pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

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

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Ponatinib (Iclusig)	
Submitted Funding Request: For the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom other tyrosine kinase inhibitor (TKI) therapy is not appropriate, including CML or Ph+ ALL that is T315I mutation positive or where there is prior TKI resistance or intolerance.	
Submitted By: ARIAD Pharmaceuticals, Inc.	**Manufactured By:** ARIAD Pharmaceuticals, Inc.
NOC Date: April 2, 2015	**Submission Date:** March 13, 2015
Initial Recommendation: July 30, 2015	**Final Recommendation:** October 1, 2015

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding ponatinib (Iclusig) conditional on cost-effectiveness being improved to an acceptable level. Funding should be for the treatment of patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom other tyrosine kinase inhibitor (TKI) therapy is not appropriate, including CML or Ph+ ALL that is T315I mutation positive or where there is resistance or intolerance to prior TKI therapy. Funding should be for patients with ECOG performance status 0-2. Treatment should continue until unacceptable toxicity or disease progression.

pERC made this recommendation because the Committee concluded there is a net clinical benefit of ponatinib based on clinically meaningful and durable cytogenetic response rates, one year progression free survival and overall survival rates, despite significant toxicities and the lack of quality of life data for this treatment. pERC further noted an unmet need for patients whose CML or Ph+ ALL is T315I mutation positive. pERC also acknowledged that the use of ponatinib aligned with patient values.

The Committee considered that when ponatinib is compared to best supportive care (e.g. hydroxyurea) or allogeneic stem cell transplant, it could not conclude that ponatinib is cost-effective because of the high level of uncertainty in the clinical data.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Collecting Evidence to Reduce Uncertainty in the Magnitude of Clinical Benefit and the Cost-Effectiveness of Ponatinib
Given the considerable uncertainty in the magnitude of clinical benefit of ponatinib in patients with chronic phase, accelerated phase, or blast phase CML or Ph+ ALL, pERC concluded that additional prospective evidence should be collected to decrease the uncertainty in the incremental effect and provide a greater understanding of the true cost-effectiveness of ponatinib. Specific information on efficacy, safety and quality of life would be of particular value.

Pricing Arrangements to Improve Cost-effectiveness
Given that pERC was satisfied that there is a net clinical benefit of ponatinib in patients with CML or Ph+ ALL, jurisdictions may want to consider pricing arrangements and/or cost structures that may improve the cost-effectiveness of ponatinib to an acceptable level as well as reduce the uncertainty in the budget impact of ponatinib. To offset the considerable uncertainty in the clinical effect estimates of ponatinib, pERC concluded that a substantial reduction in drug price would be required in order to improve cost-effectiveness. pERC noted that ponatinib should be no more costly than bosutinib.

Awaiting Evidence to Reduce Uncertainty Concerning the Optimal Starting Dose
There is uncertainty in the optimal starting dose of ponatinib. Treatment-emergent arterial thromboembolic and arterial stenosis events occurred in the PACE study. pERC noted that the majority of patients in the PACE study had dose reductions and/or interruptions and the manufacturer of ponatinib issued a dose reduction recommendation for the study. pERC acknowledged that a phase 1/2 study from Japan and the OPTIC study will provide data to address this uncertainty.

Consider Restricting the Prescribing to Enhance the Quality of Care
pERC noted that provinces may want to consider additional measures to optimize patient selection for treatment, to optimize the management of toxicity and to limit budget impact by implementing an approved prescriber list. pERC made this suggestion because there is considerable potential toxicity associated with ponatinib which may be best managed by hemato-oncologists who specialize in the management of CML/ALL.

Optimal Sequencing of Ponatinib and Other Therapies Unknown
pERC concluded that the optimal sequencing of ponatinib and bosutinib, for the treatment of CML for whom other TKI therapy is not appropriate, is currently unknown. pERC was, therefore, unable to make an informed recommendation on sequencing treatments for this patient population for whom other current TKI therapy is not appropriate. Furthermore, bosutinib is under consideration for funding by the provinces for patients for whom subsequent treatment with imatinib, nilotinib and dasatinib is not clinically appropriate. However, pERC recognized that provinces will need to address this issue upon implementation of ponatinib funding and noted that collaboration among provinces and provincial tumour groups to develop a common approach would be of value.

SUMMARY OF pERC DELIBERATIONS

Chronic myelogenous leukemia (CML) is an uncommon clonal bone marrow stem cell disorder. About 25% of acute lymphoblastic leukemia (ALL) in adults is characterized by the presence of the Philadelphia chromosome (Ph+). Ph+ ALL is associated with a particularly poor prognosis similar to the advanced (accelerated and blast) phases of CML. The majority of CML and Ph+ ALL patients are not eligible for potentially curative therapy with allogenic stem cell transplant (ASCT) as there are limited donors available and the patients are typically elderly or frail and not able to withstand the morbidity associated with ASCT. pERC noted that current treatment options include the BCR-ABL tyrosine kinase inhibitors (TKIs) imatinib, dasatinib, nilotinib, and bosutinib. Bosutinib is indicated for patients in whom subsequent treatment with imatinib, dasatinib, or nilotinib is clinically not appropriate. Bosutinib was recently reviewed by pCODR, however, it is currently not funded by the provinces. Patients with advanced CML or Ph+ ALL may also receive best supportive care which includes palliative hydroxyurea. However, in those patients whose CML or ALL develops or has the T315I mutation, the leukemia is resistant to all currently available TKIs. pERC agreed that there is a need for effective treatment options for patients whose disease develop or have the T315I mutation, as well as those who develop resistance or intolerance to prior TKI therapy. pERC acknowledged the feedback from the submitter regarding the procedural context of bosutinib as a treatment comparator. pERC clarified that while it was not a comparator in the assessment of ponatinib, the pCODR review of bosutinib provided contextual information.

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

pERC deliberated upon one non-comparative study (the PACE study) that examined the use of ponatinib in patients who were resistant or intolerant to imatinib, dasatinib, or nilotinib, including those who developed the T315I mutation after TKI therapy. pERC concluded that there is a net clinical benefit of ponatinib in patients with chronic, accelerated, or blast phase CML and Ph+ ALL for whom other current TKI therapy is not appropriate, including CML or Ph+ ALL that is T315I mutation positive or where there is resistance or intolerance to prior TKI therapy. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback from the pCODR Provincial Advisory Group that would like pERC to reconsider a recommendation for the subgroup of patients with T315I mutation positive disease separate from the broader population. In pERC's re-deliberations for ponatinib, each subgroup of disease was discussed separately; however, pERC came to the same overall recommendation for each of these subgroups of patients. pERC considered the magnitude of major cytogenetic response (MCyR) experienced by a large proportion of patients in the PACE study to be clinically meaningful. Response rates and sustained responses of at least 12 months were seen in all subgroups of patients including those with the T315I mutation. No single mutation (including T315I) has been shown to confer resistance to ponatinib. pERC acknowledged that cytogenetic response (MCyR and complete cytogenetic response (CCyR)) is a reasonable surrogate for overall survival and that the substantial benefit in the one year progression free survival and overall survival further supported the conclusion of net clinical benefit. However, pERC noted that the impact of ponatinib on quality of life is unknown, as it was not measured in the PACE study. pERC values patient quality of life outcomes in studies, and was disappointed that the PACE study did not include quality of life measurements in its study design.

pERC discussed the limitations of non-randomized studies and considered that, although the PACE trial was appropriately conducted, the conclusions that can be drawn from non-comparative data are not as robust as those that can be drawn from well-conducted randomized controlled trials (RCTs) with direct comparisons to relevant therapies. Therefore, while pERC concluded that ponatinib demonstrated clinical benefit in patients, there was considerable uncertainty with regard to the magnitude of benefit with ponatinib as RCTs comparing ponatinib to dasatinib, nilotinib, bosutinib, and/or other relevant comparators including best supportive care were not available. pERC agreed with the pCODR Clinical Guidance Panel that an indirect comparison of ponatinib and other TKIs was not appropriate given the different patient populations, lines of therapy, and small sample sizes in the available studies. The Committee felt there were sufficient numbers of patients with CP-CML who could have been randomized among currently available treatments (i.e. other TKIs) to determine comparative efficacy. Upon

reconsideration of the pERC Initial Recommendation, pERC noted that a RCT would likely not be feasible beyond the second-line setting for patients in whom other TKI therapy is not appropriate because of very small patient numbers.

pERC discussed the toxicity profile of ponatinib and noted it to be different from currently available TKIs. Ponatinib was associated with significant toxicities in comparison to other available TKIs. Treatment-emergent arterial thromboembolic and arterial stenosis events were prominent in the PACE study. Treatment-emergent serious adverse events included, but were not limited to, hemorrhage, cardiac failure, pancreatitis, thrombocytopenia, and pneumonia. The majority of patients had a dose reduction or at least one dose interruption. pERC noted that the manufacturer of ponatinib issued a dose reduction recommendation in the PACE study; however, there are currently no data on the optimal starting dose for ponatinib. pERC noted that a phase 1/2 study from Japan and the OPTIC study will provide data on the optimal starting dose. The expected completion dates of these studies are July 2018 and June 2020, respectively. pERC acknowledged that there is some evidence in CP-CML that, following an initial response, the drug dose can be reduced to as low as 15mg daily with a decrease in adverse events. Having discussed these multiple factors, pERC concluded that ponatinib should be available for adult patients with chronic, accelerated, or blast phase CML and Ph+ ALL for whom other TKI therapy is not appropriate, including CML or Ph+ ALL that is T315I mutation positive or where there is resistance or intolerance to prior TKI therapy. pERC acknowledged that patients whose disease develops the T315I mutation do not respond to currently available TKIs, including bosutinib. Mutations including the T315I mutation have not been shown to confer resistance to ponatinib and improved MCyR have been observed. As for patients who have resistance or intolerance to prior TKI therapy, this population will predominantly be comprised of those who have exhausted funded TKI treatment options. Based upon discussion of the clinical evidence and the need for effective treatment options for patients whose disease develops the T315I mutation, pERC agreed it would be reasonable to use ponatinib in these patients, as well as those who have resistance or intolerance to prior TKI therapy.

pERC deliberated on patient advocacy group input, which indicated that patients with CML and ALL value quality of life, disease control, and the management of side effects related to current therapies. The Committee expressed concerns with ponatinib's significant toxicity profile and the lack of quality of life data in the PACE study, however, pERC concluded that ponatinib aligned with patient values. This was based on improvement in MCyR which is an acceptable surrogate for overall survival, and one year progression-free survival rates, despite significant toxicities and a lack of quality of life data. pERC noted that for most patients, the currently available TKIs work well at controlling the BCR-ABL oncogene; however, patients whose disease develops the T315I mutation or resistance/intolerance to prior TKI therapy have few effective treatment options available.

pERC deliberated upon four economic analyses submitted by the manufacturer providing estimates on the cost-effectiveness of ponatinib in the four different phases of leukemia considered (CP-CML, AP-CML, BP-CML and Ph+ ALL). Each model was compared with relevant treatment options. pERC discussed feedback from the pCODR Provincial Advisory Group that hydroxyurea and stem cell transplant are not appropriate comparators for CP-CML where patients may have failed many previous treatments. pERC confirmed with the pCODR Clinical Guidance Panel that stem cell transplant remains an option in this subgroup, albeit for a limited number of patients who are sufficiently "fit" and for whom a suitable donor is found. Also, palliation with hydroxyurea is considered part of best supportive care; and, as such, remains an option in heavily pre-treated patients. pERC noted that there is currently no direct comparative data between ponatinib and other TKIs including dasatinib, nilotinib and/or bosutinib, as well as other relevant treatment options. In the absence of direct or indirect comparative data, pERC noted that multiple data sources from the literature and/or assumptions were used to populate clinical inputs within the cost utility analyses, all of which were confounded by factors that could be controlled for in an RCT. pERC, therefore, noted that due to the limitations of non-comparative evidence from the PACE study, there was substantial uncertainty in the magnitude of the clinical benefit associated with ponatinib. This made it challenging to estimate the incremental effect of treatment with ponatinib and, therefore, the resulting incremental cost-effectiveness of ponatinib. During the initial deliberation of ponatinib, differing opinions regarding the cost-effectiveness were expressed; however, at that time, the majority of pERC members felt that ponatinib may be cost-effective when compared to hydroxyurea and ASCT for patients with CP-CML. Upon reconsideration of the pERC Initial Recommendation and feedback expressing the pCODR Provincial Advisory Group's concern regarding the face validity of pERC's assessment, pERC reconsidered the submitter's and pCODR Economic Guidance Panel's estimates of cost-effectiveness. pERC noted that the following factors contributed substantially to the uncertainty in the estimate of the incremental benefits gained with ponatinib, 1) lack of direct comparative evidence; 2) extrapolation of survival from

CCyR and the unknown quantifiable relationship between CCyR and survival; 3) length of extrapolation in the model (≥10 years) given the short trial period of the PACE trial; and 4) lack of quality of life from the PACE trial to inform quality-adjusted survival estimates. Furthermore, based on contextual information from the pCODR review of bosutinib, pERC noted, although bosutinib and ponatinib are indicated for similar patient populations, the submitted economic evaluations resulted in very different estimates of incremental benefits gained and cost-effectiveness estimates. All of these factors led pERC to conclude that it could not accept either the submitter's or the pCODR Economic Guidance Panel's analyses and therefore, was unable to conclude that ponatinib is cost-effective.

Although pERC acknowledged that bosutinib is under review for funding by the provinces, the Committee expressed concerns as the economic analyses provided did not compare ponatinib to bosutinib. pERC noted in some circumstances, e.g., patients with resistance or intolerance to first and/or second generation TKIs, bosutinib would be a relevant comparator. Upon reconsideration of feedback from the submitter, pERC emphasized bosutinib was still under review when the submission for ponatinib was initiated. Therefore, pERC did not foresee bosutinib as a comparator in the economic evaluation and utilized the pCODR review of bosutinib as contextual evidence. Following a robust discussion on this contextual information, pERC noted it would be challenging to determine relative economic value of ponatinib versus bosutinib in the absence of direct comparative evidence and the large current price differential.

pERC discussed the feasibility of implementing a positive funding recommendation for ponatinib. pERC noted the non-proportional price across 15mg and 45mg tablet strengths for ponatinib. Given that dose reductions/interruptions were very frequent in the PACE study to manage toxicities, pERC felt that clinicians would likely use the 15mg tablets in order to make dose adjustments and this will increase the cost of treatment with ponatinib. pERC acknowledged feedback from the submitter indicating the potential for pill burden with the use of three tablets instead of one, however, the pCODR Clinical Guidance Panel maintained that clinicians would likely prescribe three 15mg tablets to account for dose adjustments. pERC acknowledged that jurisdictions will need to consider the potentially large budgetary impact of ponatinib given its drug cost compared to other TKIs. The Provincial Advisory Group indicated ponatinib is distributed in bulk bottles and expressed concerns related to the safe handling of cytotoxics. pERC noted that blister packaging would address these concerns. Having considered that patients are likely to be on lifelong treatment and will receive available TKIs in sequence, pERC discussed the potential sequencing of treatment with ponatinib and other currently available TKIs. pERC acknowledged that data on sequencing of TKIs are limited and not informed by controlled clinical trials. Input from the Provincial Advisory Group indicated that there were concerns about indication creep; however, given the severe adverse events associated with ponatinib, pERC considered that ponatinib would likely be for patients who have exhausted funded TKI treatment options.

EVIDENCE IN BRIEF

pERC deliberated upon:

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

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- the Submitter (ARIAD Pharmaceuticals, Inc.)

The pERC initial recommendation was to fund ponatinib (Iclusig) for treatment of patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom other tyrosine kinase inhibitor (TKI) therapy is not appropriate, including CML or Ph+ ALL that is T315I mutation positive or where there is resistance or intolerance to prior TKI therapy.

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

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of ponatinib for the treatment of chronic phase (CP), accelerated phase (AP), or blast phase (BP) CML or Ph+ ALL for whom other TKI therapy is not appropriate, including CML or Ph+ ALL that is T315I mutation positive or where there is resistance or intolerance to prior TKI therapy.

Studies included

The pCODR systematic review included one open-label single-arm phase II study (PACE) examining the use of ponatinib in patients who were resistant or intolerant to imatinib, dasatinib, or nilotinib including those who had developed the T315I mutation after TKI therapy. Ponatinib was given at a dose of 45mg/day. pERC noted 44% and 73% of patients had their dose reduced or had at least one dose interruption, respectively. The manufacturer of ponatinib issued a dose reduction recommendation for the study: for those patients with CP-CML who achieved a major cytogenetic response (MCyR), the dose could be adjusted to 15mg/day and to 30mg/day for those who had not already achieved a MCyR (including patients with advanced-phase disease). pERC acknowledged and agreed with the Clinical Guidance Panel (CGP) that there is currently no data on the optimal starting dose for ponatinib, which is the topic of ongoing trials.

Patient populations: Heavily pre-treated patients with CML/Ph+ ALL

The PACE study included 449 patients receiving treatment in the following subgroups;

- 270 in chronic phase (CP), 203 with CP-CML and resistance to or unacceptable side effects of dasatinib or nilotinib and 64 with CP-CML and the T315I mutation;
- 85 in accelerated phase (AP), 65 with AP-CML and resistance to or unacceptable side effects of dasatinib or nilotinib and 18 with AP-CML and the T315I mutation;
- 62 in blast phase (BP) and 32 in Ph+ ALL, 48 with BP-CML or Ph+ ALL and resistance to or unacceptable side effects of dasatinib or nilotinib and 46 with BP-CML or Ph+ ALL and the T315I mutation

The median age of patients was 60, 60, 53, and 62 years in the CP-CML, AP-CML, BP-CML, and Ph+ ALL groups, respectively. Patients had an ECOG PS of 0 (59%), 1 (33%), or 2 (8%). Ninety-three percent of patients had ≥2 prior TKI drugs, 58% of patients had ≥3 drugs and the median time on prior TKI therapy

was 4.6 years. Almost all patients had received prior treatment with imatinib (96%); other prior TKI therapies included dasatinib (84%), nilotinib (65%), and bosutinib (7%).

Key efficacy results: Clinically meaningful improvement in MCyR, MaHR, CCyR, 1 year OS

The key efficacy outcomes deliberated on by pERC included major cytogenetic response (MCyR), major hematologic response (MaHR), complete cytogenetic response (CCyR) and one year overall survival (OS). pERC agreed with the CGP's statement that MCyR was a reasonable surrogate for overall survival in this disease context.

MCyR within 12 months of treatment was observed in 56% of patients with CP-CML. MaHR within six months of treatment was observed in 55%, 31% and 41% of patients with AP-CML, BP-CML, and Ph+ ALL, respectively. CCyR was observed in 53%, 24%, 18%, and 38% of patients with CP-CML, AP-CML, BP-CML, and Ph+ ALL, respectively. Sustained responses of at least 12 months were seen in 91%, 48%, 42%, and 8% of patients with CP-CML, AP-CML, BP-CML, and Ph+ ALL, respectively. Although response rates and the proportions of sustained responses decreased as the disease became more advanced, for those patients whose disease developed the T315I mutation, pERC noted similar response rates to patients who had resistance to or unacceptable side effects from previous treatment with dasatinib or nilotinib. pERC noted that the proportion of patients responding did not significantly differ among patients based upon resistance/intolerance to prior TKI therapy or number of prior TKI therapies. pERC also discussed improvements in median OS and one year OS rates. At the primary data cut off, the median overall survival was not reached for the CP and AP-CML groups, and one year OS rates were 94% and 86%, respectively. The median OS for the BP-CML group was 6.9 months with a 12-month OS rate of 31%; the median OS for the Ph+ ALL group was 9.0 months with a 12-month OS rate of 47%. These data further supported the conclusion of net clinical benefit.

The high MCyR and MaHR rates observed with ponatinib across all patient subgroups including those with the T315I mutation, the achievement of OS over one year and the magnitude of one year PFS supported the CGP's conclusion that ponatinib provides a net clinical benefit. However, despite pERC's conclusion that there was a net clinical benefit of ponatinib, it could not comment on the magnitude of the benefit because there was no comparator arm in the PACE study.

Quality of life: Not measured

Quality of life was not measured in the PACE study. pERC was unable to comment on the impact of ponatinib on quality of life.

Safety: Significant toxicities requiring vigilant monitoring and early management

The most common grade 3 or 4 treatment-related adverse events were thrombocytopenia and neutropenia. Arterial thromboembolic and arterial stenosis events were prominent in the study and consisted of cardiac, central nervous system and peripheral arterial events. At the 120-day safety update, 51 (11%) of patients had an ischemic event of any grade and in 34 patients it was considered a serious ischemic event. Over half of patients with CP-CML and a greater proportion of patients with AP-CML, BP-CML, and Ph+ ALL experienced at least one serious adverse event. Other treatment-emergent serious adverse events included hemorrhage in 19 patients (4%), cardiac failure in 17 patients (4%), hypertension in 8 patients (2%), and pancreatitis in 23 patients (5%).

There were 57 (15%) deaths during the study or within 30 days of treatment discontinuation. Five deaths were considered attributable to ponatinib and these patients had pneumonia, myocardial infarction, fungal pneumonia, gastric hemorrhage, and cardiac arrest. pERC agreed with the CGP that the toxicity associated with ponatinib was substantial and that only physicians with experience with the management of CML/ALL and the use of TKIs should be eligible to prescribe it, to allow for appropriate patient selection, vigilant monitoring and early intervention if a serious adverse event is suspected.

Limitations: No direct comparison with currently available therapies

pERC discussed the limitations of non-randomized, non-comparative studies and considered that, although the PACE study was appropriately conducted, the conclusions that can be drawn from non-randomized, non-comparative data are not as robust as those that can be drawn from randomized controlled trials. pERC considered that, given the lack of randomized comparative studies, there is considerable uncertainty surrounding the magnitude of clinical benefit of ponatinib.

Need: More effective treatment options for CML or Ph+ ALL that is T315I mutation positive
Currently available therapies for patients ineligible for allogeneic stem cell transplant (ASCT) include the BCR-ABL tyrosine kinase inhibitor (TKI) imatinib in the first-line setting, as well as the second generation TKIs, dasatinib, nilotinib, as well as bosutinib, which is currently under review by the provinces. However, for patients whose CML or Ph+ ALL has developed the T315I mutation, there are few treatment options as this mutation is resistant to currently available TKIs. pERC agreed that, for the subset of patients with chronic, accelerated, or blast phase CML or Ph+ ALL who develop T315I mutations or where there is resistance or intolerance to prior TKI therapy, there remains an unmet need for more effective tolerable therapies.

PATIENT-BASED VALUES

Values of patients with CML/ALL: Quality of life, disease control, treatment options
pERC deliberated on patient advocacy input and noted that quality of life, disease control, and management of side effects related to current therapies were important to patients. Patients indicated that they were willing to tolerate some side effects to ensure the best response. For most patients, the available TKIs (imatinib, dasatinib, nilotinib and bosutinib) work well at controlling BCR-ABL which is the causative oncogene in CML/ALL. pERC noted that for a smaller population of patients, including those whose disease develops the T315I mutation, currently available treatments are either not well tolerated and/or ineffective against resistant disease.

Patient values on treatment: More treatment options, tolerable side effect profile
pERC considered the input from patients who had experience with ponatinib (n=10) which indicated that responses significantly improved their well-being while on ponatinib. Patients did report side effects of dry eyes, constipation, fatigue, and muscle pain, which were difficult to manage and patients expressed a desire for better ways to managing these side effects. While recognizing the difficulty patient advocacy groups have in accessing patients with first-hand experience with a new treatment, particularly those who experienced a significant adverse event, pERC considered that it would be helpful to get input from patients who experienced both positive and negative outcomes with ponatinib. Finally, as ponatinib is an oral treatment, pERC acknowledged and agreed with the patient input that noted oral and intravenous treatments are not equally funded and this varies by province.

Patient input indicated that ponatinib may help patients who have lost response to prior therapies and need time to locate a suitable bone marrow donor. Patients expect ponatinib to result in fewer hospital visits. Although ponatinib has severe cardiovascular effects, patients felt that these effects could be monitored through a cardio oncology program.

pERC noted that patients place importance on access to new treatment options that provide manageable toxicity profiles, sustained response rates and improved quality of life. pERC agreed that by providing improvements in MCyR rates, MaHR rates, improving one year progression free survival and one year overall survival, and despite a significant toxicity profile and no data on quality of life, ponatinib aligned with patient values. pERC also noted the importance of having more treatment options with differing side effect profiles in this patient population.

ECONOMIC EVALUATION

Economic model submitted: Multiple cost-utility analyses
The pCODR Economic Guidance Panel (EGP) assessed four cost-utility analyses comparing ponatinib to several comparators for patients with CML or Ph+ ALL for whom other TKI therapy is not appropriate, including CML or Ph+ ALL that is T315I mutation positive or where there is resistance or intolerance to prior TKI therapy. Comparators included dasatinib, nilotinib, hydroxyurea, interferon-alfa, allogenic stem cell transplant, and palliative best supportive care. In addition, pERC noted that for patients with CP-CML, the most relevant comparators were hydroxyurea and ASCT. The economic evaluation was based on the PACE study and other single-arm studies as comparators. The submitted models were Markov models.

Basis of the economic model: Non-comparative data used in cost-utility analyses

Given the lack of long term, head-to-head data, there was considerable uncertainty in the clinical inputs for each economic evaluation. Costs considered in the models provided by the submitter included drug, resource use, and adverse events costs. The key clinical outcomes were cytogenetic response, overall survival and utilities.

Drug costs: Very high drug costs, especially compared to other TKIs

Ponatinib costs $141.31 per 15mg or $330.77 per 45mg tablet. At the recommended dose of 45mg per day, the daily cost of ponatinib is $423.93 when using three 15mg tablets or $330.77 when using one 45mg tablet. The cost per 28 day course is $11,870.04 and $9,261.56 when using three 15mg tablets and one 45mg tablet, respectively.

Bosutinib costs $36.59 per 100mg tablet or $146.34 per 500mg tablet. At the recommended daily dose of 500mg, bosutinib costs $146.34 per day and $4,097.52 per 28 day course. Depending on the combination of tablets used to provide a 500mg dose (5 x 100mg or 1 x 500mg), the price of bosutinib may be as high as $182.93 per day and $5,122.04 per 28 day course.

Dasatinib costs $38.00 per 20mg tablet, $76.48 per 50mg tablet, $84.29 per 70mg tablet and $152.86 per 100mg tablet. At the recommended dose of 100mg per day, the daily cost of dasatinib is either $190.00, $152.96, or $168.58, depending on the strength of the tablet used. The cost per 28 day course is $4,720.24 when using one 100mg tablet.

Nilotinib costs $28.72 per 140mg tablet and $39.72 per 200mg tablet. At the recommended dose of 800mg per day, the daily cost of nilotinib is $158.89 and $4,448.64 per 28 day course when using the 200mg tablet.

Hydroxyurea costs $1.02 per 500mg. At the recommended dose of 2000mg per day, the daily cost of hydroxyurea is $4.08 and the cost per 28 day course is $114.24.

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

Cost-effectiveness estimates: Substantial uncertainty due to non-comparative data

pERC deliberated upon the four economic analyses submitted by the submitter providing estimates on the cost-effectiveness of ponatinib with relevant treatment options. In the absence of direct or indirect comparative data, pERC noted that multiple data sources from the literature and/or assumptions were used to populate clinical inputs within the cost-utility analysis. pERC, however, noted that due to the limitations of non-randomized evidence from the PACE study, there was substantial uncertainty in the magnitude of the clinical benefit associated with ponatinib. This made it challenging to estimate the incremental effect of treatment with ponatinib and, therefore, the resulting incremental cost-effectiveness of ponatinib. This considerable uncertainty in the magnitude of clinical benefit of ponatinib would likely lead to a wide range of incremental cost-effectiveness estimates beyond those computed. pERC noted ponatinib is currently the only TKI that can overcome resistance to the T315I mutation; however, no economic evaluation restricted to patients with this mutation was provided and, therefore, the cost-effectiveness of ponatinib in this group of patients is unknown. pERC also considered that, if feasible, the collection of additional prospective data on the clinical benefit of ponatinib would reduce the uncertainty around the magnitude of the benefit and the cost-effectiveness estimates.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: No long-term data on efficacy and safety, small patient population

pERC discussed factors affecting the feasibility of implementing a positive funding recommendation for ponatinib. Input from the Provincial Advisory Group indicated concerns about the long-term safety and efficacy data for ponatinib. pERC discussed PAG's input highlighting the absence of a comparator arm in the study. While acknowledging that ponatinib shows meaningful clinical benefit, pERC was unable to determine the magnitude of the benefit as comparative data were not available. pERC also discussed PAG's request for clarity around the sequence of previous TKI use. pERC noted that data on sequencing of

TKIs are limited and not informed by controlled clinical trials. pERC, however, agreed with the Clinical Guidance Panel that ponatinib should be the last treatment option for those who have developed resistance or intolerance to prior TKI therapy and who would otherwise be treated with palliative intent.

DRUG AND CONDITION INFORMATION

Drug Information	• Tyrosine Kinase Inhibitor (TKI) • Available in 15 mg and 45 mg tablets • Recommended dosage of 45 mg administered orally, once daily
Cancer Treated	• Chronic myelogenous leukemia (CML) • Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)
Burden of Illness	• CML accounts for approximately 10-15% of cases of leukemia diagnosed in Canada, with an incidence rate of 1-2 cases/100,000/year • Approximately 450 cases of CML are diagnosed annually in Canada with a median age at diagnosis of 65 years • The majority of patients (>95%) with CML are in chronic phase (CP) at diagnosis • Approximately 1/3 of patients treated with imatinib for CP CML discontinue therapy because of disease progression (10%) or intolerance (25%) • Acute lymphoblastic leukemia is the most common form of childhood leukemia and represents about 20% of all leukemias in adults • Ph+ ALL is associated with a particularly poor prognosis despite the availability of TKI therapies and carries a worse prognosis than other forms of ALL

Current Standard Treatment	• For Ph+ Acute lymphoblastic leukemia:
	  ○ No TKIs are approved for use in Ph+ ALL following failure on dasatinib or in patients with the T315I mutation
	  ○ Allogenic stem cell transplant
	  ○ Best supportive care
	• For Chronic myelogenous leukemia:
	  ○ No TKIs are approved for use in CML with the T315I mutation
	  ○ In patients with resistance or intolerance to imatinib, currently available treatments
	  ▪ Dasatinib
	  ▪ Nilotinib
	  ▪ Bosutinib
	  ○ Hydroxyurea
	  ○ Interferon
	  ○ Allogenic stem cell transplant
	  ○ Best supportive care

Limitations of Current Therapy	• Interferon and palliative treatment with hydroxyurea are associated with significant toxicities, and limited clinical benefit • A large number of mutations have been described in the BCR-ABL kinase domain that lead to drug resistance • Agents that are active without the risk of exacerbating significant comorbidities are needed in the treatment of CML • There is no standard of care for patients with Ph+ ALL who fail on dasatinib therapy

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

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

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

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

- Drs. Scott Berry, Kelvin Chan and Sunil Desai who were not present for the meeting
- Jo Nanson who was the designated non-voting Patient Alternate for this meeting

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

- Drs. Bill Evans and Matthew Cheung who were not present for the meeting
- Jo Nanson who was the designated non-voting Patient Alternate for this meeting

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of Ponatinib (Iclusig) for Chronic Myeloid Leukemia /Acute Lymphoblastic Leukemia, through their declarations, three members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, but none of these members was excluded from voting.

Information sources used

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

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information included in this recommendation document.

Use of this recommendation

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