. The CGP however felt that it was extremely unlikely that a direct comparison of bosutinib to ponatinib or supportive care after failure of 2 or 3 prior TKIs will be conducted in the future. A comparison to supportive care only is unlikely to be acceptable to clinicians or patients with advanced CML

Appendix 1- Critical Appraisal of Included Studies

Select quality characteristics of included studies for the Bosutinib CML Request for Advice based on the Cochrane Tool to Assess Risk of Bias in Cohort Studies & Signorovitch et al., 2012 MAIC tool.[50]

The Non-Comparative Clinical Trials and Retrospective Chart Reviews were appraised using the SIGN50 Checklist for Cohort Studies.

Table 1. Critical appraisal of Study 200

	Study 200					
SIGN50 Questions ***Responses can be from the following:*** ***✓ Yes*** ***X No*** ***? Can't Say*** ***N/A Not Applicable***	**Gambacorti-Passerini et al, 2018[18]** (Fully Published)	**Cortes et al, 2016[29]** (Fully Published)	**Gambacorti-Passerini et al, 2015[14]** (Fully Published)	**Gambacorti-Passerini et al, 2018 (39)** (Abstract)	**Kantarjian et al, 2018 (57)[40]** (Fully Published)	**Whiteley et al, 2016[39]** (Fully Published)
1. The study addresses an appropriate and clearly focused question.	✓	✓	✓	✓	✓	✓
2. The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	N/A. There is no comparison group.	N/A. There is no comparison group.	N/A. There is no comparison group.	N/A. There is no comparison group.	N/A. There is no comparison group.	N/A. There is no comparison group.
3. The study indicates how many of the people asked to take part did so, in each of the groups being studied.	N/A. There is no comparison group.	N/A. There is no comparison group.	N/A. There is no comparison group.	N/A. There is no comparison group.	N/A. There is no comparison group.	N/A. There is no comparison group.
4. The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	✓	✓	✓	✓	✓	✓
5. What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	Lost to follow-up: 4 (1%, N=284)	Lost to follow-up: 2 (2%m N=119)	Year 1 Lost to follow-up: 0 for AP CML (N=79), 1 (2%) for BP CML, 0 for ALL (N=24)	?	At treatment completion: Eq-5D: 68% CP2L; 66% CP3L FACT-Leu: 66% CP2L; 65% CP3L	At week 96: Eq-5D: 18% AP; 3% BP FACT-Leu: 16% AP; 3% BP

	Study 200					
			Year 3-4: 0 for all cohorts			
6. Comparison is made between full participants and those lost to follow up, by exposure status.	N/A. Single group study.	N/A. Single group study.	N/A. Single group study.	N/A. Single group study.	N/A. Single group study.	N/A. Single group study.
7. The outcomes are clearly defined.	✓	✓	✓	✓	✓	✓
8. The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	X Open-label study.	X Open-label study.	X Open-label study.	X Open-label study.	X Open-label study.	X Open-label study.
9. Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	X	X	X	X	X	X
10. The method of assessment of exposure is reliable.	✓	✓	✓	?	✓	✓
11. Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	✓	✓	✓	?	X	X
12. Exposure level or prognostic factor is assessed more than once.	✓	✓	✓	?	?	?
13. The main potential confounders are identified and taken into account in the design and analysis.	X	X	X	X	X	X
14. Have confidence intervals been provided?	✓	✓	✓	X	✓	✓
15. How well was the study done to minimise the risk of bias or confounding?	High quality (++) ☐ Acceptable (+) ☒ Unacceptable - reject ☐	High quality (++) ☐ Acceptable (+) ☒ Unacceptable - reject ☐	High quality (++) ☐ Acceptable (+) ☒ Unacceptable - reject ☐	High quality (++) ☐ Acceptable (+) ☐ Unacceptable - reject ☒	High quality (++) ☐ Acceptable (+) ☒ Unacceptable - reject ☐	High quality (++) ☐ Acceptable (+) ☒ Unacceptable - reject ☐
16. Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	No comparison group, wide confidence intervals on outcome measures, missing data on patient selection, and unknown confounding.	No comparison group, wide confidence intervals on outcome measures, missing data on patient selection, and unknown confounding.	No comparison group, wide confidence intervals on outcome measures, missing data on patient selection, and unknown confounding.	Limited reporting given abstract publication, no comparison group, wide confidence intervals on outcome measures, missing data on patient selection, and unknown confounding.	QoL is secondary outcome, no comparison group, wide confidence intervals, and low completion rate.	QoL is secondary outcome, no comparison group, wide confidence intervals, and low completion rate.

	Study 200					
17. Are the results of this study directly applicable to the patient group targeted in this guideline?	✓	✓	✓	✓	✓	✓
18. Notes. Summarise the authors conclusion. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.	Bosutinib demonstrated durable efficacy and manageable toxicity through year 5.	Bosutinib demonstrated durable efficacy and manageable toxicity similar to previous bosutinib studies in CP CL patients R/I to multiple TKIs.	Bosutinib demonstrates a durable response, with ~50% of AP responders maintaining a response at 4 years.	Bosutinib showed long-term efficacy in previously treated patients with CL. Incidence of cardiac, vascular and hypertension TEAEs was low and events infrequently led to treatment withdrawal.	HRQOL was maintained with long-term bosutinib treatment for patients with CP2L and CP3L CML.	Bosutinib therapy is associated with improved HRQoL in advanced phase CML patients.

Table 2. Critical appraisal of Study NCT00811070, Study BYOND and observationalstudies

	Study NCT00811070	Study BYOND	Observational studies			
SIGN50 Questions ***Responses can be from the following:*** ***✓ Yes*** ***X No*** ***? Can't Say*** ***N/A Not Applicable***	**Takahashi et al, 2017[42]** (Fully Published)	**Gambacorti-Passerini et al, 2019[43]** (Abstract)	**Attolico et al, 2018[44]** (Abstract)	**Chamoun et al, 2017[45]** (Abstract)	**Garcia-Gutierrez et al, 2019[47]** (Fully Published)	**Caocci et al, 2019[48]** **(Fully published)**
19. The study addresses an appropriate and clearly focused question.	✓	✓	✓	✓	✓	✓
20. The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	N/A. There is no comparison group.	N/A. There is no comparison group.	N/A. There is no comparison group.	? Not reported.	N/A. There is no comparison group.	? Not Reported
21. The study indicates how many of the people asked to take part did so, in each of the groups being studied.	N/A. There is no comparison group.	N/A. There is no comparison group.	N/A. There is no comparison group.	? Not reported.	N/A There is no comparison group.	? Not Reported
22. The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	✓	✓	✓	✓	✓	✓
23. What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	0%. 46% continued treatment until study completion and 54% discontinued study treatment.	Not reported.	Not reported.	Not reported.	Twenty-two patients (36%) discontinued treatment. Intolerance (16%) and lack of efficacy (9%) were the	Not reported

	Study NCT00811070	Study BYOND	Observational studies			
					most common reasons for discontinuation.	
24. Comparison is made between full participants and those lost to follow up, by exposure status.	N/A. Single group study.	N/A. Single group study.	N/A. Single group study.	? Not reported.	N/A. Single group study.	? Not reported
25. The outcomes are clearly defined.	✓	✓	? Abstract only.	? Abstract only.	✓	✓
26. The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	X Open-label study.	X Open-label study.	N/A Retrospective.	N/A Retrospective.	N/A. Retrospective.	? Unknown
27. Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	X	X	?	?	X	✓
28. The method of assessment of exposure is reliable.	✓	? Abstract only.	? Abstract only.	? Abstract only.	✓	X Dosage not reported
29. Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	✓	? Unknown	✓	✓	✓	? Unknown
30. Exposure level or prognostic factor is assessed more than once.	✓	? Unknown	? Unknown	? Unknown	✓	? Unknown
31. The main potential confounders are identified and taken into account in the design and analysis.	X	X	?	?	✓	X
32. Have confidence intervals been provided?	✓	✓	X	✓	✓ for Median EFS X for all other outcomes	X
33. How well was the study done to minimise the risk of bias or confounding?	High quality (++) ☐ Acceptable (+) ☒ Unacceptable - reject ☐	High quality (++) ☐ Acceptable (+) ☐ Unacceptable - reject ☒	High quality (++) ☐ Acceptable (+) ☐ Unacceptable - reject ☒	High quality (++) ☐ Acceptable (+) ☐ Unacceptable - reject ☒	High quality (++) ☐ Acceptable (+) ☒ Unacceptable - reject ☐	High quality (++) ☐ Acceptable (+) ☐ Unacceptable - reject ☒
34. Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	No comparison group, wide confidence intervals on outcome measures, missing data on patient selection, and unknown confounding.	No comparison group, abstract only and reporting of key methodology and outcomes were not available. The study was not powered for the primary endpoint.	Abstract only and reporting of key methodology and outcomes were not available.	Abstract only and reporting of key methodology and outcomes were not available. The statistical power of the study is not clear.	No comparison group, confidence intervals not reported. A general association identified by response at baseline.	TKI treatment is known to cause AOE events and the treatment for CML is TKI treatment. The association between TKI treatment and AOE, irrespective of CML is not explored.
35. Are the results of this study directly applicable to the patient group targeted in this guideline?	✓	✓	✓ Yes but caveat enrolled only patients from Italy.	✓ Yes but caveat enrolled patients from a single institution.	✓ Yes but caveat enrolled only patients from Spain.	✓

	Study NCT00811070	Study BYOND	Observational studies			
	Yes but caveat that only enrolled patients from Japan.					Yes but caveat enrolled only patients from one center in Italy.
36. Notes. Summarise the authors conclusion. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.	Bosutinib should be considered a promising option in the group of TKIs that have demonstrated safety and efficacy in Japanese patients with CML.	Results further supported bosutinib use for Ph+ CP CML resistant/intolerant to prior TKIs.	Real-life experience with bosutinib confirmed stable long-term efficacy in heavily pre-treated, mainly elderly patients with I/R to other TKIs, who show an initial response to treatment, as reported in clinical trials.	Dasatinib, nilotinib and bosutinib remain largely effective in inducing cytogenetic and molecular response when used as a 2-line TKI with similar OS, TFS and EFS in the overall patient population.	Bosutinib is a treatment option for heavily treated CML patients who are intolerant to previous TKIs.	CML patients with a previous history of AOE treated with second or third generation TKI may have higher probability of experiencing recurrent AOE.

Appendix 2: pERC Original Recommendation from 2015

pCODR EXPERT REVIEW COMMITTEE (pERC) FINAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

pERC Final Recommendation
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

Drug: Bosutinib (Bosulif)

Submitted Funding Request:

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, and for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate.

Submitted By: Pfizer Canada Inc.	**Manufactured By:** Pfizer Canada Inc.
NOC/c Date: March 07, 2014	**Submission Date:** May 30, 2014
Initial Recommendation: April 2, 2015	**Final Recommendation:** **April 21, 2015**

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding bosutinib conditional on the cost effectiveness being improved to an acceptable level. Funding should be for the treatment of patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) who have resistance or intolerance to prior TKI therapy, and for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate. Funding should be in patients who have a good performance status

The Committee made this recommendation because it concluded there was a net clinical benefit of bosutinib based on clinically meaningful major cytogenetic response rates, 1 and 2 year progression free survival and overall survival rates, a manageable toxicity profile and because it aligns with patient values. pERC, however, acknowledged that because of the non-comparative study design, there was considerable uncertainty around the magnitude of the net clinical benefit in comparison to other treatment options and, therefore, in the cost-effectiveness of bosutinib. This led to a wide range in the incremental cost-effectiveness estimates, all of which pERC considered unacceptable. Therefore, bosutinib could not be considered cost-effective using either the manufacturer's or the Economic Guidance Panel's reanalysis estimates.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Collecting Evidence to Reduce Uncertainty in the Clinical Benefit and Cost-Effectiveness of Bosutinib

Given the considerable uncertainty in the magnitude of clinical benefit of bosutinib in patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML), pERC concluded that any additional prospective evidence that could be collected to decrease the uncertainty in the incremental effect would be of benefit in understanding the true cost-effectiveness of bosutinib. Specific information on efficacy, safety and quality of life would be of particular value.

Pricing Arrangements to Limit Budget Impact

Given that pERC was satisfied that there is a net clinical benefit of bosutinib in patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML), jurisdictions may want to consider pricing arrangements and/or cost structures that may help reduce the uncertainty in the budget impact of bosutinib.

SUMMARY OF pERC DELIBERATIONS

pERC's Deliberative Framework for drug funding recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

Chronic Myelogenous Leukemia (CML) is an uncommon clonal bone marrow stem cell disorder. There are approximately 450 cases of CML diagnosed annually in Canada with the majority of patients diagnosed in the chronic phase (CP) of the illness. The majority of CML patients are ineligible for potentially curative therapy with allogenic stem cell transplantation (ASCT). pERC noted that for those patients who are not candidates for ASCT, current therapies include the BCR-ABL tyrosine kinase inhibitor (TKI), imatinib in the first-line setting, or second generation TKIs, dasatinib and nilotinib, used as first or second-line treatment. Patients may be considered inappropriate for dasatinib or nilotinib treatment if they have a genetic mutation that predicts for reduced efficacy of a second-line agent or if patients have co-morbidities that may predispose them to a drug-related adverse events. Patients may also receive interferon in the third-line setting while patients with disease in the accelerated phase (AP) and blast phase (BP) setting may receive palliative treatment with hydroxyurea. Some of these available treatments are associated with significant toxicities, and have limited clinical benefit. Having considered that patients with CML can receive treatment for as long as 10 years, pERC noted the importance of new agents that are active with less toxicity and less risk of exacerbating existing co-morbidities.

The pCODR systematic review included one non-comparative study (SKI-200), which examined the use of bosutinib in patients who were intolerant or resistant to imatinib, dasatinib or nilotinib. pERC concluded that there is a net clinical benefit of bosutinib in patients with chronic, accelerated or blast phase CML who have been treated with at least one previous TKI and are deemed to be intolerant or resistant to imatinib, dasatinib and nilotinib treatment. pERC considered the magnitude of major cytogenetic response (MCyR) experienced by a large proportion of patients in the SKI-200 study to be clinically meaningful. pERC accepted the Clinical Guidance Panel's conclusion that MCyR is a reasonable surrogate for overall survival and acknowledged that the substantial benefit in the one and two year progression free survival (PFS) and overall survival (OS) further supported the conclusion of a net clinical benefit. pERC discussed the quality of life (QoL) of patients in the study and noted that statistically significant improvements were observed from baseline for a number of scales in all subgroups of patients. While the patients in the trial were reflective of the clinical population and had a good QoL, the added improvement in QoL following treatment with bosutinib, particularly in the AP and BP population, were noted by pERC as improvements in QoL are not usually observed in this advanced disease setting. pERC also commended the collection and availability of long term QoL data in this study. pERC discussed the limitations of non-randomized studies and considered that, although the SKI-200 trial was appropriately conducted, the conclusions that can be drawn from non-comparative data are not as robust as those that can be drawn from randomized controlled trials. Therefore while pERC acknowledged that bosutinib demonstrates clinical benefit in patients, there was considerable uncertainty in the magnitude of benefit with bosutinib as randomized controlled trials comparing bosutinib to dasatinib, nilotinib and/or other relevant comparators including best supportive care (BSC) were not available. pERC also discussed the Clinical Guidance Panel's conclusions that a randomised controlled trial would not be feasible in this patient population. Following a robust discussion the Committee had contrary thoughts on feasibility issues and equipoise in the second-line setting as there were sufficient numbers of patients in the second-line setting who could have been randomised among currently available treatments to determine comparative efficacy. pERC, however, agreed that a randomised controlled trial would not be feasible beyond the second-line setting.

pERC discussed the toxicity profile of bosutinib and noted it to be different from currently available TKI's. Toxicities associated with bosutinib consisted mainly of gastrointestinal events (diarrhea, nausea and vomiting) and thrombocytopenia. These were noted to be more manageable in comparison to the toxicities associated with the other available TKI's (exacerbation of diabetes or peripheral vascular disease with nilotinib and asthma or prior/existing pleural effusion with dasatinib). In discussing treatment options other than TKIs, pERC noted that patients currently receive other treatments that are associated with a negative impact on quality of life and significant toxicities (interferon in third-line CP patients and hydroxyurea in AP). Having discussed these multiple factors, pERC concluded that, subject to improved cost-effectiveness, bosutinib should be available for adult patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) with resistance or intolerance to prior TKI therapy, and for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate. pERC acknowledged that this population will predominantly be comprised of those who have exhausted funded TKI treatment options (i.e. in the third-line setting) but there will also be rare circumstances in which patients will have pre-existing comorbidities or resistance/intolerance to dasatinib or nilotinib and may benefit from treatment with bosutinib (i.e. in the second-line setting).

pERC deliberated on patient advocacy group input, which indicated that patients with CML value the addition of new treatment options that provide manageable toxicity profiles and improve quality of life. pERC agreed that bosutinib aligned with patient values based on the improvement in MCyR which is an acceptable surrogate for overall survival, one and two year progression-free survival rates, a manageable toxicity profile, and notable improvements in quality of life. pERC noted input from patients who had experience with bosutinib indicating that in some instances patients were able to return to work. This was consistent with the study results which showed notable improvements in quality of life (QoL).

pERC deliberated upon two economic analyses submitted by the manufacturer providing estimates on the cost-effectiveness of bosutinib compared with relevant treatment options. pERC discussed a comparison of bosutinib to dasatinib or nilotinib through a cost-minimization analysis (CMA). pERC noted that this type of economic analysis is only appropriate in instances where all efficacy outcomes (clinical effect, safety and QoL) have been demonstrated to be similar through a randomized controlled trial or an appropriately conducted network meta-analysis. In this submission, pERC noted that there is no direct or indirect evidence to validate assumptions of similar efficacy between bosutinib and dasatinib or nilotinib. pERC additionally considered that bosutinib has a different toxicity profile than the currently available TKIs and agreed with the Economic Guidance Panel (EGP) that the use of a CMA is inappropriate in this circumstance. A cost utility analysis addressing differences in cost and effectiveness is needed to determine the true cost-effectiveness of bosutinib compared to dasatinib or nilotinib. pERC was, therefore, unable to determine the cost-effectiveness of bosutinib. pERC acknowledged that the first deliberation by pERC on this review was deferred pending the provision of a cost-utility analysis to address the limitations discussed above. Additionally, the EGP had requested a cost-utilization analysis from the submitter on a number of occasions, in order to examine best supportive care as a comparator but this was not provided at the time.

pERC also discussed the results of a cost utility analysis it requested from the submitter, comparing bosutinib to hydroxyurea, interferon or stem cell transplant (SCT). In the absence of direct or indirect comparative data, pERC noted that multiple data sources from the literature and/or assumptions were used to populate clinical inputs within the cost utility analysis, all of which were confounded by factors that would be controlled for in an RCT. pERC, therefore, noted that due to the limitations of relying on non-comparative evidence from the SKI-200 study, there was substantial uncertainty in the magnitude of the clinical benefit associated with bosutinib. This made it challenging to estimate the incremental effect of treatment with bosutinib and, therefore, the resulting incremental cost-effectiveness estimates for bosutinib. This considerable uncertainty in the magnitude of clinical benefit of bosutinib led to a wide range of incremental cost-effectiveness estimates, all of which pERC considered unacceptable. Therefore, bosutinib could not be considered cost-effective at the submitted price.

pERC discussed the feasibility of implementing a positive funding recommendation for bosutinib. Input from the pCODR's Provincial Advisory Group indicated that there were concerns about indication creep into the first and second-line setting. Based upon discussion of the clinical evidence and the need for alternative treatment options in patients that have pre-existing conditions that make currently available second-line treatments, pERC agreed that it would be reasonable to use bosutinib in patients that have failed at least one previous TKI. pERC agreed that this would likely occur only in rare circumstances and that the patient population which will predominantly be treated with bosutinib are those who will have exhausted all available treatment options. pERC acknowledged that jurisdictions will need to consider the potential budgetary impact of making bosutinib available in the second or third-line setting. pERC noted that the first line use of bosutinib is not likely as there is no evidence that bosutinib is superior to imatinib. Having considered that patients are likely to be on lifelong treatment and will receive available TKIs in sequence, pERC discussed the potential sequencing of treatment with bosutinib and other currently available TKIs. pERC acknowledged that data on sequencing of TKIs are limited and not informed by controlled clinical trials. pERC, however, agreed with the Clinical Guidance Panel that decisions beyond first-line therapy will likely be guided by the agents available for first-line therapy, clinical judgment, CML mutation status, and patient comorbidities. pERC discussed PAG's input highlighting the absence of a comparator arm in the study and acknowledging that although bosutinib shows meaningful clinical benefit, pERC was unable to determine the magnitude of the benefit as comparative data were not available.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from one patient advocacy groups (The Chronic Myelogenous Leukemia Society of Canada)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- the Submitter (Pfizer Canada Inc.)

The pERC initial recommendation was to fund bosutinib conditional on the cost effectiveness being improved to an acceptable level

Feedback on the pERC Initial Recommendation indicated that the manufacturer and pCODR's Provincial Advisory Group agreed with the initial recommendation.

The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The objective of this review is to evaluate the effectiveness of bosutinib monotherapy for the treatment of chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) CML in adult patients with resistance or intolerance to prior TKI therapy, and for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate.

Studies included

The pCODR systematic review included one phase 1/2, open label study (SKI-200) examining the use of bosutinib in patients who were intolerant or resistant to imatinib, dasatinib or nilotinib. Bosutinib was given at a dose of 500mg/day. The dose could be adjusted to 600mg/day if patients were not responding and lowered to 300mg/day if patient's experienced severe drug related adverse events. pERC noted that a significant minority of patients who did not achieve response at the 500mg dose received an increase in dose to 600mg. pERC agreed that jurisdictions will need to consider the budgetary impact of this dose increase during implementation.

No randomized controlled trials were identified that met the eligibility criteria of this systematic review. pERC discussed the limitations of non-comparative data and the feasibility of conducting a randomized controlled trial in this population. Having noted the Clinical Guidance Panel's conclusion that a randomized controlled trial is likely not feasible, members expressed a variety of opinions regarding equipoise. Although previous regulatory approvals in CML have been made using non-comparative data, pERC noted that the second-line cohort within the study may have had sufficient patient numbers for randomization among appropriate comparators. pERC however agreed that a randomised trial would not be feasible for patients in the setting of third-line setting and beyond.

The pCODR review also provided contextual information on results from the BELA study (Cortes et al 2012 and Brummendorf et al 2014), an open-label randomized multinational phase III trial funded by Pfizer comparing bosutinib to imatinib for adult patients with a new (≤ 6 months) diagnosis of Ph-positive CP CML who had received no prior anti-leukemia treatment (except ≤ 6 months of anagrelide or hydroxyurea). pERC discussed the summary of results provided on the BELA study and agreed with the Clinical Guidance Panel's conclusion that the use of bosutinib as first-line therapy would be unlikely as the trial data did not support the superior efficacy of bosutinib compared to imatinib in this setting.

Patient populations: Heterogeneous CML population

The SKI-200 study included 546 patients receiving treatment in the following lines;

- 288 second-line CP (n=200 imatinib resistant and n=88 imatinib intolerant), of these 115 patients had mutations at baseline;
- 144 third-line CP (n=37 imatinib resistant or intolerant and dasatinib resistant, n=50 imatinib resistant or intolerant and dasatinib intolerant, n=27 imatinib resistant or intolerant and nilotinib resistant), of these 39 patients had mutations at baseline;
- 4 fourth line CP;
- 76 AP and 64 BP patients

The median age of patients was 53, 56, 50.5 and 48.5 in the second-line CP, third/fourth line CP, AP and BP arms of the trial, respectively. The majority of patients had an ECOG PS of 0 or 1 in the second-line CP (77% or 23%), third/fourth line CP (72% or 27), AP (54% or 43%) and BP (34% or 44%) arms, respectively. Twenty two percent of patients in the BP arm also had an ECOG PS of 2.

Key efficacy results: Clinically meaningful improvement in MCyR, 1 and 2 year OS

Key efficacy outcomes deliberated on by pERC included major cytogenic response (MCyR) and progression free survival (PFS). MCyR was achieved in 59%, 32%, 35% and 30% of second line CP, third/fourth line CP, AP and BP patients, respectively. Although response rates decreased as the disease became more aggressive, pERC noted that the proportions of patients responding in each line of therapy did not differ among patients based upon resistance or intolerance to previous therapies. Similar rates of MCyR were also observed between patients with and without BCR-ABL mutations, with the exception of the T315I mutation. pERC also discussed improvements in 1 and 2 year PFS rates of 91% and 81% in the second-line CP patients and a 2 year OS rate of 91% in the second line cohort. This further supported the conclusion of net clinical benefit. One and two year OS rates were also 91% and 83% in the third and fourth-line cohorts.

pERC discussed the magnitude of MCyR experienced by patients and concluded it to be clinically meaningful. Although median OS data was not available, pERC considered the CGP's rationale regarding the association of OS with cytogenetic response in previous CML studies assessing second line therapy. Although recognizing that there is no direct evidence to support this correlation for bosutinib, pERC considered the high MCyR rates observed with bosutinib across all patient subgroups, the preservation of overall survival over one and two years and the magnitude of one and two year PFS supported the CGP's conclusion that bosutinib likely provides an OS benefit over BSC, hydroxyurea or interferon. pERC was, however, unable to determine the magnitude of benefit in comparison to other available therapies (dasatinib or nilotinib). Additionally, pERC noted the use of cytogenetic response in informing regulatory approvals for other drugs in this setting and the consensus within the CML treating community regarding MCyR being a surrogate for OS after over 10 years' experience of using TKI's in clinical practice. Having considered these factors, pERC accepted that the Clinical Guidance Panel's conclusion that MCyR is a reasonable surrogate for OS.

Quality of life: Improved quality of life during treatment

pERC noted input from patients highlighting the importance of a good quality of life during therapy. Patients indicated that this is important aspect for long term therapy as it would enable them to consistently stay on this therapy. pERC discussed that bosutinib provided improvements in quality of life to patients in most subgroups. Significant changes were observed as early as four weeks in both imatinib resistant and intolerant 2nd line CP patients. There were minimally important differences observed in the imatinib intolerant group only. Significant changes were also measured in 3rd line patients using the leukemia symptoms tool (LEUS) in dasatinib intolerant patients at weeks 12 and 24 ($p<0.01$), and in nilotinib-resistant subjects at weeks 4 and 8 ($p<0.05$). In AP and BP patients, clinically meaningful improvements in excess of the minimally important difference (MID) were observed at weeks 24 and 48 in the accelerated phase patients and in week 48 in the blast phase patients. pERC noted this to be of importance as improvements in quality of life are not routinely observed in patients with CML while on treatment, particularly in the AP and BP stage of their disease. Patients also reported that there can be exacerbations of pre-existing conditions with currently available TKI's (e.g. asthma, diabetes]'s, and a negative impact on quality of life due to the toxicities associated with agents such as interferon in third-line setting. They also noted that for CML patients in the acute blast phase, therapy is largely supportive care. Further to this, pERC noted that patients entered into the trial, although reflective of the clinical population, generally had a good QoL. The added improvement in quality of life further supported the benefit of bosutinib in preserving and improving the quality of life of patients. pERC also commended the collection and availability of long term QoL data in this study as it is of great importance to patients.

Safety: Manageable toxicity profile
pERC noted that the side effect profile of bosutinib differed from dasatinib and imatinib. Bosutinib toxicities consisted mainly of gastrointestinal effects (nausea, vomiting, diarrhea) and myelosuppression which may be successfully managed with dose interruptions and/or dose reductions without an apparent loss of benefit. Adverse events for patients with AP and BP CML were also similar to chronic phase patients. pERC contrasted this with the toxicities associated with the other available TKI's, including the exacerbation of underlying conditions (e.g. nilotinib: diabetes or peripheral vascular disease; dasatinib: asthma or prior/existing pleural effusion). Although comparative evidence is not available, pERC considered that bosutinib related toxicities are generally more manageable.

Limitations: No direct comparison with currently available TKIs for use in 2nd line and beyond setting and no ongoing trials
pERC noted the absence of a direct comparison to other TKI's to be a limitation in the presented evidence for bosutinib. pERC discussed the limitations of non-randomized, non-comparative studies and considered that, although the SKI-200 trial was appropriately conducted, the conclusions that can be drawn from non-randomized, non-comparative data are not as robust as those that can be drawn from randomized controlled trials. pERC considered that, given the lack of randomized comparative studies, there is considerable uncertainty surrounding the magnitude of clinical benefit of bosutinib. pERC also discussed the feasibility of conducting a randomized controlled trial and had varying opinions. pERC noted that the pivotal study recruited 288 second line patients and considered that randomization may have been reasonable and equipoise may have been present. pERC also noted that there are no planned or ongoing trials that will compare bosutinib with relevant comparators in this setting. pERC, however, acknowledged that the limited prevalence of patients in third line setting and beyond does not make randomization feasible.

Need: Resistant and intolerant patients
Chronic Myelogenous Leukemia is an uncommon clonal bone marrow stem cell disorder with approximately 450 cases diagnosed annually in Canada with a median age of diagnosis 65 years. The majority of patients are diagnosed in the chronic phase (CP) of the illness. pERC noted that, although curative therapy is available with allogeneic stem cell transplant (ASCT), only approximately 20-25% of patients are eligible for this treatment. Currently available therapies in patients ineligible for ASCT include the BCR-ABL tyrosine kinase inhibitor (TKI) imatinib in the first-line setting as well as the second generation TKIs, dasatinib and nilotinib, agents which are used as first or second-line treatment for CML. pERC noted that there is no information on the optimal sequencing of therapies and the inclusion of bosutinib into this algorithm will likely be influenced by the agents available for first-line therapy and second-line settings, clinical judgment, CML mutation status and patient comorbidities.

pERC noted that patients face life long treatment that can be is long as 10 years or greater and adherence to treatment is acknowledged to be an important factor in optimizing outcomes in chronic phase CML. While intolerance and resistance to second-line TKIs occurs in some patients, allogeneic stem cell transplantation, an available treatment option at that progressed stage of disease, has very limited applicability and carries a risk of treatment-related mortality of 20-30% in the first year. pERC agreed that, in patients who develop resistance or intolerance to current therapies, there remains an unmet need for more effective and tolerable therapies in the treatment of chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML).

PATIENT-BASED VALUES

Values of patients with Chronic Myelogenous Leukemia: Quality of life, disease control, treatment option
pERC deliberated on patient advocacy group input and noted that quality of life and the availability of new treatment options were important to patients. pERC noted that for a smaller population of CML patients, the available treatments are either not well tolerated and/or their disease becomes resistant. Patients thus reported experiencing fear and anxiety of not having their disease well controlled and the possibility of progressing into the accelerated or blast phase, for which few treatments currently exist.
Patient values on treatment: treatment options, tolerable side effect profile
pERC noted that patients place importance on access to new treatment options that provide manageable toxicity profiles and improve quality of life. pERC agreed that in providing improvements in MCyR rates, which is an acceptable surrogate for overall survival, improving 1 and 2 year progression-free survival, providing a manageable toxicity profile and notable improvements in quality of life, bosutinib aligned with patient values. pERC also noted that the importance of having treatments that have a safer toxicity profile and do not exacerbate any pre-existing conditions (e.g. asthma, COPD) was highlighted by patients. In alignment with these patient values, pERC agreed that bosutinib provided a treatment option with notable improvements in QoL, an

observation not generally seen in this setting. pERC also noted that the toxicity profile of bosutinib was unlike other TKI's and was easier to manage. Overall, pERC concluded that bosutinib aligned with patient values. pERC noted input from patients who had experience with bosutinib which indicated that the side effects of bosutinib were easier to manage compared to those associated with the currently available treatment options. In some instances patients were able to return to work which pERC noted to be in aligned with the results of the study reporting notable improvements in QoL.

ECONOMIC EVALUATION

Economic model submitted: Cost-minimization and cost utility analysis

The pCODR Economic Guidance Panel (EGP) assessed a cost-minimization analysis comparing the cost of bosutinib with dasatinib or nilotinib 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, and for whom subsequent treatment with imatinib, nilotinib and dasatinib was not clinically appropriate (advanced treatment lines, i.e. second-line therapy and beyond). pERC expressed disappointment in the provision of an economic analysis that was inappropriate for the available clinical data and deferred making a recommendation during the first deliberations on this submission. pERC requested a cost-utility analysis to address the limitations discussed above. Additionally, the EGP had requested a cost-utilization analysis from the submitter, on a number of occasions in order to examine best supportive care as a comparator but this was not provided.

The EGP also assessed a cost-utility analysis, requested by pERC, comparing the cost of bosutinib with hydroxyurea, interferon or stem cell transplant 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, and for whom subsequent treatment with imatinib, nilotinib and dasatinib was not clinically appropriate (advanced treatment lines, i.e. second-line therapy and beyond).

Basis of the economic model: Non-Comparative data used in a Cost Minimization and Cost Utility analysis

Costs considered in the cost-minimization analysis included only the drug cost. pERC noted that there were likely additional costs associated with the management of adverse events but these were not included.

Costs considered in the cost-utility analysis included drug costs, health care resource utilization costs, costs for adverse events and end of life care costs. The clinical effect considered in the cost utility analysis was based on overall survival (CP patients), progression-free survival (CP patients), time spent in the phase (AP and BP patients), treatment duration, and utilities.

Drug costs: submitted confidential price

At the list price, bosutinib costs $36.59 per 100mg tablet or $146.34 per 500mg tablet. At the recommended daily dose of 500mg for all phases (CP, AP, BP), bosutinib costs $146.34 per day and $4,097.52 per 28 day course. Depending on the combination of tablets used to provide a 500mg dose (5 x 100mg or 1 x 500mg), the price of bosutinib may be as high as $182.93 per day and $5,122.04 per 28 day course. At the recommended dose of 500mg for all phases (CP, AP, BP), and using the confidential price, bosutinib costs $[redacted] per day and $[redacted] per 28-day course. *(The cost of bosutinib is based on a confidential price submitted by the manufacturer and cannot be disclosed to the public according to the pCODR Disclosure of Information guidelines.)*

pERC noted potential concerns for drug wastage in patients who may be dispensed the 500mg tablets but do not tolerate it and then have their dose reduced to 400mg. pERC also noted that 15% of imatinib resistant chronic phase patients and 17% of third-line patients had an inadequate response to the initial 500mg dose and received an escalated dose of 600mg, with no apparent increase in adverse events. pERC noted that this increase in dosage will likely result in increased drug cost and should be considered in jurisdiction's budget impact analysis.

Dasatinib costs $38.00 per 20mg tablet, $76.48 per 50mg tablet, $84.29 per 70mg tablet and $152.86 per 100mg tablet. At the recommended daily dose of 100mg in the CP patients, dasatinib costs $152.86 per day and $4,280.08 per 28 day course. In AP and BP patients and at the recommended dose of 140mg, dasatinib costs $168.58 per day and $4,720.24 per 28 day course.

Nilotinib costs $28.72, per 150mg tablet and $39.72 per 200mg tablet. At the recommended daily dose of 800mg for the CP and AP (nilotinib was not examined for the BP), nilotinib costs $158.88 per day and $4,448.64 per 28 day for both phases.

Hydroxyurea costs $1.0203 per 500 mg capsule. At the recommended average daily dose of 20-30 mg/kg, hydroxyurea costs $3.06 - $4.08 per day and $85.71 - $114.27 per 28 day cycle.

Interferon costs $218.76, $364.60 and $729.19 per 18mu, 30mu, and 60mu, respectively. At the recommended average daily dose of 4-5 million units/m2, interferon costs $82.64 per day and $2,313.99 per 28 day cycle.

Cost-effectiveness estimates: Substantial uncertainty in incremental effect and resulting estimates of cost effectiveness due to limitations of non-randomized, non-comparative data

pERC deliberated upon the two economic analyses submitted by the manufacturer providing estimates on the cost-effectiveness of bosutinib compared with relevant treatment options. The first involved a cost-minimization analysis based on the assumption of similar efficacy and toxicity between bosutinib and currently available second generation TKIs (dasatinib or nilotinib). This analysis only took into consideration differences in drug cost. pERC discussed the appropriateness of this approach and agreed that, in the absence of direct or indirect evidence, there was considerable uncertainty in the assumption of similar efficacy and toxicity between dasatinib, nilotinib and bosutinib. Additionally, pERC noted that bosutinib demonstrated a side effect profile that is different from currently available second generation TKI's and agreed that a cost-minimization analysis was inadequate to explore the impact these differences may have on the cost effectiveness of bosutinib. pERC concluded that, until the assumptions of similar efficacy and safety have been validated, a cost-minimization analysis is not a valid approach and a standard cost-effectiveness/cost-utility analysis is required, which incorporates differences in efficacy, safety, quality of life and costs between the treatments under consideration. pERC requested this additional economic information from the submitter.

pERC also discussed the results of a cost-utility analysis provided by the submitter comparing bosutinib to hydroxyurea, interferon or stem cell transplant (SCT). In the absence of direct or indirect comparative data, pERC noted that multiple data sources from the literature and/or assumptions were used to populate clinical inputs within the cost-utility analysis, which was understandable. pERC, however, noted that due to the limitations of relying on non-randomized evidence from the SKI-200 study, there was substantial uncertainty in the magnitude of the clinical benefit associated with bosutinib. This made it challenging to estimate the incremental effect of treatment with bosutinib and, therefore, the resulting incremental cost-effectiveness estimates for bosutinib. This considerable uncertainty in the magnitude of clinical benefit of bosutinib led to a wide range of incremental cost-effectiveness estimates, all of which pERC considered unacceptable. The Committee noted that in order to improve the cost-effectiveness of bosutinib and offset the considerable uncertainty in the incremental effect, a substantial reduction in drug price would likely be required. pERC also considered that, if feasible, the collection of additional prospective data on the clinical benefit of bosutinib would reduce the uncertainty around the magnitude of the benefit and improve the cost-effectiveness estimates. Therefore, pERC considered that bosutinib could not be considered cost-effective at the list or submitted price.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Second line population, unknown magnitude of clinical benefit, budget impact

pERC discussed factors affecting the feasibility of implementing a positive funding recommendation for bosutinib.

Input from the pCODR's Provincial Advisory Group indicated concerns for indication creep into the first and second line setting. Given the available options which have evidence demonstrating efficacy for first line treatment and the evidence demonstrating no additional clinical benefit to support the use of bosutinib in the first-line setting, pERC noted that it is unlikely bosutinib will be used in the first-line setting. Within the second-line setting, pERC discussed the available evidence and agreed that bosutinib offers a therapeutic option in patients that have preexisting conditions making them inappropriate for treatment or patients that have mutations conferring resistance to currently available TKI's. Having agreed that it would be reasonable to use bosutinib in patients that have failed at least one previous TKI, pERC acknowledged that jurisdictions will need to consider the potential budgetary impact of making bosutinib available in the second or third-line setting. pERC also discussed PAG's request on clarity around the sequence of previous TKI use. pERC acknowledged that data on sequencing of TKIs are limited and not informed by controlled clinical trials. pERC however agreed with the Clinical Guidance Panel that decisions beyond first-line therapy will likely be guided by the agents available for front-line therapy, clinical judgment, CML mutation status and patient comorbidities. pERC discussed PAG's concern about the absence of a comparator arm in the study. pERC discussed the limitations associated with non-randomized studies and noted that, although not feasible in the third-line setting and beyond, a randomized study could have been conducted within the second-line cohort to determine comparative efficacy against currently available treatment options. Due to the absence of this comparative evidence, pERC was unable to determine the magnitude of the benefit associated with bosutinib.

pERC considered several factors related to drug cost and dosing that may affect the feasibility of implementing a positive funding recommendation. pERC noted that the potential for dose adjustments (increase and decrease of doses) will need to be considered by provinces as this could affect the incremental cost of bosutinib relative to the other second generation TKI's. pERC acknowledged that a significant minority of patients received dose escalations to 600mg due to inadequate response to the initial 500mg dose, noting that this may have an impact on the cost of bosutinib as an additional 100mg tablet will be required to achieve this dose. While bosutinib is priced per tablet, when considering the per mg cost, pERC noted that the cost of five 100mg tablet is more expensive than the one 500mg tablet and a dose reduction to 400mg would not result in no cost savings over the cost of the 500mg tablet. Lastly, pERC acknowledged the introduction of generic imatinib and noted that this may shift the pricing of other tyrosine kinase inhibitors.

DRUG AND CONDITION INFORMATION

Drug Information	• Oral, dual Src/Abl Tyrosine Kinase Inhibitor • 100mg tablet and 500mg tablet reviewed by pCODR • Recommended dosage of 500 mg administered orally, once daily
Cancer Treated	• Chronic Myelogenous Leukemia
Burden of Illness	• Chronic Myelogenous Leukemia accounts for approximately 10-15% of cases of leukemia diagnosed in Canada, with an incidence rate of 1-2cases/100,000/year. • Approximately 450 cases are diagnosed annually in Canada with a median age at diagnosis of 65 • The majority of patients (>95%) with CML are in chronic phase (CP) at diagnosis • Approximately 1/3 of patients treated with imatinib for CP CML discontinue therapy because of disease progression (10%) or intolerance (25%)

Current Standard Treatment	• In patients with resistance or intolerant intolerance to currently available treatments
	  ○ Dasatinib
	  ○ Nilotinib
	• Hydroxyurea
	• Interferon
	• Allogenic stem cell transplant
	• Best supportive care

Limitations of Current Therapy	• interferon and palliative treatment with hydroxyurea, are associated with significant toxicities, and limited clinical benefit • A large number of mutations have been described in the BCR-ABL kinase domain that lead to drug resistance • Presence of a mutation may predict for reduced efficacy of a second-line agent; patients may have co-morbidities that predict for drug-related adverse events and make the use of dasatinib or nilotinib inappropriate. • Agents that are active without the risk of exacerbating significant comorbidities are needed in the treatment of CML.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Matthew Cheung, Oncologist
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Wasney, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Tallal Younis, Oncologist
Dr. Kelvin Chan

All members participated in deliberations and voting on the initial recommendation except:

- Scott Berry and Mario De Lemos who were not present for the meeting
- Carole McMahon who did not vote due to her role as a patient member alternate

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of bosutinib (Bosulif) for chronic myeloid leukemia, through their declarations, five members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, and none of these members was excluded from voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. Pfizer Canada Inc., as the primary data owner, did not agree to the disclosure of economic information, therefore, this information has been redacted in this recommendation and publicly available guidance reports.

Use of this recommendation

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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Appendix 3: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials March 2019, Embase 1974 to 2019 April 08, Ovid MEDLINE(R) ALL 1946 to April 08, 2019

#	Searches	Results
1	(Bosulif* or bosutinib* or SKI606 or SKI 606 or SK606 or SK 606 or EC 700-455-1 or 5018V4AEZ0).ti,ab,ot,kf,kw,hw,nm,rn.	2769
2	Leukemia, Myeloid/ or exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/ or Leukemia, Myelomonocytic, Chronic/	94621
3	(((Chronic or Ph1 positive or Philadelphia positive or stable-phase or accelerated phase or aggressive phase or blast phase) adj5 leuk?emia*) or chronic myeloleuk?emia* or blast cell crisis or blast crisis or blastic cell crisis or blastic crisis).ti,ab,kw,kf.	124932
4	1 and (2 or 3)	1739
5	4 use medall	266
6	4 use cctr	77
7	*bosutinib/ or (bosulif* or bosutinib* or SKI606 or SKI 606 or SK606 or SK 606 or EC 700-455-1).ti,ab,kw,dq.	1534
8	Myeloid Luekemia/ or exp Chronic Myeloid Leukemia/	61326
9	(((Chronic or Ph1 positive or Philadelphia positive or stable-phase or accelerated phase or aggressive phase or blast phase) adj5 leuk?emia*) or chronic myeloleuk?emia* or blast cell crisis or blast crisis or blastic cell crisis or blastic crisis).ti,ab,kw,dq.	124827
10	7 and (8 or 9)	1011
11	10 use oemezd	697
12	11 not conference abstract.pt.	346
13	5 or 6 or 12	689
14	remove duplicates from 13	446
15	11 and conference abstract.pt.	351
16	limit 15 to yr="2014 -Current"	216
17	14 or 16	662
18	limit 17 to english language	622

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#5	Search **#4 AND publisher[sb]** Filters: **English**	10
#4	Search **bosutinib*[supplementary concept] OR bosutinib*[tiab] or bosulif*[tiab] OR ski-606*[tiab] OR ski606*[tiab] OR sk606*[tiab] OR sk 606*[tiab] OR EC 700-455-1[tiab] OR 5018V4AEZ0[rn]** Filters: **English**	457

3. Cochrane Central Register of Controlled Trials (Central)
   Searched via Ovid

4. Grey Literature search via:

Clinical Trial Registries:

U.S. NIH ClinicalTrials. gov
http://www.clinicaltrials.gov/

World Health Organization
http://apps.who.int/trialsearch/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Bosulif/bosutinib, chronic myeloid leukemia

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Bosulif/bosutinib, chronic myeloid leukemia

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

American Society of Hematology (ASH)
http://www.hematology.org/

Search: Bosulif/bosutinib, chronic myeloid leukemia – last 5 years

Detailed Methodology

The literature search was performed by the pCODR Methods Team using the search strategy above.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-Apr 8,2019) with in-process records & daily updates via Ovid; Embase (1974-Apr 8,2019) via Ovid; The Cochrane Central Register of Controlled Trials (March 2019) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Bosulif, bosutinib and chronic myeloid leukemia.

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of July 4, 2019.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov, World Health Organization International Clinical Trials Registry and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO) and the American Society of Hematology (ASH) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel.

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