pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Bosutinib (Bosulif) for Chronic Myelogenous Leukemia

April 21, 2015

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of bosutinib (Bosulif) as compared to an appropriate comparator in patients with

1. chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) with
2. resistance or intolerance to prior tyrosine kinase inhibitors (TKI) therapy, and for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate.

Bosutinib is a TKI that inhibits the BCR-ABL and the Src-family kinases. Bosutinib has a Health Canada indication which is the same as the indication under pCODR review. Bosutinib is an oral tablet available as 100 mg and 500 mg; it has Health Canada approval with conditions for 500 mg once daily.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one open label single arm phase 1/2 study (SKI-200) examining the use of bosutinib in patients who were intolerant or resistant to imatinib, dasatinib or nilotinib. [1-5]

The study had a total of 546 patients receiving bosutinib,

- 288 in second-line chronic phase (CP) treatment (n=200 imatinib resistant and n=88 imatinib intolerant). There were 115 patients with known mutations at baseline.
- 144 in third-line CP treatment (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). There were 39 3rd and 4th line CP patients with known Bcr-Abl kinase domain mutations at baseline.
- 4 in fourth-line CP treatment,
- 76 in accelerated phase (AP) and 64 in blast phase (BP).

Imatinib, nilotinib and dasatinib intolerance, acquired resistance and resistance are defined in Section 6.3.2.1.a

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, 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. [1-5]

Efficacy

The primary outcome was major cytogenetic response (MCyR) at 24 weeks in imatinib resistant patients with chronic phase (CP) disease. Secondary endpoints included major cytogenetic response (MCyR) in CP second-line imatinib intolerant patients and CP third-line CML patients, complete cytogenetic response (CCyR), and complete hematologic response (CHR).

Second line CP patients:

Of the total evaluable second line CP patients with a valid baseline cytogenetic assessment, MCyR rates were newly achieved or baseline MCyR maintained for ≥4 weeks, in 59% of patients including 58% vs. 61% achieving MCyR in the imatinib-resistant vs. imatinib-intolerant populations, respectively. The complete cytogenetic response (CCyR) rate was 48% in the total evaluable second line CP patients with 46% vs. 54% achieving CCyR in the imatinib-resistant vs. imatinib-intolerant populations, respectively. CHR was observed for 85% of all evaluable second line CP patients. Similar rates of CHR or MCyR were observed between patients with and without mutations. Responses were observed broadly across Bcr-Abl mutants, except for T315I. [2]

Third and Fourth line CP patients:

MCyR was attained in 32% (n = 35) of 3rd and 4th line CP patients, with MCyR seen in 31% of patients resistant to dasatinib and 35% of patients resistant to nilotinib. CCyR achieved 24% (n = 26) of 3rd and 4th line CP patients, including one of 3 patients who were previously treated with all 3 TKIs. 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. CHR was observed for 65% of all 3rd and 4th line CP patients. CHR and MCyR were observed broadly across Bcr-Abl mutants. No major cytogenetic responses were observed following bosutinib in the seven patients with T3151 mutations. [4]

AP and BP patients:

MCyR was attained by 35% and 30% of patients in the AP and BP, respectively. Complete haematological response was attained in 35% vs 28% AP and BP patients, respectively.[6]

Quality of life was measured through the FACT-Leu scale in all patients. Significant changes were observed as early as four weeks in both imatinib resistant and intolerant 2nd line CP patients.[5] There were minimally important differences observed in the imatinib intolerant group only. Significant changes were also measured in 3rd line patients in 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 ($p<0.05$).[7] 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. [7]

Harms

Deaths were reported in the study with 12 occurring in the 2nd and 3rd line cohorts within 30 days after the last bosutinib dose (May 15, 2013 update) [3] and 30 and 44 deaths occurring in the AP and BP groups, respectively (May 2014 update). [7] Reasons for deaths in the 2nd and 3rd line patients included CML disease progression (n = 6) and AEs considered unrelated to bosutinib by the investigators (n = 5). One death was attributed to an AE considered bosutinib-related by the investigator (lower gastrointestinal hemorrhage with thrombocytopenia). [3]

The most frequently reported grade 3/4 treatment emergent adverse events (TEAEs) were gastrointestinal events (diarrhea, nausea, and vomiting) rash, anemia, increased alanine transaminase (ALT), neutropenia and thrombocytopenia.[3] Although diarrhea was common the maximum severity was grade 1 or 2 in most patients. Adverse events for AP and BP patients were similar to chronic phase patients, with the exception of diarrhea which was 20% less BP patients.[7]

Dose reduction and interruptions were common in the 2nd line CP (49% and 72%) and third-line CP (50% and 66%) cohorts. Common AEs leading to dose reduction included thrombocytopenia. Treatment discontinuation was required in 22% and 25% of 2nd and 3rd line patients, respectively. The majority of toxicities resulting in discontinuation were hematologic, specifically thrombocytopenia. Dose reductions and interruptions were not available for accelerated and blast phase patients.[3]

1.2.2 Additional Evidence

pCODR received input on bosutinib for CML from one patient advocacy group, the Chronic Myelogenous Leukemia Society of Canada. Provincial Advisory group input was obtained from the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

In addition, the following information relevant to the pCODR review of bosutinib is discussed as supporting information.

- A summary of results from BELA, an open-label randomized multinational phase III trial funded by Pfizer comparing bosutinib to imatinib for adult patients with new (≤ 6 months) diagnosis of Ph-positive CP CML who had received no prior anti-leukemia treatment (except ≤ 6 months of anagrelide or hydroxyurea).

1.2.3 Interpretation and Guidance

CML is an uncommon clonal bone marrow stem cell disorder with approximately 450 cases diagnosed annually in Canada with a median age of 65 years[8]. The majority of patients are diagnosed in the chronic phase (CP) of the illness. The only curative therapy available is allogeneic stem cell transplant, however only approximately 20-25% of patients are eligible for this treatment. Current therapies include the BCR-ABL tyrosine kinase inhibitor (TKI) imatinib as well as second generation TKIs of dasatinib and nilotinib. These agents are used as first or second line treatment for CML.

Approximately one-third of patients treated with imatinib for CP CML discontinue therapy due to disease progression or intolerance. Patients can expect to be on lifelong therapy. Intolerance and resistance to second-line TKIs occur as well. In summary, there remains an unmet need for more effective and tolerable therapies in treatment of chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML).

Effectiveness

Based on the high MCyR rate observed in the SKI-200 study, bosutinib therapy appears to be an appropriate therapeutic option for 2nd and 3rd line patients and is an important addition to the treatment armamentarium for chronic myeloid leukemia. Although the follow-up of this study is short and the ability to comment on overall survival is limited, the high MCyR rate suggests that bosutinib may provide survival benefit over supportive care alone or interferon treatment.

As data on sequencing of TKIs are limited and not informed by controlled clinical trials; decisions beyond first line therapy are significantly influenced by the agents available for front-line therapy, clinical judgement, CML mutation status and patient comorbidities. While bosutinib is not likely to be the therapy of first choice in all patients who have

experienced disease progression on imatinib, circumstances where bosutinib would be appropriate include 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). Bosutinib does appear to have activity in patients with mutations conferring resistance to other TKIs, although new mutations emerged on bosutinib therapy and no activity was seen in patients with T315I mutations.

Acknowledging that data on use of bosutinib in accelerated or blast phase CML are limited, current results reported with bosutinib indicate that bosutinib may be of value for BP and AP patients who have received one or two prior TKIs. This is considering that the prognosis of patient with AP and BP disease is very poor and the results with older aggressive induction chemotherapies are unsatisfactory.

There is insufficient data to determine the benefit of bosutinib in patients who have been treated with all three TKIs previously. The CGP however felt that it was extremely unlikely that a direct comparison of bosutinib to supportive care after failure of 2 or 3 prior TKIs will be conducted in the future, or that such a study would be acceptable to clinicians or patients with advanced CML, where an active treatment is always a preferred option.

Safety

While a significant number of patients discontinued bosutinib due to treatment-related adverse events, this did not to vary according to prior therapy, and seemed comparable to discontinuation rates with the use of imatinib, dasatinib, and nilotinib in previous trials of those agents. The side effect profile of bosutinib also differs from dasatinib and imatinib, making this attractive option for patients who are intolerant to previous TKI therapy. 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.

1.3 Conclusions

The Clinical Guidance Panel concluded 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 also considered that from a clinical perspective:

- 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 the follow-up of this study is short, and ability to comment on overall survival is limited, the high MCyR rate observed in suggests that bosutinib therapy may provide survival benefit over supportive care alone, and would appear to be an appropriate therapeutic option.
- 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.
- 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.
- 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).
- Patients would prefer the option of a third line oral TKI to that of more aggressive and risky therapy including allogeneic stem cell transplant, or toxic agents such as interferon.
- 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. The CGP however felt that it was extremely unlikely that a direct comparison of bosutinib to supportive care after failure of 2 or 3 prior TKIs will be conducted in the future, or that such a study would be acceptable to clinicians or patients with advanced CML.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding bosutinib (Bosulif) for chronic myelogenous leukemia (CML). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website, www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding bosutinib (Bosulif) conducted by the Leukemia Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on bosutinib (Bosulif) and a summary of submitted Provincial Advisory Group Input on bosutinib (Bosulif) are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Chronic Myeloid Leukemia (CML) CML accounts for approximately 10-15% of cases of leukemia diagnosed in Canada. The median age at diagnosis of CML is 65 years. There were 590 cases of CML diagnosed in Canada in 2010, and 126 deaths due to CML in 2011.[9] The majority of patients (>95%) with CML are in chronic phase (CP) at diagnosis.

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 a cure for 70-80% of patients treated in CP, but this treatment remains limited to younger patients and those with available donors[10] so less than 25% of the population affected. With the introduction of imatinib in 2001, the use of oral tyrosine kinase inhibitors targeting the BCR-ABL kinase is now the standard of care for patients with newly diagnosed CP CML. 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. [11] However, roughly 1/3 of patients treated with imatinib will discontinue therapy, due either to intolerance from side effects or loss of previous molecular, cytogenetic or hematologic response because of the emergence of drug resistance. A large number of mutations have been described in the BCR-ABL kinase domain that leads to drug resistance. The second generation TKIs dasatinib and nilotinib have a much smaller spectrum of resistance mutations, but neither is able to overcome the T315I mutation. Both of these agents produce similar rates of major molecular response? (MMR) and have similar progression-free and overall survival when used as second-line therapies.[12,13]

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. Therefore, bosutinib represents a potentially attractive new therapy for patients who

have experienced treatment failure after imatinib and nilotinib or dasatinib, with an acceptable toxicity profile.[14]

2.1.2 Objectives and Scope of pCODR Review

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.

See Table 4 in Section 6.2.1 for outcomes of interest.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

One phase 1/2, open label study examining the use of bosutinib in patients who were intolerant or resistant to imatinib, dasatinib or nilotinib was identified and included in this clinical guidance report.[1-5] The study had 546 patients; 288 second line chronic phase, 144 third line chronic phase, 4 fourth line chronic phase, 76 accelerated phase and 64 blast phase patients. 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, 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. Bosutinib was given at 500mg/day. The dose could be adjusted to 600mg/day if the patients were not responding and lowered to 300mg/day if the patient's experienced severe drug related adverse events.

The primary outcome of the study was the percentage of patients with a major cytogenic response (MCyR) at 24 weeks in chronic phase second-line imatinib resistant cohort. Imatinib, nilotinib and dasatinib intolerance, acquired resistance and resistance are defined in Section 6.3.2.1.a. Secondary outcomes of interest include: duration of MCyR, duration of complete hematologic response, time to achieve hematologic response, progression free survival rate, overall survival rate and percentage of patients with treatment emergent adverse events. A brief summary of the key trial outcomes can be found in tables 1 and 2. For a more detailed description of the trials' designs and patient characteristics, please see Table 5 in the Systematic Review (Section 6.3.2.1).

In the total group of evaluable second line CP patients with a valid baseline cytogenetic assessment, 59% of patients newly achieved a MCyR or maintained their baseline MCyR for ≥4 weeks, including 58% of imatinib-resistant patients and 61% of imatinib-intolerant patients. The complete cytogenetic response (CCyR) rate was 48%.[2] In second line therapy major molecular response (MMR) was achieved in 35% of treated patients (the analysis excluded patients from China, India, Russia, and South Africa), including 28% of patients who achieved a complete molecular response, with the proportion of patients who achieved an MMR being similar for imatinib-resistant (34%) and imatinib-intolerant (35%) patients. For third and fourth line patients MCyR was attained by 32% (n = 35) of patients, with CCyR in 24% (n = 26) of patients, including one of 3 patients who were previously treated with all 3 TKIs. [4]

Table 1: Best overall response for 2nd and third line chronic phase patients[2,4]

Response	Imatinib resistant 2nd line CP	Imatinib intolerant 2nd line CP	Total for 2nd line CP	3rd and 4th line CP
Cytogentic response, [a] n(%) [95% CI]				
Evaluable patients	186	80	266	108
MCyR	108 (58) [51–65]	49 (61) [50–72]	157 (59) [53–65]	35 (32)
CCyR	85 (46) [38-53]	43 (54) [42-65]	128 (48) [42-54]	26 (24)
Molecular response, [b] n(%) [95% CI]				
Evaluable patients	132	68	200	108
MCyR	45 (34) [26-43]	24 (35) [24-48]	69 (35) [28-42]	35 (32)
CCyR	33 (25) [18-33]	22 (32) [22-45]	55 (28) [21-34]	26 (24)
Hematologic response, [c] n(%) [95% CI]				
Evaluable patients	199	88	287	116
Complete response	170 (85) [80-90]	74 (84) [75-91]	244 (85) [80-89]	85 (73)
Hematologic response among patients with no baseline CHR to previous therapy n(%) [95% CI]				
Evaluable patients	100	41	141	68
Complete response	76 (76) [66-84]	33 (81) [65-91]	109 (77) [70-84]	44 (65)

A -Evaluable patients must have had an adequate baseline cytogenetic assessment. Cytogenetic response was determined using standard cytogenetics (G-band karyotype) with ≥20 metaphases counted for post baseline assessments; if <20 metaphases were available post baseline, FISH analysis of bone

marrow aspirate with ≥200 cells for the presence of Bcr-Abl fusion gene was used. MCyR included PCyR (1–35% Ph^{+1} metaphases) and CCyR (0% Ph^{+1} metaphases; <1% if using FISH). Cytogenetic response could be achieved during the study or maintained from baseline for 4 weeks, unless otherwise noted within the table.

B -Patients enrolled in China, India, Russia, and South Africa could not be evaluated for molecular response due to logistical constraints; treated patients not from these four countries were evaluable for molecular response. Molecular response was assessed at a central laboratory (Quest Diagnostics) using non-nested real time PCR for the ratio of Bcr-Abl to Abl transcripts. MMR was categorized as a ≥3-log reduction from standardized baseline and included CMR (undetectable Bcr-Abl transcript with a PCR sensitivity of ≥5 logs). To be considered a responder for MMR/CMR, the patient should also have had detectable Bcr-Abl transcript levels at baseline or any time postbaseline, and have achieved/maintained a CCyR; patients with cytogenetic assessments not showing CCyR on the same day of molecular assessment were not considered to have an MMR/CMR at that time. MMR was not assessed using the International Scale because it was not widely available when the study was initiated.

C -Evaluable patients must have had an adequate baseline hematologic assessment. The definition of CHR was standard; hematologic response was required to be confirmed and to last for ≥4 weeks, with peripheral blood and/or bone marrow documentation, and could be achieved during the study or maintained from baseline for ≥5 weeks, unless otherwise noted within the table.

MCyR was attained by 35% of patients in the accelerated phase and 30% of patients in blast phase. Sixty two percent of accelerated phase patient kept their response for 1 year and so did 7.9% of blast phase patients. Complete haematological response was attained in 35% of accelerated phase patients and 28% of blast phase patients.[6]

Table 2: Responses for Accelerated and Blast Phase patients[6]

	Accelerated Phase n=76	**Blast Phase n=64**
Major cytogenetic response	35%; (95%CI, 24%-47%)	30% (95%CI, 18%-44%)
Duration of major cytogenetic response		
Kaplan Meir at 1 year	62%; (95%CI, 39%-79%)	7.9%; (95%CI, 0.5%-30%)
Complete hematological response	35%; (95%CI, 24%-47%)	28%; (95%CI, 18%-41%)

Quality of life was measured through the FACT-Leu scale in all patients. 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.[5] Significant changes were also measured in 3rd line patients in 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.[7]

Dose reductions and interruptions were common in the chronic phase second line (49% and 72%) and third line (50% and 66%) cohorts. The intolerant patients were more likely to discontinue bosutinib treatment because of AEs, particularly thrombocytopenia. Treatment interruptions due to AEs occurring ≤4 weeks after bosutinib initiation were frequent in second and third line patients who were intolerant vs resistant to prior TKIs.[3]

Bosutinib toxicities were generally of mild to moderate severity and managed with concomitant medication, dose interruption and/or dose reduction, or resolved spontaneously. The most frequently reported grade 3/4 treatment emergent adverse events (TEAEs) were gastrointestinal events (diarrhea, nausea, and vomiting) rash, anemia, increased alanine transaminase, neutropenia and thrombocytopenia.[3] Although diarrhea was common the maximum severity was grade 1 or 2 in most patients. Based on differences of ≥10% for TEAEs occurring in ≥10% of patients, rash was more common and pyrexia less common in patient's intolerant vs resistant to prior imatinib treatment in the second line cohort. In the third line cohort, vomiting, rash, dyspnea, and pleural effusion were more common and neutropenia was less common in patients intolerant to prior dasatinib therapy vs patients resistant to prior TKI therapy. Thrombocytopenia was most common in third line patients resistant to nilotinib.[3] Adverse events for accelerated and blast phase patients were similar to chronic phase patients. The exception was diarrhea in blast patients. Twenty percent fewer blast phase patients reported suffering from diarrhea across all grades.[7]

As of May 15, 2013, twelve deaths in the 2nd and 3rd line cohorts occurred within 30 days after the last bosutinib dose. Reasons included CML disease progression (n = 6 [1.4%]) and AEs considered unrelated to bosutinib by the investigators (n = 5 [1.2%]). One death was

attributed to an AE considered bosutinib-related by the investigator (lower gastrointestinal hemorrhage with thrombocytopenia. All deaths in the second line cohort occurred in patients with resistance (not intolerance) to prior imatinib treatment. All deaths in the third line cohort occurred in patients with resistance or intolerance to prior dasatinib (not nilotinib) treatment.[3] As of May 2014, there were 30 deaths in the accelerated phase and 44 deaths in the blast phase group. Death were equally split between patients who received imatinib only and those who has received multiple TKIs.[7]

2.1.4 Comparison with Other Literature

Relevant literature identified jointly by the pCODR Clinical Guidance Panel and Methods Team and providing supporting information to the systematic review is summarized below. This information has not been systematically reviewed.

BELA is an open-label randomized multinational phase III trial funded by Pfizer[15,16]. BELA is fully published and at the time of publication was still ongoing. The trial enrolled adult patients with new (≤ 6 months) diagnosis of Ph-positive CP CML who had received no prior antileukemia treatment (except ≤ 6 months of anagrelide or hydroxyurea). Patients were randomized 1:1 to bosutinib 500 mg per day or imatinib 400 mg per day. Details pertaining to the methods of randomization, allocation, generating the randomization sequence and patient stratification were not provided. Since the study was open label (both patients and investigators were not blinded to treatment assignment), there exists the potential for bias. Patients could continue study treatment until disease progression or early discontinuation.[15,16]

The primary outcome was complete cytogenetic response (CCyR) at 12 months. Secondary outcomes include: major molecular response, major cytogenetic response, and complete hematologic response (CHR) at 12 months, time to on-treatment transformation to accelerated phase (AP) or blast phase (BP) CML, time to first response, duration of response, response by Sokal risk group, on-treatment event-free survival (EFS) and overall survival. A total of 502 patients were enrolled between February 2008 and July 2009, in 139 centers in 31 countries. Two hundred and fifty patients were randomly assigned to bosutinib, and 252 patients were randomly assigned to imatinib[16]. Median duration of treatment for both study arms was 27.5 months (bosutinib range, 0.03 to 41.3 months; imatinib range, 0.5 to 38.8 months).[15] During the study, fifteen patients (6%) receiving bosutinib and 46 patients (18%) receiving imatinib had their dose escalated to 600 mg per day because of lack of efficacy. As of the data cut off date, 63% of patients in the bosutinib arm and 71% in the imatinib arm were still receiving study treatment.[15]

The CCyR rate at 12 months was similar between patients receiving bosutinib (70%; 95% CI, 64% to 76%) and imatinib (68%; 95% CI, 62% to 74%; *P* = .601). A superior CCyR for bosutinib was not demonstrated. Therefore, the primary study endpoint was not met. However, median time to first CCyR was faster with bosutinib (12.9 weeks; 95% CI, 12.6 to 13.4 weeks) compared with imatinib (24.6 weeks; 95% CI, 24.3 to 25.6 weeks; *P* < .001), with higher rates of CCyR at months 3, 6, and 9 for bosutinib. The cumulative rate of CCyR by 12 months was also similar between bosutinib and imatinib (79%; 95% CI, 74% to 84% *v* 75%; 95% CI, 69% to 80%, respectively).[16] At 24 months the CCyR rate was still similar between patients receiving bosutinib (58%) and imatinib (65%) rate difference -8% (95% CI 16-1%).[15] The cumulative rate of CCyR by 24 months was also similar between bosutinib and imatinib (79%; and 80%, respectively).[15]

The major cytogenetic response rate at 12 months was 73% for bosutinib and 78% for imatinib.[16] The MMR rate at 12 months was higher with bosutinib (41%; 95% CI, 35% to 47%) than imatinib (27%; 95% CI, 22% to 33%; *P* < .001, with the complete molecular response rate at 12 months being 12% compared with 3%, respectively (*P* < .001).[16] At 24 months the MMR was 47% for bosutinib and 41% for imatinib. Median time to first MMR was faster with bosutinib (37.1 weeks; 95% CI, 36.1 to 48.6 weeks) compared with imatinib (72.3 weeks; 95% CI, 61.1 weeks to not reached; *P* < .001). The cumulative rate of MMR by 12 months was also higher with bosutinib (47%; 95% CI, 41% to 53%) versus imatinib (32%; 95% CI, 26% to 38%; *P* < .001).[16] At 24 months the cumulative MMR rate was 59% with bosutinib and 49% with imatinib.[15] The rate of confirmed CHR at 12 months was 71% for bosutinib versus 85% for imatinib (*P* > .999). Median times to first CHR were 4.4 weeks (95% CI, 4.3 to 4.7 weeks) for bosutinib and 4.6 weeks (95% CI, 4.4 to 5.0 weeks) for imatinib (*P* = .5790).[16]

At the 12 month time interval fewer patients had an on-treatment event free survival (EFS) event with bosutinib (n = 11) than imatinib (n = 18).[16] Kaplan-Meier estimates of on-treatment EFS at 24 months were 92% for bosutinib compared with 88% for imatinib. Fewer patients in the bosutinib arm (n = 4, 2%) experienced on-treatment transformation to AP/BP CML compared with the imatinib arm (n = 10, 4%). At 24 months no new on-treatment transformations occurred with bosutinib versus four with imatinib.[15]

There were fewer deaths in the bosutinib arm (n = 7; causes were CML related [n = 6] and mesenteric embolism/intestinal necrosis [n = 1]) compared with the imatinib arm (n = 13; causes were CML related [n = 2], cardiovascular disease [n = 1], and lung embolism [n = 1], pneumonia [n=1].[15] None of the deaths were considered related to study treatment. Kaplan-Meier estimates of overall survival at 12 months were greater than 97% in the bosutinib arm and 95% in the imatinib arm.[15]

Treatment-emergent AEs were reported by 96% of patients treated with bosutinib versus 95% treated with imatinib. [16] Bosutinib, compared with imatinib, was associated with higher incidences of diarrhea (70% *v* 26%, respectively, p<0.001), vomiting (33% *v* 16%, respectively, p<0.001), and abdominal pain (14% *v*s. 8%, respectively, p=0.029) upper abdominal pain (15% vs. 8% respectively, p=0.015), pyrexia (19% vs. 12% respectively, p=0.046). [17] Conversely, bosutinib, compared with imatinib, was associated with lower incidences of periorbital edema (2% *v* 14%, respectively, p<0.001), peripheral edema (5% *v* 12%, respectively, p<0.006), bone pain (4% *v* 11%, respectively, p=0.003), and muscle spasms (5% *v* 22%, respectively, p<0.001). [17] The aggregate incidence of grade 3 or 4 AEs was 64% in the bosutinib arm and 48% in the imatinib arm (*P* < .001), with median durations of 13 and 15 days, respectively. [16] Specific grade 3 or 4 nonhematologic AEs observed for more than 2% of patients included diarrhea (bosutinib, 11%; imatinib, 1%) and vomiting (bosutinib, 3%; imatinib, 0%), all were grade 3 events in both treatment arms.[16]

There exists the possibility of bias given the lack of information needed to assess the quality of the BELA trial. There is no information on the randomization allocation and methods. This can lead to bias as there is no way of knowing whether the methods of randomization were appropriate. From observing the patient baseline characteristics it looks as if the two groups of patients were balanced, however no mention of patient stratification groups was mentioned. This can also lead to bias as the groups may be unbalanced and therefore skew the results. The results of this trial need to be interpreted with caution, as it is not possible to ascertain whether any serious biases exist.

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) Input, respectively.

Patient Advocacy Group Input

From a patient perspective, while the efficacy of currently available treatments for CML has been significant for the majority of patients; however, in a smaller population of CML patients, the available treatments are either not well tolerated and/or the disease becomes resistant to treatment. This results in a constant fear and anxiety of not having the disease well controlled and progressing into accelerated or blast crisis phase, for which no treatment currently exists. Although the side effect profile of bosutinib suggests a higher incidence of gastrointestinal effects, CMLSC contend these side-effects are much easier to manage than side effects experienced with other tyrosine-kinase inhibitors (TKI), such as, pleural effusion or cardiac effects. As an example, CMLSC reported that patients who used a TKI, and who had borderline asthma, were required to stay on inhalers prior to the availability of bosutinib. Once these patients were switched to bosutinib they were either able to stop inhalers or reduce their use significantly. CMLSC believe that bosutinib will change the outcomes in a positive way for the patient who needs it, as it represents an additional option for the healthcare team to help the patient achieve stability in their disease and avoid transplantation, progression and an earlier death.

PAG Input

Input on bosutinib (Bosulif) for CML was obtained from the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, bosutinib has enablers that include being an oral therapy that can be easily delivered in the community setting and that is once daily administration. Key barriers identified include the potential for use in the first-line or second-line setting and the uncertainty of the clinical benefits for an additional line of therapy that is based on data from a phase 1/2 trial that has no comparator arm.

2.2 Interpretation and Guidance

Burden of Illness and Need

CML is an uncommon clonal bone marrow stem cell disorder with an incidence in North America of 1-2 cases/100,000/year. There are approximately 450 cases diagnosed annually in Canada with a median age of approximately 65 years.[8] The majority of patients are diagnosed in chronic phase (CP) of the illness. The only curative therapy available is allogeneic stem cell transplant from a sibling or unrelated donor; because of limitations of age at diagnosis and limited available donors, only approximately 20-25% of patients might be eligible for this treatment. Current initial therapy in Canada is with the BCR-ABL tyrosine

kinase inhibitor (TKI) imatinib. Second generation TKI's dasatinib and nilotinib, have been shown in randomized trials to have higher rates of major cytogenetic and major molecular responses compared to imatinib. These second generation agents are now used as first or second line treatment for CML

Approximately 1/3 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. 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.

Effectiveness

The study SKI-200 is an open label single arm phase I/2 study that tested the response rate and toxicity of bosutinib in 288 patients requiring second-line CP treatment (200 imatinib resistant, 88 imatinib intolerant) and 114 needing third-line CP treatment (37 imatinib resistant/intolerant and dasatinib resistant; 50 imatinib resistant/intolerant and dasatinib intolerant; 27 imatinib resistant/intolerant, and nilotinib resistant); 4 patients also were enrolled to receive fourth-line therapy[1-5]. In this trial, imatinib intolerance was defined as an inability to take imatinib because of grade 4 hematologic toxicity greater than 7 days; grade 3 or greater non-hematologic toxicity; persistent grade 2 toxicity not responding to dose reductions and medical management; or loss of previously attained response on lower-dose imatinib among patients with previous toxicity. The starting dose of bosutinib was 500 mg daily, with dose reductions to 400 and 300 mg in the event of side effects, or dose increase to 600 mg for inadequate response.[1]

Second line use: At 24 months, 58% of patients who were imatinib resistant achieved major cytogenetic response and 46% complete cytogenetic response. For imatinib intolerant patients the MCyR and CCR rates were 61% and 54% respectively. In a smaller number of patients evaluable for molecular response, major molecular responses were seen in 34% of imatinib resistant patients and 35% of imatinib intolerant patients. Complete hematologic responses were seen in 85% of patients.[2]

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 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.[4]

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: while improvement greater than the minimally important difference was seen for blast phase patients, the degree of improvement was greater for those in accelerated phase.

Bosutinib would appear to be an important addition to the treatment armamentarium for chronic myeloid leukemia. Although cytogenetic response to second-line dasatinib has been associated with improved survival[1,3] and has been used to inform regulatory approval, it seems likely that the use of bosutinib, which also produces MCyRs, would result in superior survival compared to supportive care or hydroxyurea or interferon, where such cytogenetic responses are not observed. However there are no data to support this notion with bosutinib. 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.

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. Switching from one second-generation agent to the other in the absence of a known mutation where the latter has been found to be effective is not an appropriate strategy. Based on the data from the SKI200 trial, bosutinib would be appropriate for patients experiencing treatment failure following dasatinib or nilotinib, either as initial or second-line therapy. For patients who have experienced intolerance to a second-generation agent, the use of the other 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; in both cases the patients remained on therapy.

The CGP felt that adoption of bosutinib as first line therapy would be unlikely; in the phase III trial comparing bosutinib to imatinib, the rate of CCyR at 12 months, the primary study endpoint, were the same. While time to MMR and CCyR was faster with bosutinib, more patients discontinued bosutinib because of intolerance compared to imatinib, and EFS and OS at 12 months were similar.

Safety

An extensive safety evaluation from the phase II SKI-200 has been reported,[1-5] and the side effect profile of bosutinib appears to be distinct from other TKI's used for the treatment of CML, as demonstrated in the first-line comparison of bosutinib to imatinib described in section 2.1.4. The number of dose delays and treatment interruptions in the phase II trial appeared similar across all patient subgroups (2nd or 3rd line chronic phase treatment,

imatinib resistant or intolerant), as was the duration of treatment interruptions. Approximately 25-40% of adverse events requiring treatment interruption occurred within the first four weeks of therapy. Treatment discontinuation was necessary in approximately 40% of patients intolerant to first line treatment with imatinib or second-line therapy with dasatinib; cross intolerance to bosutinib occurred in 11/50 patients who were dasatinib intolerant. The majority of toxicities resulting in discontinuation were hematologic, specifically thrombocytopenia. The median duration of treatment as second line therapy was 24 months, compared to eight months for third-line treatment, reflecting the unfavourable biology of CML at the latter stage. Dose reductions to manage side effects occasionally resulted in loss of major cytogenetic response, but this appeared to be infrequent. Dose escalations to 600 mg occurred in 29/189 (15%) imatinib resistant patients in chronic phase and 20/117 patients treated in 3rd line (17%) because of inadequate response to the initial 500mg dose, with no apparent increase in adverse events. Approximately 25% of patients discontinued therapy after a dose reduction for toxicity, due to lack of efficacy. 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]

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 to other therapeutic alternatives, either an alternative TKI, older agents such as hydroxyurea or interferon, or supportive care. Neither the study subjects nor the investigators were blinded in this study. The definitions of imatinib and dasatinib intolerance are necessarily somewhat subjective and the definition used in this trial 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. The data on major molecular responses are much more limited with bosutinib, because such monitoring was not available in many of the countries participating in the SKI-200 trial. There are insufficient data to determine the benefit of bosutinib in patients who have been treated with all three TKIs previously (ie. fourth line). The CGP felt that it was extremely unlikely that a direct comparison of bosutinib to supportive care after failure of 2 or 3 prior TKIs will be conducted in the future, or that such a study would be acceptable to clinicians or patients with advanced CML, as active treatment is always offered.

2.3 Conclusions

The Clinical Guidance Panel concluded 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 also considered that from a clinical perspective:

- 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 the follow-up of this study is short, and ability to comment on overall survival is limited, the high MCyR rate observed in suggests that bosutinib therapy may provide survival benefit over supportive care alone, and would appear to be an appropriate therapeutic option.
- 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.
- 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.
- 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).
- Patients would prefer the option of a third line oral TKI to that of more aggressive and risky therapy including allogeneic stem cell transplant, or toxic agents such as interferon.
- 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. The CGP however felt that it was extremely unlikely that a direct comparison of bosutinib to supportive care after failure of 2 or 3 prior TKIs will be conducted in the future, or that such a study would be acceptable to clinicians or patients with advanced CML.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Hematology Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 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 will be diagnosed in the United States in 2014, and CML will be responsible for approximately 800 deaths.[19] There were 447 cases of CML diagnosed in Canada in 2006, the most recent year for which there are incidence data.[8] Ph+ CML is very rare in children. The identified risk factors for development of CML, in addition to age, is significant radiation exposure (such as in atomic bomb survivors or nuclear reactor incidents).

The majority of patients (>95%) with CML are in chronic phase (CP) at diagnosis. In the distant past, without treatment or with previous chemotherapy using busulfan or hydroxyurea, this was followed by progression to accelerated and blast phases which was 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 thus limited 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.[11]

3.2 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.[20] 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.[21] The starting dose of imitinib 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.[13]

With additional follow up of patients treated with TKIs for CP CML, response criteria have been refined, and are summarized in table 3:[12]

Table 3: Response criteria for Chronic Phase CMP patients[12]

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 nolotinib 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 nolotinib 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%).[22] 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%).[14] 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. 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 (eg 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, patient 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; clearly however agents that are active without the risk of exaccerbating significant comorbities are very much needed in the treatment of CML.

3.3 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.[1] 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 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%). Therefore, bosutinib represents a potentially attractive new therapy for patients who have experienced treatment failure after imatinib and nolotinib or dasatinib, 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.

3.4 Other Patient Populations in Whom the Drug May Be Used

None identified

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Patient advocacy groups are invited to provide input on drug reviews to ensure patients' experiences of living with cancer and undergoing treatment are routinely considered as part of the pCODR Review Process. The patient advocacy groups are independent of pCODR.

One patient advocacy group, The Chronic Myelogenous Leukemia Society of Canada (CMLSC), provided input on bosutinib (Bosulif) 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, and their input is summarized below.

CMLSC conducted one-on-one interviews and used an online survey to obtain information from approximately 10 respondents across Canada who were either part of the bosutinib clinical trial or receiving the drug through the compassionate use program in Canada. These were supplemented with literature reviews and conversations with clinical trial investigators.

From a patient perspective, while the efficacy of currently available treatments for CML has been significant for the majority of patients; however, in a smaller population of CML patients, the available treatments are either not well tolerated and/or the disease becomes resistant to treatment. This results in a constant fear and anxiety of not having the disease well controlled and progressing into accelerated or blast crisis phase, for which no treatment currently exists. Although the side effect profile of bosutinib suggests a higher incidence of gastrointestinal effects, CMLSC contend these side-effects are much easier to manage than side effects experienced with other tyrosine-kinase inhibitors (TKI), such as, pleural effusion or cardiac effects. As an example, CMLSC reported that patients who used a TKI, and who had borderline asthma, were required to stay on inhalers prior to the availability of bosutinib. Once these patients were switched to bosutinib they were either able to stop inhalers or reduce their use significantly. CMLSC believe that bosutinib will change the outcomes in a positive way for the patient who needs it, as it represents an additional option for the healthcare team to help the patient achieve stability in their disease and avoid transplantation, progression and an earlier death.

Please see below for a summary of specific input received from the patient advocacy group.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with chronic myeloid leukemia

CMLSC noted that patients with chronic myeloid leukemia (CML) feel fear and constant anxiety of not having that disease well controlled and potentially progressing into accelerated or blast crisis phase, for which no treatment currently exists. There is also fear and constant anxiety of not having access to new therapeutic options in cases of intolerance or resistance/failure to all other available treatment. In particular, the psychological effects of being diagnosed with CML play a significant role in possible depression and fatigue.

CMLSC stated that most patients with CML report pain and discomfort caused by enlarged spleen due to uncontrolled white blood cell overproduction. CMLSC noted that reducing spleen size would allow a patient's appetite to return to normal, reduces fatigue, allows the patient to move more freely and, if pain in the left shoulder is present, eliminates this pain.

4.1.2 Patients' Experiences with Current Therapy for Chronic Myeloid Leukemia

CMLSC reported that TKI's used in the treatment of CML not only extend the lives of patients treated with them, but are also reporting functional cures in some patients. Patients who have the ability to be managed well and achieve optimal drug responses to treatment may be eligible to enrol in clinical trials designed to withdraw treatment, in a well-controlled setting, providing them with the opportunity to enjoy a Treatment Free Remission (TFR).

CMLSC reported that the efficacy of currently available treatments for CML is exceptional overall. However, in a small subset of CML patients, the available treatments are either not well tolerated and/or the disease becomes resistant to the drug and/or the patient has a co-morbidity, such as long term asthma and/or COPD, and/or cardiovascular risks which precludes treatment with available treatment options.

CMLSC reported that patients who used a tyrosine-kinase inhibitor (TKI), and who had borderline asthma, were required to stay on inhalers prior to the availability of bosutinib. Once these patients were switched to bosutinib they were either able to stop inhalers or reduce their use significantly. According to CMLSC, this means that side effects from the inhalers can be resolved or at least be better managed, and the patient can have a better quality of life.

Although the side effect profile of bosutinib suggests a higher incidence of gastrointestinal effects, CMLSC contend these side-effects are much easier to manage than side effects experienced with other tyrosine-kinase inhibitors (TKI), such as, pleural effusion or cardiac effects.

CMLSC believes that it is important to have access to an additional Src kinase inhibitor other than dasatinib, for reasons of safer profile regarding lung side effects, especially for patients with pre-existing lung disease (e.g. asthma, COPD).

CMLSC believes that seeing physical improvements in health and CML milestones helps the patient to understand that the disease is responding to therapy. Moreover, additional options to treatment would create a 'safe haven' for patients failing or intolerant to existing drugs.

4.1.3 Impact of Chronic Myeloid Leukemia and Current Therapy on Caregivers

CMLSC noted that, depending on the age of the patient, caregivers and/or family members may experience high levels of stress brought on by fear and anxiety of unknown outcomes if the patient does not respond well to treatment.

In addition, CMLSC noted that the lack of response or intolerance to current options may also reduce a patient's ability to work, resulting in a loss or reduction in household income.

According to CMLSC, most patients who used bosutinib have found the side effects relatively easy to manage, which translated to reducing the burden on the caregiver and/or household.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Chronic Myeloid Leukemia

CMLSC noted that respondents are aware of the need to ensure that their disease is well controlled (i.e. obtain a deep response); and understand that managing and avoiding side effects (and adverse effects) of the TKIs would support treatment compliance, which may lead to a deep response. It was important for respondents to have the option to reduce the threat of pulmonary problems that can be experienced with current therapies.

CML patients are aware of the issues related to drug side effects and expect the availability of bosutinib would help them to achieve better outcomes without exacerbating their other health concerns.
Because the average CML patient is older, often with comorbidities, CMLSC anticipate that with more treatment options, clinicians are able to better stratify the right patient to the right drug at the right dose and at the right time in the treatment plan to improve the patient's chance at achieving the best response possible.

There is also an expectation that CML patients being treated with the most effective TKI for their specific disease burden will have fewer hospital visits and are at lower risk to require intensive hospital based care.

Moreover, there may be better access to this drug product because it is an oral agent, and may be self-administered outside the hospital healthcare setting by patients themselves.

CMLSC stated that once good control of the CML is obtained through the use of an oral TKI, the positive physical and psychological effects on the patient are quite remarkable. Patients who have well controlled disease show no symptoms of CML and reintegrate well into society. Respondents reported that they had more energy and were able to continue to work or at least contribute more effectively to the running of the household and/or raising children.

CMLSC recognized that with all drugs, bosutinib does have side effects (namely, diarrhea and gastrointestinal issues), but these are generally well managed. CMLSC believe that bosutinib will change the outcomes in a positive way for the patient who needs it, as it represents an additional option for the healthcare team to help the patient achieve stability in their disease and avoid transplantation, progression and an earlier death.

4.3 Additional Information

CMLSC believe that bosutinib will help CML patients who have exhausted all available options to become future stopping trial candidates, as stopping TKI trials in Canada exist for both nilotinib and dasatinib given that key opinion leaders have stated that they have no reason to expect less with bosutinib.

CMLSC submits that the availability of bosutinib will fill a currently unmet need for additional options aimed at saving lives and potentially curing some patients, as well as providing another option for patients who cannot tolerate other TKIs.

As one of the goals of long term therapy is to help patients achieve a good quality of life during therapy so that they can stay consistently on the drugs, CMLSC suggest that this new therapy will help patients on many levels such as:

- Physical - the ability to stay active and manage their own affairs
- Mental – knowing that their an array of treatment options to help them achieve their best response and/or quality of life
- Financial/societal - improved QoL will allow patients to maximize their potential as full, contributing members of society

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for bosutinib (Bosulif) for chronic myeloid leukemia (CML). The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on bosutinib (Bosulif) for CML was obtained from the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, bosutinib has enablers that include being an oral therapy that can be easily delivered in the community setting and that is once daily administration. Key barriers identified include the potential for use in the first-line or second-line setting and the uncertainty of the clinical benefits for an additional line of therapy that is based on data from a phase 1/2 trial that has no comparator arm.

Please see below for more details.

5.1 Factors Related to Comparators

The current treatment of CML involves nilotinib, dasatinib, or imatinib. In some provinces, imatinib is publicly funded only for first-line treatment but in other provinces, imatinib is funded for first-line and second-line treatment, depending on mutational analysis. Dasatinib is funded for second-line treatment in all nine participating provinces and nilotinib is funded for first-line, second-line or both lines of treatment in most of the provinces. PAG noted that although only two lines of treatment are publicly funded, the third tyrosine kinase inhibitors (TKI) would be funded for patients who do not tolerate the second TKI for second-line treatment and patients with private drug insurance could be treated with all three TKI in any sequence.

PAG noted that the phase 1/2 trial [4] submitted is for the third or fourth-line treatment of CML with bosutinib after imatinib first-line followed dasatinib and/or nilotinib. However, PAG indicated that not all patients would be treated with imatinib first or treated with imatinib for the same duration as the patient population in the trial. PAG is requesting clarity on the patient population for bosutinib and the sequence of previous TKI use. In addition, PAG noted that the trial does not have a comparator arm and the third or fourth-line treatment for CLL is best supportive care for most patients or stem cell transplant for some patients.

Bosutinib is a fourth TKI available for the treatment of CML and PAG noted that each TKI has a different side effect profile.

5.2 Factors Related to Patient Population

PAG noted that the number of patients with CML is small and the number of patients requiring for third or fourth line treatment would be very small. Bosutinib would be a new treatment option for patients where best support care is the current third or fourth-line treatment. These factors are enablers. However, PAG questioned the value of adding a new line of treatment that has a limited response rate and seeks to understand its added benefits over best supportive care. PAG would like this be addressed in the clinical and economic analysis.

Bosutinib has a different side effect profile that may be a better option over imatinib, dasatinib or nilotinib for certain patients. As the Health Canada indication does not specify the line of therapy for bosutinib, PAG has concerns with indication creep for second-line treatment. PAG also has concerns with use of bosutinib in the first-line setting since there is a phase 3 trial published. PAG is requesting for data on the use of bosutinib in the second-line setting and would like pERC to address the data for first-line use.

In addition, there is potential for patients to be treated with all four TKI and any information on the sequence of TKI use would be helpful from an implementation perspective.

5.3 Factors Related to Accessibility

PAG noted that bosutinib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings. PAG identified the oral route of administration is similar to the other oral TKI and is an enabler to implementation.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

5.4 Factors Related to Dosing

PAG indicated that the once daily dosing is an enabler, as it is a very convenient dosing schedule for patients.

PAG noted that there are two tablet strengths, 100mg and 500mg, available for starting dose of 500mg and dosage reductions in increments of 100mg. PAG has concerns with the potential for drug wastage for patients who may be dispensed the 500mg tablets but do not tolerate and then have dose reduced to 400mg prior to finishing. PAG also noted the potential for patients to be confused with the number of tablets and which strength to take when dose adjustments are required.

In the phase 1/2 trial[4], dose escalation to 600mg was allowed only in patients who failed to reach complete hematological response (CHR) by week 8 or a complete cytogenetic response (CCyR) by week 12. PAG is requesting clarity on the clinical benefits at the higher dose and the number of patients requiring dose escalation.

At the time of PAG input, the price was not available. PAG has concerns that if the tablets are not priced per mg, there would be additional costs for dose adjustments and would like the economic analysis to take this into account.

5.5 Factors Related to Implementation Costs

PAG noted that healthcare providers are familiar with tyrosine kinase inhibitors, although bosutinib has different side effects to monitor.

PAG indicated that there may be a small incremental budget impact as bosutinib is an additional line of therapy that would be funded, although it was noted that there would be a very small patient population who would require third or fourth-line treatment. PAG indicated that if bosutinib is used instead of dasatinib or nilotinib, the cost of bosutinib relative to these other TKI would determine whether there would be cost savings or additional expenditures or no budget impact. PAG also noted that the introduction of generic imatinib may have shifted the pricing of other tyrosine kinase inhibitors as well.

5.6 Other Factors

None identified.

6 SYSTEMATIC REVIEW

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

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 4: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCT In the absence of RCT data, fully published clinical trials investigating the efficacy of bosutinib should be included. Reports of trials with only a dose-escalation design should be excluded. Reports of trials with a mixed design are to be included only if separate data were reported for the cohort of patients who were included in the efficacy-determining phase of the study.	Patients with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) CML with resistance or intolerance to prior TKI therapy, and for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate.	Bosutinib monotherapy 500 mg QD	Best Supportive Care No comparator in the case of single arm studies Transplants Interferon Hydroxycarbamide or *hydroxyurea*	**OS** **PFS** **Hematologic Response** **Cytogenic Response** **Molecular Response** **Quality of Life** **Grade 3 or 4 Adverse events** **Subgroups analysis for Dose adjustments; Lines of previous therapy and mutation status**

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.

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-October 7, 2014) with in-process records & daily updates via Ovid; EMBASE (1980- October 7 2014) via Ovid; The Cochrane Central Register of Controlled Trials (2014, September 2014, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Bosutinib or Bosulif and chronic myeloid leukemia.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year. Retrieval was limited to the English language.

The search is considered up to date as of March 9, 2015.

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 – clinicatrials.gov and Ontario Institute for Cancer Research – Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of this pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.

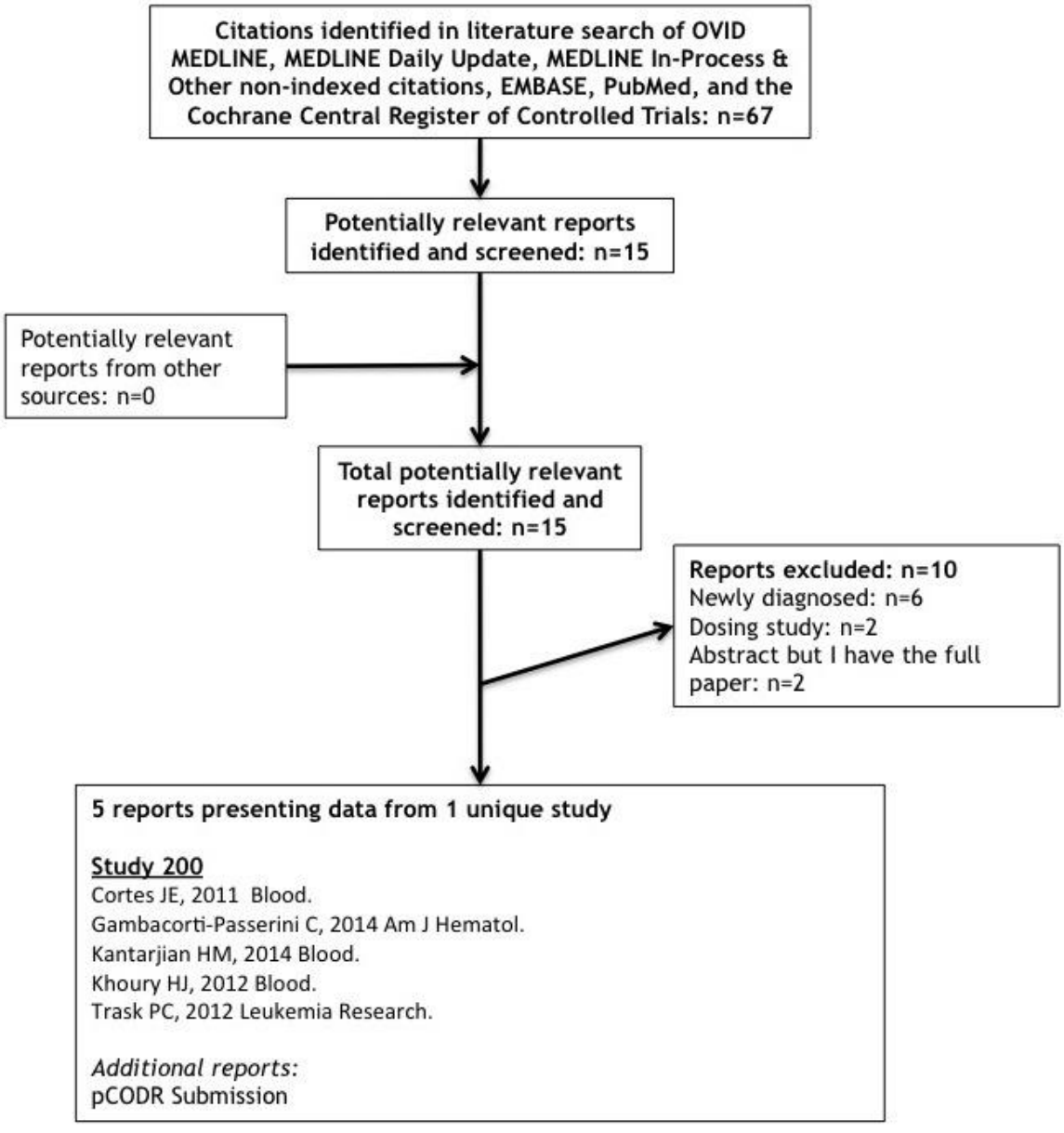
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 13 potentially relevant reports identified, 5 studies were included in the pCODR systematic review [1-5] and 7 studies were excluded. Studies were excluded because they were [newly diagnosed patients[15,16,17, 23,24,25]], [dosing studies[26,27]], [in abstract form, but the complete paper was available[28,29]].

Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of Studies.



Note: Additional data related to the study was also obtained through requests to the Submitter by pCODR.

6.3.2 Summary of Included Studies

One phase 1/2 single arm study was identified that met the eligibility criteria of this systematic review (see Table 5).

6.3.2.1 Detailed Trial Characteristics

6.2.1.1 Table 5. Summary of study characteristics of the included study of bosutinib in patients resistant or intolerant to imatinib with chronic myeloid leukemia. Study 200[1-5,30]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
Study 200 NCT0-0261846 Phase 1/2 open label single arm N=288 for second line chronic phase treatment n=200 imatinib resistant n=88 imatinib intolerant N=114 for third line chronic phase 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 N=4 fourth line chronic phase n=2 imatinib, dasatinib and nilotinib resistant	• Aged ≥18 • Cytogenetic- or PCR-based diagnosis of any phase of Ph+ CML • Disease resistant to full-dose imatinib (≥600 mg/day) or intolerant to any dose of imatinib • Adequate duration of prior imatinib therapy • ECOG Performance Status of 0 or 1 for chronic phase patients • No antiproliferative or antileukemia treatment within 7 days of the first dose of bosutinib (except hydroxyurea and anagrelide) • At least 3 months post-allogeneic stem cell transplantation • Recovery to grade 0/1, or to baseline, from any toxicities from prior anticancer treatment (excluding alopecia) • Able to take daily oral capsules or tablets reliably • Adequate bone marrow function for imatinib-resistant patients in chronic phase only (ANC > 1000 × 10^9/L, platelets ≥100,000 × 10^9/L, and absence of any platelet transfusions during the preceding 14 days) • Adequate hepatic function (AST/ALT ≤ 2.5 × ULN or ≤ 5 × ULN if attributable to liver involvement of leukemia; total bilirubin ≤ 1.5 × ULN) • Adequate renal function (creatinine ≤ 1.5 × ULN) QTc interval < 470 msec at screening • Willingness to use reliable birth control (if applicable) throughout the study and 30 days after the last dose • Documented normal INR if not on oral anticoagulant therapy, or if on anticoagulants, consistent target INR ≤3	• Bousutinib 500mg/day • Inpatient dose escalation to 600mg/day was allowed for lack of efficiency (failure to achieve CHR by week 8 or CCyR by week 12 • If grade 3 or greater bosutinib-related toxicity had not been observed. Doses were held or reduced in 100-mg decrements on the basis of severity and duration of treatment-related toxicities. • Patients were removed from the study if they were unable to tolerate a bosutinib dose of ≥ 300 mg/day.	<u>Primary:</u> Percentage of chronic phase second-line imatinib resistant patients with Major Cytogenetic Response (MCyR) at week 24 in <u>Secondary:</u> Percentage of chronic phase second-line imatinib intolerant and chronic phase third-line patients with Major Cytogenetic Response (MCyR) Duration of MCyR in chronic phase patients Time to achieve MCyR in chronic phase patients Duration of complete hematologic response Time to achieve complete hematologic response

6.2.1.1 Table 5. Summary of study characteristics of the included study of bosutinib in patients resistant or intolerant to imatinib with chronic myeloid leukemia. Study 200[1-5,30]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
n=1 imatinib, resistant and nilotinib intolerant n=1 imatinib dasatinib and nilotinib intolerant N=76 Accelerated phase N=64 Blast Phase 95 centres in 27 countries Asia, Europe, Australia, and North and South America Patients enrolled from January 2006 to July 2008 This study was sponsored by Wyeth Research, which was acquired by Pfizer Inc in October 2009.	**Exclusion criteria:** • Ph chromosome − negative or Bcr-Abl − negative CML • Overt leptomeningeal leukemia (free of CNS involvement for < 2 months) • Extramedullary disease only • No treated or untreated GVHD within 60 days of study initiation) • Documented history of T315I Bcr-Abl mutation • Pregnant or breastfeeding		Progression Free Survival Rate Overall Survival Rate Percentage of participants with treatment-emergent adverse events or serious adverse events

ALT = alanine aminotransferase; **ANC** = absolute neutrophil count; **AST** = Aspartate aminotransferase; **CHR** = Complete Hematologic Response; **CML** = Chronic Myeloid Leukemia; **GVHD** = Graft-versus-host disease; **INR** = International normalized ratio*;* **MCyR =** Major Cytogenetic Response; **msec** = milliseconds; **PCR =** polymerase chain reaction*;* **Ph+** = Philadelphia chromosome positive; **PS** = Performance Status; **ULN** = Upper limit of normal

a) Trial

One open label phase 1/2 single arm study was found for this review. This study consisted of two parts. Part one was a dose-escalation study in in CML to establish the maximum tolerated dose in this subject population. Part one will not be discussed in this report. Part 2 began after the completion of Part 1 and after a dose had been established. Characteristics of the study's design can be found in Table 5. The study included patients who were resistant

or intolerant to imatinib, dasatinib or nilotinib. The study dose was 500mg a day of bosutinib. The study was open labelled and not blinded. The study was multicentred with 95 sites in Asia, Europe, Australia, and North and South America. The study was initially funded by Wyeth Research, which was then acquired by Pfizer Inc in October 2009.[1]

The primary outcome in the study was the percentage of patients with a major cytogenic response (MCyR) at 24 weeks in chronic phase second-line imatinib resistant population. Secondary outcomes include the percentage of chronic phase second-line imatinib intolerant and chronic phase third-line patients with Major Cytogenetic Response (MCyR), the duration of MCyR in chronic phase patients, time to achieve MCyR in chronic phase patients, the duration of complete hematologic response, time to achieve hematologic response, progression free survival, overall survival, quality of life, and adverse events.[28]

Imatinib resistance for chronic phase patients was defined as failure to achieve or maintain any of the following measurements: hematologic improvement within 4 weeks, a complete hematologic response (CHR) after 12 weeks, any cytogenetic response by 24 weeks, or a MCyR by 12 months with an imatinib treatment dose of 600 mg or greater.[1] Acquired resistance was defined as loss of a MCyR or any hematologic response. Imatinib intolerance was defined as the inability to take imatinib because of imatinib-related grade 4 hematologic toxicity lasting longer than 7 days, imatinib-related grade 3 or greater nonhematologic toxicity, persistent grade 2 toxicity not responding to dose reductions and medical management or loss of previously attained response on lower-dose imatinib among patients with previous toxicity.[1]

Nilotinib and Dasatinib resistance was defined as as the failure to achieve or maintain any of the following: hematologic improvement within 4 weeks, CHR after 12 weeks, any cytogenetic response by 24 weeks, or MCyR by 12 months. Acquired resistance was defined as loss of a MCyR or any hematologic response. Patients could also have resistance related to a Bcr-Abl mutation(s). Intolerance 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 inability to receive a higher dose because of drug-related toxicity at higher doses.[4]

The study was not terminated early and four-year follow-up data is available.[2] The rate of MCyR at 24 weeks was evaluated for all treated patients by the use of response rates and confidence intervals. Secondary end points were summarized with the use of descriptive statistics, such as the Kaplan-Meier method, and response rates. Overall survival was calculated from the start date of therapy to the date of death, with patients censored at the last contact (patients were followed for 2 years after stopping treatment). Progression-free survival was calculated from the start date of therapy to the date of progression (until study completion) or death. Time to response was calculated from the start date of therapy to the first date of response (confirmed response for hematologic response and unconfirmed response for cytogenetic and molecular responses). Duration of response was calculated from the first date of response to confirmed loss, progressive disease, or death. For time-to-event end points, except overall survival, patients were censored at the last follow-up visit for those not known to have the respective end point. Evaluable patients for response for a given end point (secondary efficacy analyses) included those patients who had an adequate baseline assessment for that particular end point. All patients who received at least one dose of bosutinib were included in the safety analysis.[1]

b) Populations

A total of N=546 patients were included in this study. Two hundred and eighty eight chronic phase second line CML patients (n=200 imatinib resistant, n=88 imatinib intolerant), 114 chronic phase CML third and fourth line patients, (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), n=4 fourth line CML chronic phase patients (n=2 imatinib, dasatinib and nilotinib resistant n=1 imatinib, resistant and nilotinib intolerant, n=1 imatinib dasatinib and nilotinib intolerant) and, n=76 CML accelerated phase and n=64 CML blast phase patients.[28]. The study baseline patient demographics can be seen in Tables 6 and 7.

Table 6: Baseline patient demographic and disease characteristics for 2nd and 3rd line Chronic phase patients[3]

	Chronic phase 2nd line			**Chronic phase 3rd line**			
	IM-R (n = 196)	**IM-I (n = 90)***	**Total (n = 286)**	**IM-R/I + D-R (n = 38)**	**IM-R/I + D-I (n = 50)***	**IM-R/I + N-R (n = 26)**	**Total† (n = 118)**
Median age (range), y	51 (18-86)	55 (23-91)	53 (18-91)	56 (23-76)	57 (25-79)	53 (20-73)	56 (20-79)
Male sex, n (%)	114 (58)	36 (40)	150 (52)	18 (47)	19 (38)	14 (54)	53 (45)
White	131 (67)	55 (61)	186 (65)	28 (74)	38 (76)	17 (65)	86 (73)
Asian	42 (21)	22 (24)	64 (22)	4 (11)	9 (18)	2 (8)	15 (13)
Black	11 (6)	5 (6)	16 (6)	1 (3)	1 (2)	3 (12)	6 (5)
Other	12 (6)	8 (9)	20 (7)	5 (13)	2 (4)	4 (15)	11 (9)
Median time since CML diagnosis(range), y	4.1 (0.6-15.1)	2.6 (0.1-13.6)	3.7 (0.1-15.1)	7.0 (1.2-17.6)	5.8 (0.6-18.3)	5.9 (1.2-16.3)	6.6 (0.6-18.3)
ECOG performance status, n (%)‡							
0	152 (78)	67 (74)	219 (77)	28 (74)	31 (62)	24 (92)	85 (72)
1	44 (22)	21 (23)	65 (23)	10 (26)	18 (36)	2 (8)	32 (27)
2	0	1 (1)	1 (<1)	0	0	0	0
No. of prior therapies, n (%)							
1	119 (61)	67 (74)	186 (65)	0	0	0	0
2	77 (39)	23 (26)	100 (35)	12 (32)	26 (52)	13 (50)	52 (44)
3	0	0	0	26 (68)	24 (48)	13 (50)	64 (54)
4	0	0	0	0	0	0	2 (2)
Prior TKI therapy, n (%)							
Imatinib only	196 (100)	90 (100)	286 (100)	0	0	0	0

	Chronic phase 2nd line			Chronic phase 3rd line			
	IM-R (n = 196)	**IM-I (n = 90)***	**Total (n = 286)**	**IM-R/I + D-R (n = 38)**	**IM-R/I + D-I (n = 50)***	**IM-R/I + N-R (n = 26)**	**Total† (n = 118)**
Imatinib + dasatinib	0	0	0	38 (100)	50 (100)	0	88 (75)
Imatinib + nilotinib	0	0	0	0	0	26 (100)	27 (23)
Imatinib + dasatinib + nilotinib	0	0	0	0	0	0	3 (3)
Other prior therapies, n (%)							
Interferon	77 (39)	23 (26)	100 (35)	26 (68)	24 (48)	13 (50)	65 (55)
Stem cell transplant	6 (3)	2 (2)	8 (3)	2 (5)	5 (10)	0	9 (8)

IM-R, imatinib resistant; IM-I, imatinib intolerant; IM-R/I, imatinib resistant/intolerant; D-R, dasatinib resistant; D-I, dasatinib intolerant; N-R, nilotinib resistant; ECOG, Eastern Cooperative Oncology Group.
* The subgroups of patients with intolerance to prior TKI therapy.
† Includes patients (n = 4) in whom prior imatinib therapy failed and who were intolerant to prior nilotinib or resistant or intolerant to prior nilotinib and dasatinib therapy (because of low n, data not shown separately).
‡ ECOG performance status at baseline was missing for 1 patient each in the second and third line cohorts.

Table 7: Baseline patient demographic and disease characteristics for Accelerated and Blast phase patients[31]

	Accelerated Phase n=76	Blast Phase n=64
Median age	50.5 (range 18.0-83.0)	48.5 (range 19.0-82.0)
Male	55%	64%
Race		
White	61%	59%
Asian	26%	22%
ECOG performance status		
0	54%	34%
1	43%	44%
2	N/A	22%
Prior therapies		
Dasatinib	33%	36%
Nilotinib	20%	19%
Stem cell transplant	9%	6%
Interferon	50%	30%
N/A: not available		

c) *Interventions*

Bosutinib was administered orally at 500mg a day. Details of the dose and administration of treatment can be found in Table 12. As of May 15, 2013 in the second line treatment group the median duration of bosutinib treatment was 24.8 (0.2-83.4) months. In the third line treatment group it was 8.5 (0.2-78.1) months. The time from the last patient's first dose to the cut off was ≥48 months for the second line treatment group and ≥36 months for the third line treatment group.[3] As of May 2014 in the accelerated phase group the median duration

of treatment was 10.2 (0.1-88.55) months and 2.78(0.03-55-92) months in the blast phase group.[7]

d) *Patient Disposition*

All analyses were done on patients who received at least one dose of bosutinib. At the time of the latest analysis (May 15 3013) 147 (26%) of patients were receiving treatment.[3]

e) *Limitations/Sources of Bias*

Please see Table 5 for a summary of key quality-related characteristics of the included study.
This study was a single arm open label study phase 1/2 study and therefore there was 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.[1,2,4] Data is also not disclosable for some outcomes for accelerated and blast phase patients.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes for Chronic Phase patients

Percentage of Chronic Phase participants with MCyR, Duration of MCyR, Time to achieve MCyR, Duration of complete hematologic response, Time to achieve complete hematologic response

Results for the best overall response for second line chronic phase patients can be seen in Table 8. Evaluable patients had received at least 1 dose of bosutinib and had a valid baseline assessment for the respective endpoint. In the total group of evaluable second line CP patients with a valid baseline cytogenetic assessment, 59% of patients newly achieved a MCyR or maintained their baseline MCyR for ≥4 weeks, including 58% of imatinib-resistant patients and 61% of imatinib-intolerant patients. The complete cytogenetic response (CCyR) rate was 48%. Median (range) time to a confirmed CHR among responders was 2.0 weeks (0.3–72.4 weeks) for imatinib-resistant patients and 1.7 weeks (0.9–36.3 weeks) for imatinib-intolerant patients.[2]
In second line therapy major molecular response (MMR) was achieved in 35% of treated patients (the analysis excluded patients from China, India, Russia, and South Africa), including 28% of patients who achieved a complete molecular response, with the proportion of patients who achieved an MMR being similar for imatinib-resistant (34%) and imatinib-intolerant (35%) patients.[2] These results can be seen in Table 8.

Table 8: Best Overall response after 24 month follow-up for chronic phase second line patients[2]

Response	Imatinib resistant (n=200)	Imatinib intolerant (n=88)	Total (n=288)
Median (range) treatment duration months	22.1 (0.2–60.8)	20.7 (0.3–52.3)	22.1 (0.2–60.8)
Cytogentic response, [a] n(%) [95% CI]			

Response	Imatinib resistant (n=200)	Imatinib intolerant (n=88)	Total (n=288)
Evaluable patients	186	80	266
MCyR	108 (58) [51–65]	49 (61) [50–72]	157 (59) [53–65]
CCyR	85 (46) [38-53]	43 (54) [42-65]	128 (48) [42-54]
Evaluable patients without a CCyR at baseline to previous therapy	181	69	250
MCyR	103 (57) [49-64]	39 (57) [44–68]	142 (57) [50-63]
CCyR	80 (44) [37-52]	34 (49) [37-62]	114 (46) [39-53]
Molecular response, [b] n(%) [95% CI]			
Evaluable patients	132	68	200
MCyR	45 (34) [26-43]	24 (35) [24-48]	69 (35) [28-42]
CCyR	33 (25) [18-33]	22 (32) [22-45]	55 (28) [21-34]
Hematologic response, [c] n(%) [95% CI]			
Evaluable patients	199	88	287
CHR	170 (85) [80-90]	74 (84) [75-91]	244 (85) [80-89]
Evaluable patients without a CHR at baseline to previous therapy	100	41	141
CHR	76 (76) [66-84]	33 (81) [65-91]	109 (77) [70-84]
Probability of retaining MMR % [95% CI]			
Evaluable patients	45	24	69
at 1 year	78 [61-88]	91 [68-93]	82 [70-90]
at 2 years	78 [61-88]	91 [68-93]	82 [70-90]

[a]Evaluable patients must have had an adequate baseline cytogenetic assessment. Cytogenetic response was determined using standard cytogenetics (G-band karyotype) with ≥20 metaphases counted for post baseline assessments; if <20 metaphases were available post baseline, FISH analysis of bone

marrow aspirate with ≥200 cells for the presence of Bcr-Abl fusion gene was used. MCyR included PCyR (1–35% Ph^{+1} metaphases) and CCyR (0% Ph^{+1} metaphases; <1% if using FISH). Cytogenetic response could be achieved during the study or maintained from baseline for 4 weeks, unless otherwise noted within the table.

[B] Patients enrolled in China, India, Russia, and South Africa could not be evaluated for molecular response due to logistical constraints; treated patients not from these four countries were evaluable for molecular

Response	Imatinib resistant (n=200)	Imatinib intolerant (n=88)	Total (n=288)
response. Molecular response was assessed at a central laboratory (Quest Diagnostics) using non-nested real time PCR for the ratio of Bcr-Abl to Abl transcripts. MMR was categorized as a ≥3-log reduction from standardized baseline and included CMR (undetectable Bcr-Abl transcript with a PCR sensitivity of ≥5 logs). To be considered a responder for MMR/CMR, the patient should also have had detectable Bcr-Abl transcript levels at baseline or any time postbaseline, and have achieved/maintained a CCyR; patients with cytogenetic assessments not showing CCyR on the same day of molecular assessment were not considered to have an MMR/CMR at that time. MMR was not assessed using the International Scale because it was not widely available when the study was initiated. c Evaluable patients must have had an adequate baseline hematologic assessment. The definition of CHR was standard; hematologic response was required to be confirmed and to last for ≥4 weeks, with peripheral blood and/or bone marrow documentation, and could be achieved during the study or maintained from baseline for ≥5 weeks, unless otherwise noted within the table.			

Results for the best cumulative response for third and fourth line chronic phase patients can be seen in table 9. MCyR was attained by 32% (n = 35) of patients, with CCyR in 24% (n = 26) of patients, including one of 3 patients who were previously treated with all 3 TKIs. Patients with CCyR or PCyR at baseline were considered nonresponders for this analysis despite potential maintenance of their response. When patients with a baseline CCyR or PCyR who maintained their response after baseline were included as responders in the analysis, the rates of MCyR and CCyR were 39% (n = 42) and 31% (n = 33), respectively.[4]

Table 9: Best cumulative overall response after 28.5-month follow-up for 3rd and 4th line chronic phase patients[4]

Response, n (%)	IM + DAS resistant (n = 37)	IM + DAS intolerant (n = 50)	IM + NI resistant (n = 27)	IM + DAS ± NI (n = 4)*	Total (n = 118)
Median follow-up, mo (range)	20.0 (2.7-51.3)	34.5 (0.3-56.2)	23.0 (7.1-54.0)	34.5 (22.8-40.0)	28.5 (0.3-56.2)
Hematologic response†					
Evaluable patients	37	49	26	4	116
Complete response	23 (62)	39 (80)	20 (77)	3 (75)	85 (73)
Hematologic response among patients with no baseline CHR					
Evaluable patients	22	24	20	2	68
Complete response	11 (50)	16 (67)	15 (75)	2 (100)	44 (65)
Cytogenetic response‡					
Evaluable patients	35	43	26	4	108
Major response	11 (31)	13 (30)	9 (35)	2 (50)	35 (32)

Response, n (%)	IM + DAS resistant (n = 37)	IM + DAS intolerant (n = 50)	IM + NI resistant (n = 27)	IM + DAS ± NI (n = 4)*	Total (n = 118)
Complete response	5 (14)	12 (28)	7 (27)	2 (50)	26 (24)
Partial response	6 (17)	1 (2)	2 (8)	0	9 (8)
Minor response	0	4 (9)	2 (8)	0	6 (6)
Molecular response§					
Evaluable patients	35	48	19	3	105
Major response	1 (3)	12 (25)	2 (11)	1 (33)	16 (15)
Complete response	0	9 (19)	2 (11)	1 (33)	12 (11)
Duration of MCyR					
Evaluable patients	11	13	9	2	35
Median duration of MCyR; weeks [95% CI]	24.1[18.0-NA]	NA [NA]	NA [NA]	NA [57.0-NA]	NA [47.3-NA]
Kaplan-Meier estimate of retaining response at 2 years	34%	76%	86%	50%	59%

IM indicates imatinib; DAS, dasatinib; and NI, nilotinib.
* Includes 3 patients who previously received all 3 inhibitors and 1 patient with NI intolerance.
† Evaluable patients had a baseline disease assessment. Patients with CHR at baseline were evaluable for hematologic response and were considered responders if they maintained their response at 2 consecutive post-baseline assessments ≥ 4 weeks apart.
‡ Evaluable patients had a baseline disease assessment. Patients with CCyR at baseline were considered nonresponders for assessment of cytogenetic response.
§ Because of logistical constraints, patients from sites in China, India, Russia, and South Africa were not assessed for molecular response. MMR indicates ≥ 3 log reduction from standardized baseline Bcr-Abl:Abl ratio; and CMR, undetectable Bcr-Abl, with a sensitivity of ≥ 5 log. Molecular response was not assessed according to the International Scale.

Many patients had mutations at baseline, however, due to the small subgroups it is difficult to draw conclusions with certainty. In the second line chronic phase cohort there were 115 patients with known mutations at baseline. The most common were M351T (n = 7), F359V (n = 7), F317L (n = 4), L248V (n = 4), G250E (n = 3), M244V (n = 3), and T315I (n = 3). Similar rates of CHR or MCyR were observed between patients with and without mutations. Responses were observed broadly across Bcr-Abl mutants, except for T315I.[1]

There were 39 chronic phase patients receiving third or fourth line therapy with known Bcr-Abl kinase domain mutations at baseline. The most common were F317L (n = 8), T315I (n = 7), G250E (n = 6), and Y253H (n = 6). CHR and MCyR were observed broadly across Bcr-Abl mutants, including those conferring clinical resistance to dasatinib (F317L) and nilotinib (Y253H, E255K/V, F359C/I/V). Nine patients developed new mutations during treatment, including 8 patients who already had a baseline mutation and one patient who developed 2 emergent mutations. Specific emergent mutations included V299L (n = 4), L248V (n = 2), T315I (n = 2), F359C (n = 1), and G250E (n = 1). Of the 9 patients with emergent mutations,

one patient had 2 emergent mutations (G250E and V299L) and 8 had discontinued bosutinib because of progressive disease or unsatisfactory response.[4]

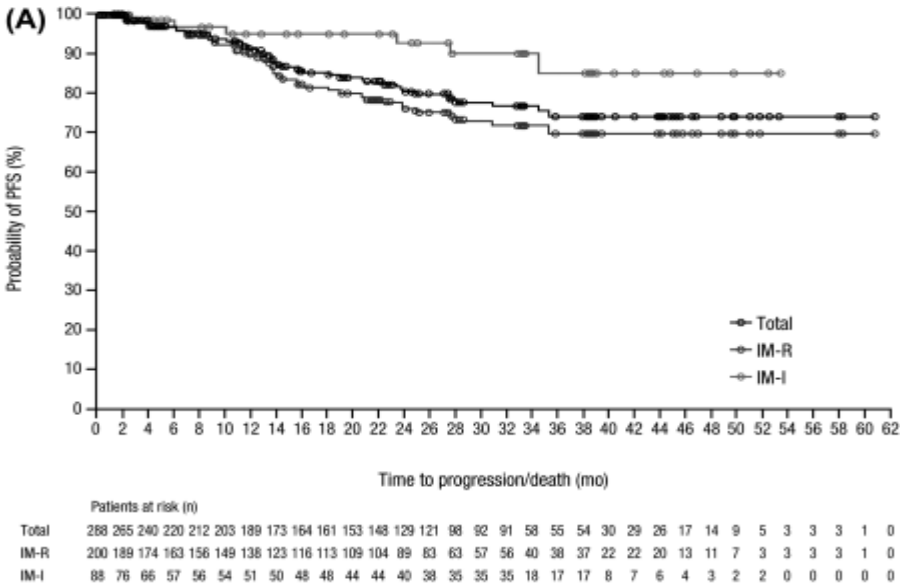
Progression Free Survival (PFS) and Overall Survival (OS) for Chronic Phase patients

Median progression free survival for chronic phase second line patients was not reached. The 2-year Kaplan–Meier estimate of PFS was 81%, this can be seen in figure 2. Progression free survival was calculated for the all-treated population from the start date of therapy until treatment discontinuation due to disease progression (as assessed by the investigator including transformation to AP or BP CML) or death, or death within 30 days of the last dose. Patients without events were censored at their last assessment visit.[2]

Disease progression included transformation to AP/BP CML, which occurred in 11 patients during bosutinib treatment. Among imatinib-resistant patients, 4 patients transformed to AP with a time to transformation ranging from 415 to 630 days after bosutinib initiation and 6 patients transformed to BP with a time to transformation ranging from 42 to 476 days after bosutinib initiation. One imatinib-intolerant patient transformed to AP 246 days after bosutinib initiation. However, with continued bosutinib treatment, this patient returned to CP and regained a confirmed CHR.[2]

Overall survival was calculated for the all-treated population from the start date of therapy to the date of death due to any cause. Patients without events were censored at the last contact (patients were followed up for 2 years after treatment discontinuation). The 2-year Kaplan–Meier estimate for OS for the whole second line cohort was 91% (95%CI: 87-94). It was 88% (95%CI; 82-92) for the imatinib resistant population and 98% (95%CI: 91-99) for the imatinib intolerant population.[2]

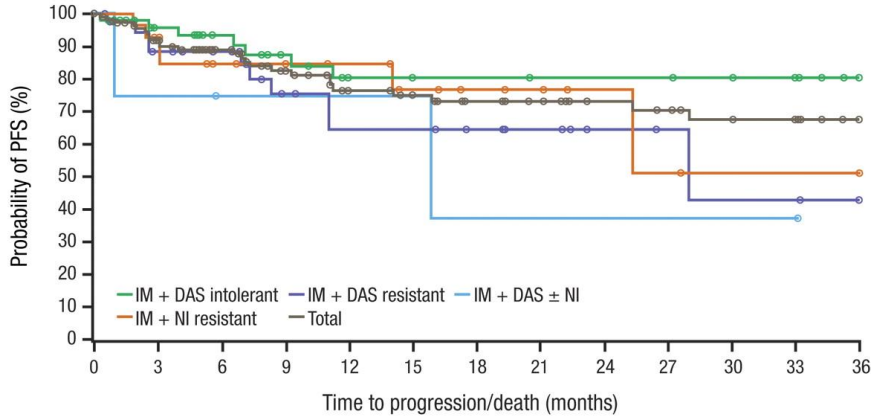
Figure 2: Progression free survival in second line chronic phase patients.[2]



	n	PFS at 1 year (95% CI)	PFS at 2 years (95% CI)
Total population	288	91% (87–94)	81% (74–85)
IM-R	200	90% (84–94)	76% (68–82)
IM-I	88	95% (86–98)	93% (82–97)

Progression free survival at a median follow-up of 28.5 months in the third and fourth line populations can be seen in figure 3. The Kaplan-Meier estimate of progression free survival for all treated patients at 1 year was 77% and at 2 years was 73%. The median PFS has not been reached. Progression was determined by the investigator and defined as on-treatment transformation to accelerated or blast phase, loss of CHR, loss of MCyR with Philadelphia chromosome rate increased by 30%, doubling of white blood cell count to > 20×10^9/L, or death because of any cause within 30 days of the last study dose.[4]

Figure 3: Progression free survival for third and fourth line chronic phase patients[4]



Patients at risk (n)												
Total population	118	94	75	58	47	43	38	32	27	25	22	20
IM + DAS resistant	37	28	24	15	12	12	10	7	4	3	2	2
IM + DAS intolerant	50	40	31	26	21	20	20	19	19	19	18	16
IM + NI resistant	27	23	18	15	12	9	7	5	3	2	1	1
IM + DAS ± NI*	4	3	2	2	2	2	1	1	1	1	1	1

	n	Median PFS (95% CI), mo	PFS estimate at 1 year,† %	PFS estimate at 2 years,† %
Total population	118	NA (NA–NA)	77	73
IM + DAS resistant	37	27.9 (11.0–NA)	65	65
IM + DAS intolerant	50	NA (NA–NA)	81	81
IM + NI resistant	27	NA (25.3–NA)	85	77
IM + DAS ± NI*	4	15.8 (0.9–NA)	75	38

Overall Survival at a median follow-up of 28.5 months in third and fourth line populations can be seen in table 10. At 1 year, the Kaplan-Meier estimate of overall survival was 91% and at 2 years was 83%, with the median for overall survival not yet reached.[4]

Table 10: Overall Survival for third and fourth line patients[4]

Population	N	Overall survival estimate at 1 year %	Overall survival estimate at 2 year %
Total population	118	91	83
IM + Das resistant	37	83	75
IM + DAS intolerant	50	94	85
IM + NI resistant	27	96	92
IM + DAS ± NI	4	100	75

Quality of Life for Chronic phase patients

Health related quality of life (QOL) was measured using the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu). Data was available for 84% of the Imatinib resistant and 91% of the imatinib intolerant patients for second line treatment groups. The data show that the baseline results are similar to samples of individuals used to validate the measure.[5]

Table 11 shows the mean FACT-Leu change from baseline over a period of 96 weeks for second line patients. Significant changes were observed as early as four weeks in both groups of patients. There are minimally important difference observed in the imatinib intolerant group only. The authors state that "Minimally important differences (MIDs) have been identified for the different FACT-Leu scales: Physical Well-being, 2–3 points; Social/Family Well-being, not available; Emotional Well-being, 2 points; Functional Well-being, 2–3 points; FACT-G, 3–7 points; Leukemia-specific subscale, 4–7 points; FACT-Trial Outcome Index, 5–6 points; and FACT-Leukemia Total, 6–12 points. When examining differences for groups, the lower end of the MID range is utilized."[5]

Table 11: Mean FACT-Leu change from baseline scale overtime for second line chronic phase patients[5]

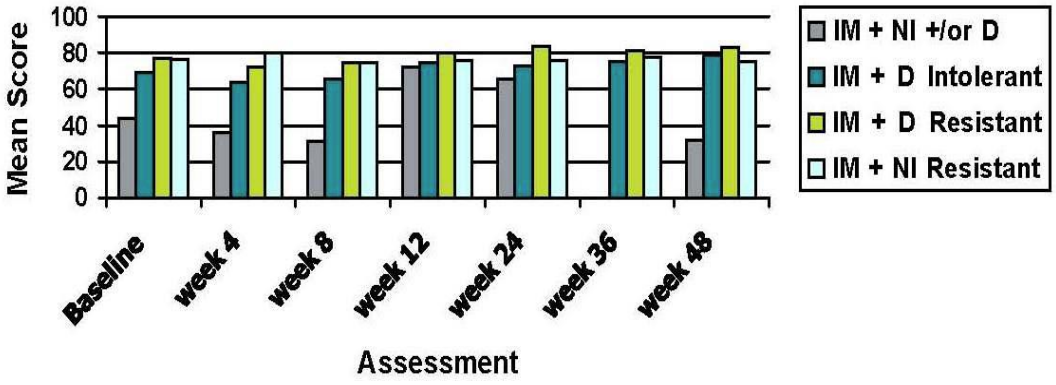
FACT-Leu Scale	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 96
IM resistant	*n* =148	*n* =144	*n* =143	*n* =130	*n* =126	*n* =108	*n* =77
Physical Well-being	−0.81 *	0.17	0.76 *	0.66 *	0.81 *	0.23	1.11 **
Social/Family Well-being	−0.32	−0.32	−0.59	−0.63	−0.51	−0.34	−1.20 **
Emotional Well-being	0.99 +	1.01 +	0.94 +	1.30 +	1.18 +	0.79 *	1.43 +
Functional Well-being	−0.56	0.02	−0.01	−0.11	0.36	0.37	−0.09
Leukemia-specific subscale	0.72	1.27	2.02 +	2.49 +	2.51 +	2.17 +	3.26 +
FACT-General	−0.70	0.88	1.11	1.19	1.90	1.05	1.18
FACT-Leukemia Total	−0.12	2.04	3.07 **	3.67 **	4.31 +	3.21	4.30 **
FACT-Trial Outcome Index	−0.70	1.44	2.75 +	3.04 **	3.62 +	2.75 *	4.19 +
IM intolerant	*n* =65	*n* =66	*n* =63	*n* =51	*n* =48	*n* =48	*n* =40
Physical Well-being	−0.79	0.37	0.11	1.11	1.69 +	1.66 +	1.69 *
Social/Family Well-being	−0.90	−0.56	−0.91	−0.49	0.75	0.57	0.41
Emotional Well-being	1.16 *	1.09 **	0.95	1.55 +	***2.60*** +	***2.45*** +	***2.46*** +
Functional Well-being	−1.64 **	−0.68	−0.25	0.29	1.13	1.15	0.70
Leukemia-specific subscale	1.20	1.30	1.78	3.03 **	***4.46*** +	**3.94** +	***4.35*** +
FACT-General	−2.31	0.34	−0.10	2.46	***6.17*** +	***5.83*** +	***5.15*** **
FACT-Leukemia Total	−1.41	1.69	1.68	5.50 *	***10.63*** +	***9.56*** +	***9.31*** +
FACT-Trial Outcome Index	−1.50	1.13	1.64	4.44 *	***7.27*** +	***6.52*** +	***6.74*** +

FACT-Leu Scale	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 96
* p <0.05; ** p ≤0.01; + p <0.005							
Negative changes reflect a reduction in health-related quality of life. Text in ***bold italics*** denotes a change in excess for minimally important difference, indicating not only statistical significance but also clinical significance.							

Quality of Life was assessed through the FACT-Leu scale for the third line chronic patients. There are significant changes in 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 ($p<0.05$).[7]

In addition improvements or maintenance of baseline levels of overall health status as assessed by the EQ-5D tool were observed for dasatinib-intolerant, dasatinib-resistant, and nilotinib resistant subjects over the course of treatment (figure 4). Patients who were nilotinib intolerant and those who had received prior nilotinib and dasatinib were not considered given the small sample size (n=4 at baseline).[7]

Figure 4: EQ-5D Overall Health Status for chronic third line patients[7]



Harms Outcomes for Chronic Phase patients

Dose reductions and interruptions due to adverse effects (AEs) can be seen in table 12. Dose reductions and interruptions were common in the chronic phase second line (49% and 72%) and third line (50% and 66%) cohorts. The intolerant patients were more likely to discontinue bosutinib treatment because of AEs, particularly thrombocytopenia. Treatment interruptions due to AEs occurring ≤4 weeks after bosutinib initiation were frequent in second and third line patients who were intolerant vs resistant to prior TKIs.[3]

The median cumulative duration of dose reductions for the second line treatment group to 400 mg per day was 169 days, for the third line cohort it was 63.5 days. The dose reduction duration to 300 mg per day was 115 days for the second line group, and 180 days for the third line group. In patients with bosutinib dose reduction to 400 mg per day in the second and third line groups 18 of 130 (14%) and 4 of 52 (8%), respectively, had a major cytogenetic

response (MCyR) before and after reduction, and an additional 56 of 130 (43%) and 15 of 52 (29%) patients first achieved MCyR after reduction. Three, second line and two third line patients lost their previously attained MCyR after reduction. Among those with dose reduction to 300 mg per day in the second and third line cohorts, 17 of 49 (35%) and 4 of 21 (19%) patients had MCyR both before and after reduction. In the second and third line cohorts 8 of 49 (16%) and 4 of 21 (19%) patients first achieved MCyR after reduction. In addition 2 patients lost their previously attained MCyR after reduction.[3] Among second line chronic phase patients 15% of imatinib resistant and 3% of imatinib intolerant patients had their dose increased to 600/mg/day.[1] During the study 17% of third and fourth line patients had their dose of bosutinib increased to 600.mg/day for lack of efficacy.[4] Treatment was discontinued due to adverse events in 22% of the second line group and 25% in the third and forth line groups. The primary reasons for treatment discontinuation by adverse event were as follows, thrombocytopenia, increased ALT, neutropenia, diarrhea vomiting and increased AST.[3]

Table 12: Treatment modifications and discontinuations due to adverse effects[3]

Parameter, n (%) or median (range)	**Chronic phase 2nd line**			**Chronic phase 3rd line**			
	IM-R (n = 196)	**IM-I (n = 90)***	**Total (n = 286**	**IM-R/I + D-R (n=38)**	**IM-R/I + D-I (n=50)**	**IM-R/I + N-R (n=26)**	**Total † (n=118)**
Patients with ≥1 dose reduction‡,§	87 (44)	52 (58)	139 (49)	13 (34)	32 (64)	13 (50)	59 (50)
Number of dose reductions per patient‖							
1	45 (23)	33 (37)	78 (27)	10 (26)	16 (32)	10 (39)	36 (31)
2	37 (19)	15 (17)	52 (18)	2 (5)	13 (26)	2 (8)	18 (15)
≥3	5 (3)	4 (4)	9 (3)	1 (3)	3 (6)	1 (4)	5 (4)
Patients with ≥1 dose interruption	130 (66)	75 (83)	205 (72)	19 (50)	40 (80)	16 (62)	78 (66)
Number of dose interruptions per patient							
1	51 (26)	34 (38)	85 (30)	11 (29)	14 (28)	6 (23)	32 (27)
2	33 (17)	21 (23)	54 (19)	3 (8)	11 (22)	5 (19)	19 (16)
3	21 (11)	7 (8)	28 (10)	1 (3)	5 (10)	2 (8)	9 (8)
≥4	25 (13)	13 (14)	38 (13)	4 (11)	10 (20)	3 (12)	18 (15)
Median cumulative duration of interruption (range), d	21.5 (1-582)	22.0 (1-429)	22.0 (1-582)	24.0 (1-144)	29.5 (1-181)	28.0 (1-150)	27.0 (1-181)
Early (≤4 wk) interruptions	53 (27)	38 (42)	91 (32)	8 (21)	19 (38)	5 (19)	32 (27)

* The subgroups of patients with intolerance to prior TKI therapy.
† Includes patients (n = 4) in whom prior imatinib therapy failed and who were intolerant to prior nilotinib therapy or resistant or intolerant to prior nilotinib and dasatinib therapy (because of low n, data not shown separately).
‡ Dose reduction defined as a decrease in the dose level from the previous dose level administered.
§ For patients who started bosutinib treatment at a dose of 500 mg per day, dose could have been reduced to 400 mg per day because of toxicity and then subsequently escalated to 500 mg per day or reduced further to 300 mg per day. Patients whose dose was escalated to 500 mg per day could have had another dose reduction due to toxicity at another time; therefore, patients could have had multiple dose reductions to 400 or 300 mg per day.
|| Subcategory percentages may not add to the total due to rounding.
¶ All AEs leading to treatment discontinuation in ≥1.0% of patients in the CP2L, CP3L, or ADV cohorts are shown in the table.

Bosutinib toxicities were generally of mild to moderate severity and managed with concomitant medication, dose interruption and/or dose reduction, or resolved spontaneously. These can be seen in table 13. The most frequently reported treatment emergent adverse events (TEAEs) were gastrointestinal events (diarrhea, nausea, and vomiting) and thrombocytopenia.[3] Although diarrhea was common the maximum severity was grade 1 or 2 in most patients. Based on differences of ≥10% for TEAEs occurring in ≥10% of patients, rash was more common and pyrexia less common in patients intolerant vs. resistant to prior imatinib treatment in the second line cohort. In the third line cohort, vomiting, rash, dyspnea, and pleural effusion were more common and neutropenia was less common in patients intolerant to prior dasatinib therapy vs. patients resistant to prior TKI therapy. Thrombocytopenia was most common in third line patients resistant to nilotinib.[3]

Table 13: Treatment emergent adverse events reported for ≥10% of patients[3]

TEAE, n (%)	Chronic phase 2nd line			Chronic phase 3rd line			
	IM-R (n = 196)	IM-I (n = 90)*	Total (n = 286)	IM-R/I + D-R (n = 38)	IM-R/I + D-I (n = 50)*	IM-R/I + N-R (n = 26)	Total (n = 118)†
Diarrhea							
All grades	168 (86)	77 (86)	245 (86)	30 (79)	42 (84)	22 (85)	98 (83)
Grade 3/4	19 (10)	10 (11)	29 (10)	3 (8)	5 (10)	2 (8)	10 (9)
Nausea							
All grades	85 (43)	47 (52)	132 (46)	20 (53)	23 (46)	12 (46)	57 (48)
Grade 3/4	1 (1)	3 (3)	4 (1)	1 (3)	0	0	1 (1)
Vomiting							
All grades	73 (37)	34 (38)	107 (37)	14 (37)	24 (48)	7 (27)	45 (38)
Grade 3/4	3 (2)	8 (9)	11 (4)	1 (3)	0	0	1 (1)
Thrombocytopenia‡							
All grades	77 (39)	43 (48)	120 (42)	11 (29)	19 (38)	13 (50)	45 (38)
Grade 3/4	45 (23)	29 (32)	74 (26)	7 (18)	16 (32)	8 (31)	31 (26)
Rash							
All grades	63 (32)	39 (43)	102 (36)	10 (26)	18 (36)	3 (12)	32 (27)
Grade 3/4	15 (8)	11 (12)	26 (9)	0	3 (6)	0	3 (3)
Pyrexia							
All grades	57 (29)	17 (19)	74 (26)	6 (16)	8 (16)	3 (12)	18 (15)
Grade 3/4	1 (1)	1 (1)	2 (1)	0	0	0	0
Anemia‡							
All grades	51 (26)	25 (28)	76 (27)	8 (21)	7 (14)	6 (23)	22 (19)
Grade 3/4	23 (12)	9 (10)	32 (11)	3 (8)	4 (8)	1 (4)	8 (7)
Fatigue							
All grades	49 (25)	25 (28)	74 (26)	8 (21)	14 (28)	2 (8)	27 (23)
Grade 3/4	1 (1)	2 (2)	3 (1)	0	1 (2)	0	2 (2)
Abdominal pain							
All grades	50 (26)	25 (28)	75 (26)	9 (24)	12 (24)	7 (27)	28 (24)
Grade 3/4	3 (2)	2 (2)	5 (2)	0	1 (2)	0	1 (1)
Headache							
All grades	35 (18)	18 (20)	53 (19)	8 (21)	14 (28)	8 (31)	31 (26)
Grade 3/4	0	0	0	1 (3)	3 (6)	0	4 (3)
Cough							
All grades	44 (22)	19 (21)	63 (22)	7 (18)	11 (22)	4 (15)	23 (20)
Grade 3/4	0	0	0	0	0	0	0
Increased ALT							
All grades	41 (21)	23 (26)	64 (22)	6 (16)	6 (12)	5 (19)	18 (15)
Grade 3/4	15 (8)	10 (11)	25 (9)	0	4 (8)	3 (12)	7 (6)
Upper abdominal pain							

TEAE, n (%)	Chronic phase 2nd line			Chronic phase 3rd line			
	IM-R (n = 196)	IM-I (n = 90)*	Total (n = 286)	IM-R/I + D-R (n = 38)	IM-R/I + D-I (n = 50)*	IM-R/I + N-R (n = 26)	Total (n = 118)†
All grades	41 (21)	17 (19)	58 (20)	8 (21)	9 (18)	4 (15)	21 (18)
Grade 3/4	1 (1)	0	1 (<1)	0	0	0	0
Neutropenia‡							
All grades	29 (15)	17 (19)	46 (16)	9 (24)	7 (14)	7 (27)	24 (20)
Grade 3/4	16 (8)	11 (12)	27 (9)	6 (16)	7 (14)	4 (15)	18 (15)
Increased AST							
All grades	37 (19)	18 (20)	55 (19)	2 (5)	3 (6)	4 (15)	9 (8)
Grade 3/4	6 (3)	5 (6)	11 (4)	0	1 (2)	2 (8)	3 (3)
Arthralgia							
All grades	30 (15)	15 (17)	45 (16)	5 (13)	10 (20)	6 (23)	21 (18)
Grade 3/4	2 (1)	1 (1)	3 (1)	0	1 (2)	0	1 (1)
Decreased appetite							
All grades	30 (15)	11 (12)	41 (14)	3 (8)	7 (14)	4 (15)	14 (12)
Grade 3/4	2 (1)	0	2 (1)	0	1 (2)	0	1 (1)
Constipation							
All grades	22 (11)	18 (20)	40 (14)	2 (5)	8 (16)	3 (12)	15 (13)
Grade 3/4	0	1 (1)	1 (<1)	0	0	0	0
Dyspnea							
All grades	23 (12)	10 (11)	33 (12)	2 (5)	10 (20)	1 (4)	13 (11)
Grade 3/4	4 (2)	0	4 (1)	0	1 (2)	0	1 (1)
Asthenia							
All grades	25 (13)	16 (18)	41 (14)	2 (5)	1 (2)	4 (15)	8 (7)
Grade 3/4	6 (3)	0	6 (2)	0	0	0	0
Back pain							
All grades	22 (11)	17 (19)	39 (14)	5 (13)	5 (10)	3 (12)	14 (12)
Grade 3/4	1 (1)	0	1 (<1)	0	2 (4)	1 (4)	3 (3)
Dizziness							
All grades	17 (9)	9 (10)	26 (9)	5 (13)	8 (16)	2 (8)	16 (14)
Grade 3/4	0	0	0	0	0	0	0
Leukopenia‡							
All grades	21 (11)	14 (16)	35 (12)	4 (11)	0	0	4 (3)
Grade 3/4	8 (4)	7 (8)	15 (5)	0	0	0	0
Peripheral edema							
All grades	18 (9)	13 (14)	31 (11)	1 (3)	5 (10)	4 (15)	11 (9)
Grade 3/4	1 (1)	0	1 (<1)	0	0	0	0
Nasopharyngitis							
All grades	24 (12)	13 (14)	37 (13)	4 (11)	5 (10)	4 (15)	14 (12)
Grade 3/4	0	0	0	0	0	0	0
Extremity pain							
All grades	26 (13)	5 (6)	31 (11)	1 (3)	5 (10)	3 (12)	9 (8)
Grade 3/4	2 (1)	0	2 (1)	0	0	0	0
Pleural effusion							
All grades	18 (9)	5 (6)	23 (8)	5 (13)	12 (24)	1 (4)	18 (15)
Grade 3/4	4 (2)	2 (2)	6 (2)	2 (5)	2 (4)	0	4 (3)

TEAEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.
* The subgroups of patients with intolerance to prior TKI therapy.
† Includes patients (n = 4) for whom prior imatinib therapy failed and who were intolerant to prior nilotinib therapy or resistant or intolerant to prior nilotinib and dasatinib therapy (because of low n, data not shown separately).
‡ Individual hematologic TEAEs were clustered with the related terms from investigations.

As of May 15, 2013, twelve deaths occurred within 30 days after the last bosutinib dose (Table 14). Reasons included CML disease progression (n = 6 [1.4%]) and AEs considered unrelated to bosutinib by the investigators (n = 5 [1.2%]). One death was attributed to an AE considered bosutinib-related by the investigator (lower gastrointestinal hemorrhage with thrombocytopenia. All deaths in the second line cohort occurred in patients with resistance (not intolerance) to prior imatinib treatment. All deaths in the third line cohort occurred in patients with resistance or intolerance to prior dasatinib (not nilotinib) treatment.[3]

Table 14: Summary of study deaths[3]

Event	Chronic phase 2nd line			Chronic phase 3rd line			
	IM-R (n = 196)	IM-I (n = 90)	Total (n = 286)	IM-R/I + D-R (n = 38)	IM-R/I + D-I (n = 50)*	IM-R/I + N-R (n = 26)	Total[a] (n = 118)
Deaths within 30 days of last dose[c]	7(4)	0	7(2)	2(5)	3(6)	0	5(4)
Reason for death							
Disease progression	4(2)	0	4(1)	2(5)	0	0	2(2)
AE unrelated to study drug	3(2)	0	3(1)	0	2(4)	0	2(2)
AE related to study drug[b]	0	0	0	0	1(2)	0	1(1)

[a] Includes patients (n = 4) for whom prior imatinib therapy failed and who were intolerant to prior nilotinib or resistant or intolerant to prior nilotinib and dasatinib therapy (because of low n, data not shown separately).
[b] Includes lower gastrointestinal bleeding (3rd line cohort),
[c] Represents a subset of overall deaths.

Efficacy Outcomes for Accelerated and Blast Phase patients

Percentage of Accelerated and Blast Phase participants with MCyR, Duration of MCyR, Time to achieve MCyR, Duration of complete hematologic response, Time to achieve complete hematologic response

Results for the accelerated and blast phase patients can be seen in tables 15 and 16. In table 15, MCyR was attained by 35% of patients in the accelerated phase and 30% of patients in blast phase. Sixty two percent of accelerated phase patient kept their response for 1 year and so did 7.9% of blast phase patients. Complete haematological response was attained in 35% of accelerated phase patients and 28% of blast phase patients.[6]
In table 16, showing the detailed results from the May 2014 data snap shot 40.3 % of accelerated phase patients and 37% of blast phase patients obtained a major cytogenic response. In the accelerated phase group the median duration of this response was 209 weeks in the previous imatinib therapy group and 84 weeks in the total group. In the total Blast Phase group it was 29.1 weeks. The percentage of accelerated phase patients with a complete hematologic response was 33.3% and the percentage of blast phase patients was 16.7%. These results are not as high as the second line chromic phase patients (table 5), but are in line with the chronic phase 3rd and 4th line patients (table 6).[7]

Table 15: Responses for Accelerated and Blast Phase patients[6]

	Accelerated Phase n=76	Blast Phase n=64
Major cytogenetic response	35%; (95%CI, 24%-47%)	30% (95%CI, 18%-44%)
Duration of major cytogenetic response		
Kaplan Meir at 1 year	62%; (95%CI, 39%-79%)	7.9%; (95%CI, 0.5%-30%)
Complete hematological response	35%; (95%CI, 24%-47%)	28%; (95%CI, 18%-41%)

Table 16: Detailed Primary and Secondary Outcomes for Accelerated and Blast Phase Patients from May 20 2014 data snapshot[7]

	Accelerated Phase			Blast Phase		
	IM only (n=49)	Multi TKI (n=30)	AP total (n=79)	IM only (n=36)	Multi TKI (n=28)	BP total (n=64)
Percentage of participants with MCyR (%)	47.8	26.9	40.3	50.0	20.8	37.0
Duration of MCyR (weeks), median	209.0*	**24.0**	**84.0**	**29.1**	**34.3**	**29.1**
Time to achieve MCyR among responders (weeks), median	**12**	**23.6**	**12**	**8.4**	**7**	**8.2**
Percentage of participants with CHR (%)	**39.5**	**24.1**	**33.3**	**26.5**	**3.8**	**16.7**
Duration of CHR (weeks), median	**138.0**	**Not reached**	**138.0**	**28.6**	**40.0**	**29.1**
Time to achieve CHR among responders (weeks), median	**12.1**	**12.1**	**12.1**	**8**	**12.1**	**10**

Date of Snapshot: 23MAY2014

Note: MCyR and CHR information shown for treated subjects with a valid baseline assessment;

*Subject to change since after the minimum follow-up of 48 months;

** Only 2 year rates shown as per Protocol subjects were only followed for survival for 2 years after treatment discontinuation. Complete follow-up for survival is only 2 years.

Progression Free Survival (PFS) and Overall Survival (OS) for accelerated and Blast Phase Patients

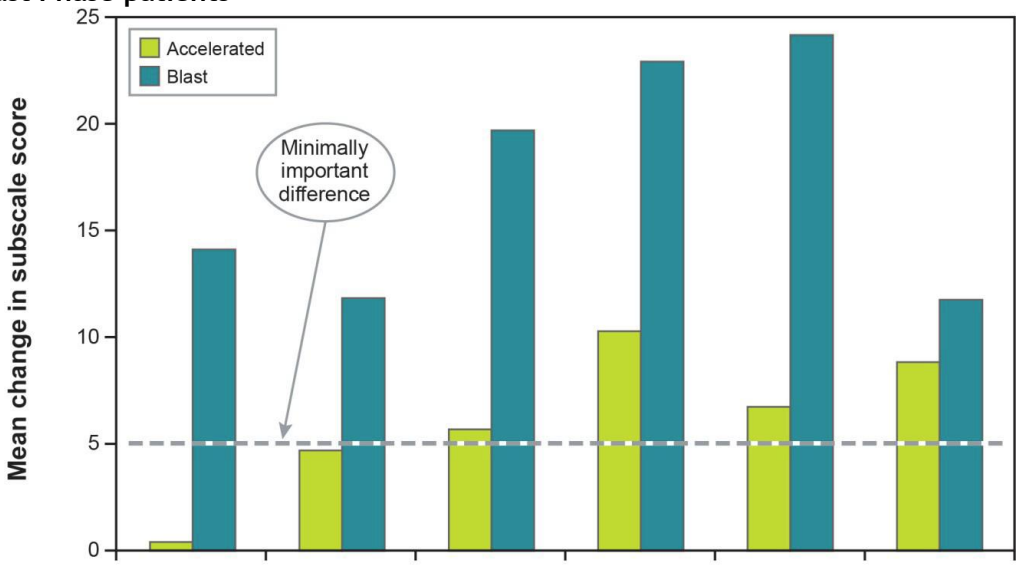
Progression free survival at 1 year for the accelerated phase patients was 65% (95%CI, 52%-75%). Overall survival at 1 year was 76% (95% CI, 65%-84%).[6]

Progression free survival at 1 year for the blast phase patients was 14% (95%CI, 6.0%-26%). Overall survival at 1 year was 44% (95% CI, 31%-56%).[6]

Quality of Life for Accelerated and Blast Phase Patients

Health related quality of life (QOL) was measured using the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu). Clinically meaningful improvement in excess of the minimally important difference (MID) was observed at weeks 24 and 48 in the accelerated phase patients in week 48 in the blast phase patients. This can be seen in figure 5.[7]

Figure 5. FACT-Leu Total score over time (mean change from baseline) in Accelerated and Blast Phase patients[7]



Assessment	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48
Advanced (N) Baseline 76	43	39	41	38	31	26
Blast (N) Baseline 64	35	36	27	18	13	6

Quality of Life was also measured using the EQ-5D scale. Table 17 shows the changes over time in accelerated and blast phase patients.

Table 17: Quality of Life changes using the EQ-5D scale for accelerated and Blast Phase patients.[7]

	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 96
Accelerated phase							

	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 96
EQ-5D Utility Score: mean (SD) change from	–0.00 (0.20)	–0.01 (0.25)	–0.00 (0.25)	0.01 (0.22)	0.04 (0.23)	0.02 (0.24)	0.01 (0.13)
EQ-5D Health State today Mean (SD) change from	–3.49 (25.83)	6.93 (21.03)*	3.44 (26.58)	7.78 (24.37)	9.26 (24.15)*	10.68 (24.62)*	4.77 (20.79)
Blast Phase							
EQ-5D Utility Score: mean (SD) change from	0.13 (0.31)*	0.12 (0.30)*	0.17 (0.31)*	0.19 (0.37)	0.15 (0.22)*	–0.05 (0.25)	–0.10
EQ-5D Health State today Mean (SD) change from	8.81 (24.01)*	14.39 (24.08)*	18.96 (30.26)*	17.39 (29.93)*	20.15 (26.76)*	6.00 (9.98)	10.50 (0.71)*
*$P < 0.05$.							

Data for dose reductions and interruptions were not available for accelerated and blast phase patients.

Harms Outcomes for Accelerated and Blast Phase patients

Adverse events for accelerated and blast phase patients were similar to chronic phase patients. The exception was diarrhea in blast patients. Twenty percent fewer blast phase patients reported suffering from diarrhea across all grades. This can be seen in table 18.[7]

Table 18 Summary of the most common TEAS (≥ 20% incidence) in Accelerated and blast phase patients[7]

	Accelerated phase			Blast phase		
	IM only (n=49)	Multi TKI (n=30)	AP total (n=79)	IM only (n=36)	Multi TKI (n=28)	BP total (n=64)
Anemia	20 (40.8)	16 (53.3)	36 (45.6)	11 (30.6)	8 (28.6)	19 (29.7)
Leukopenia	6 (12.2)	4 (13.3)	10 (12.7)	6 (16.7)	6 (21.4)	12 (18.8)
Neutropenia	7 (14.3)	7 (14.3)	15 (19.0)	10 (27.8)	7 (25.0)	17 (26.6)
Thrombocytopenia	25 (51.0)	17 (56.7)	42 (53.2)	13 (36.1)	11 (39.3)	24 (37.5)
Abdominal pain	17 (34.7)	4 (13.3)	21 (26.6)	10 (27.8)	2 (7.1)	12 (18.8)
Diarrhea	41 (83.7)	26 (86.7)	67 (84.8)	23 (63.9)	18 (64.3)	41 (64.1)
Nausea	19 (38.8)	17 (56.7)	36 (45.6)	18 (50.0)	14 (50.0)	32 (50.
Vomiting	25 (51.0)	10 (33.3)	35 (44.3)	13 (36.1)	14 (50.0)	27 (42.2)
Fatigue	5 (10.2)	12 (40.0)	17 (21.5)	6 (16.7)	6 (21.4)	12 (18.8)

Deaths

Table 19 summarizes the deaths in the accelerated and blast phase patients as of May 2014. Deaths were even distributed between imatinib only and multiple TKI groups. However, there were more deaths in the blast phase group.

Table 19: Deaths in the Accelerated and Blast phase patients groups[7]

	IM only (n=49)	Multi TKI (n=30)	AP total (n=79)	IM only (n=36)	Multi TKI (n=28)	BP total (n=64)
Deaths	15	15	30	21	23	44

6.3 Ongoing Trials

Two ongoing non-randomized trials investigating the use of bosutinib in patients previously treated with imatinib were identified. Details of these trial can be found in Table 20.

Table 20. Study NCT00811070: A Phase 1/2 Study Of SKI-606 (Bosutinib) Administered As A Single Agent In Japanese Subjects With Philadelphia Chromosome Positive Leukemias[30], Study NCT02228382: A Phase 4 Safety And Efficacy Study Of Bosutinib (Bosulif (Registered)) In Patients With Philadelphia Chromosome Positive Chronic Myeloid Leukemia Previously Treated With One Or More Tyrosine Kinase Inhibitors[33]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
A Phase 1/2 Study Of SKI-606 (Bosutinib) Administered As A Single Agent In Japanese Subjects With Philadelphia Chromosome Positive Leukemias[32]			
Study NCT00811070 Non-Randomized, phase 1/2, open Label Start date: December 2007 Expected completion date: September 2014-07-09 Active: but not recruiting patients Estimated enrolment: 63 Sponsor: Pfizer	**Inclusion Criteria:** • Ph + CML. • Disease is resistant or refractory to full-dose imatinib or intolerant of any dose of imatinib. • Adequate duration of prior therapy. • No prior exposure to Src, Abl, or Src/Abl kinase inhibitors other than imatinib. • ECOG PS of 0 or 1 for chronic phase, and 0, 1 or 2 for Advanced Stage. • 7 days since any anti-proliferative treatment before the first (except hydroxyurea). • Recovered to NCI grade 0-1, or to baseline, from any toxicities of prior treatment, other than alopecia or thrombocytopenia due to active prior treatment (intolerant subjects). • At least 3 months post allogeneic stem cell transplantation before the first dose of SKI-606. • Able to take daily oral capsules. • Adequate hepatic, and renal function. • Documented normal INR or, if on oral anticoagulant therapy INR less than 3. • Age greater than 20 years • Patients, must agree to use of birth control for the duration of the study and for 30 days after the last dose of SKI-606. **Exclusion Criteria:**	Bosutinib: 100 mg Capsule for Part 1, 100 mg tablet for Part1 and Part 2. SKI-606 (Bosutinib) will be taken by mouth with water and food as continuous once-daily dosing.	Primary outcomes: • Percentage of Participants With Major Cytogenetic Response (MCyR) up to Week 24 in Chronic Phase Second-line Cohort Secondary outcomes: • Percentage of Participants With Maintained Major Cytogenetic Response (MCyR) at Week 24 in Chronic Phase Second-line and Third-line Cohort • Percentage of Participants With Major Cytogenetic Response (MCyR) up to Week 24 in Chronic Phase Third-line Cohort • Time to Major Cytogenetic Response (MCyR) in Chronic Phase Second-line and Third-line Cohort □ Duration of Major Cytogenetic Response (MCyR) in Chronic Phase Second-line and Third-line Cohort • Percentage of Participants With Complete Hematologic Response (CHR) up to Week 24 in Advance Phase Second-line Cohort • Time to Achieve Complete Hematologic Response (CHR) in Advanced Phase Second-line Cohort.

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
	• Ph- CML • Overt leptomeningeal leukemia. • Subjects with extramedullary disease only. • No treated or untreated Graft Vs. Host Disease within 60 days of first dose. • Major surgery within 14 days or radiotherapy within 7 days of the first dose. • History of clinically significant or uncontrolled cardiac disease. • Baseline QTcF greater than 0.45 sec (average of triplicate readings). • Concomitant use of or need for medications known to prolong the QT interval. • Uncorrected hypomagnesemia or hypokalemia due to potential effects on the QT interval. • Recent (14 days before the first dose) or ongoing clinically significant gastrointestinal disorder. • Pregnant or breastfeeding women. • Evidence of serious active infection, or significant medical or psychiatric illness.		• Duration of Complete Hematologic Response (CHR) in Advanced Phase Second-line Cohort • Percentage of Participants With Overall Hematologic Response (OHR) Up to Week 24 in Accelerated Phase/Blast Phase Third-line Cohort • Time to Achieve Overall Hematologic Response (OHR) in Accelerated Phase/Blast Phase Third-line Cohort • Duration of Overall Hematologic Response (OHR) in Accelerated Phase/Blast Phase Third-line • Time to Treatment Failure (TTF) • Progression-free Survival (PFS) • Overall Survival (OS)
A Phase 4 Safety And Efficacy Study Of Bosutinib (Bosulif (Registered)) In Patients With Philadelphia Chromosome Positive Chronic Myeloid Leukemia Previously Treated With One Or More Tyrosine Kinase Inhibitors[33]			
NCT02228382 Single Arm, phase 4, open Label Start date: November 2014 Expected completion date: October 2020 Active: recruiting patients Estimated enrolment: 165 Sponsor: Pfizer	**Inclusion Criteria:** • Confirmed Philadelphia Chromosome positive Chronic Myeloid Leukemia or Confirmed BCR-ABL1 (Abelson-break point cluster) Positive if Philadelphia Chromosome negative Chronic Myeloid Leukemia (from initial diagnosis). • Prior treatment with 1 or more TKI drugs (imatinib, dasatinib and/or nilotinib) for Philadelphia Chromosome positive Chronic Myeloid Leukemia (CML). • Any Chronic Myeloid Leukemia disease phase, as long as the patient is unable to receive treatment with imatinib, dasatinib and/or nilotinib for any reason. • Exclusion Criteria:	Bosutinib 100 mg and 500 mg tablets, once daily dosage up to 4 years duration	**Primary Outcome Measures:** • Percentage of patients with (MCyR) by Week 52 in Chronic Phase 2nd line and 3rd line Population of Ph+ CML patients. • Percentage of Participants with (MCyR) by Week 52 in Chronic Phase 4th line and later-line Population of Ph+ CML. • Percentage of Participants with Overall Hematologic Response (OHR) by Week 52 in Advanced Leukemia Population patients. **Secondary Outcome Measures:** • Estimate cumulative probability of Percentage of Participants with MCyR in Chronic Phase

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
	• Participation in any other clinical studies involving investigational drug(s) within 14 days or within 3 half-lives of drug levels in blood (whichever is longer) prior to the first dose of bosutinib. • Prior treatment with bosutinib. • Prior treatment with ponatinib. • Known T315I or V299L mutation.		and Advanced Phase Ph+ CML populations • Estimate cumulative probability of Percentage of Participants with Overall Hematologic Response in the Accelerated Phase and Blast Phase Ph+ CML population by number of lines of prior therapy. • Characterize distribution of best response (molecular, cytogenetic, or hematologic) in the Chronic Phase, Accelerated Phase and Blast Phase Ph+ CML. • Estimating probability of Percentage of Participants with Major Cytogenetic Response at 3, 6, 12, 18, and 24 months in the Chronic Phase, Accelerated Phase and Blast Phase Ph+ CML populations. • Estimating the probability of confirmed Overall Hematologic Response at 3, 6, 9, 12, 18, and 24 months in the Accelerated Phase and Blast Phase Ph+ CML populations. • Estimating the probability of cumulative confirmed Complete Hematologic Response in the Chronic Phase, Accelerated Phase and Blast Phase Ph+ CML populations. • Estimating the probability of cumulative major molecular response in the Chronic Phase, Accelerated Phase and Blast Phase Ph+ CML populations.

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review

8 ABOUT THIS DOCUMENT

This initial Clinical Guidance Report was prepared by the pCODR **Leukemia Group** Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on Bosutinib (Bosulif) for Chronic Myeloid Leukemia. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Leukemia Clinical Guidance Panel is comprised of three clinical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY 1. Ovid MEDLINE (R), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, and Ovid MEDLINE (R) Daily Update, EMBASE.

1. *bosutinib/
2. (bosutinib or bosulif or ski-606 or ski606 or "ski 606").ti,ab.
3. *chronic myeloid leukemia/
4. (chronic adj3 (myeloid or myelogenous) adj3 leuk?emia).ti,ab.
5. 1 or 2
6. 3 or 4
7. 5 and 6
8. exp clinical trial/ or exp clinical trial, phase i/ or exp clinical trial, phase ii/ or exp clinical trial, phase iii/ or exp clinical trial, phase iv/ or exp controlled clinical trial/ or exp randomized controlled trial/ or exp multicentre studies/
9. 7 and 8
10. remove duplicates from 9

2. Literature Search via PubMed
bosutinib* OR bosulif* OR ski-606* OR ski606* OR ski 606*
publisher[sb]
1 AND 2

3. Literature Search via Cochrane Central Register of Controlled Trials (CENTRAL)
bosutinib* OR bosulif* OR ski-606* OR ski606* OR ski 606*

4. Grey Literature Searches
Clinical Trial Registries:
U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov
Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca
Search terms: bosutinib OR bosulif OR ski-606 OR ski606 OR ski 606

Select International Agencies:
Food and Drug Administration (FDA):
www.fda.gov
Search terms: bosutinib OR bosulif OR ski-606 OR ski606 OR ski 606

Conference Abstracts:
American Society of Clinical Oncology (ASCO)
via the *Journal of Clinical Oncology* search portal: http://jco.ascopubs.org/search

American Socety of Hematology (ASH)
Via Blood search portal: http://www.bloodjournal.org/ash-annual-meeting-abstracts?sso-checked=1

Search terms: bosutinib OR bosulif OR ski-606 OR ski606 OR ski 606

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