PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Ponatinib (Iclusig) for Chronic Myeloid Leukemia / Acute Lymphoblastic Leukemia

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of ponatinib (Iclusig) as compared to an appropriate comparator in 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.

Ponatinib has a Health Canada indication which is the same as the indication under pCODR review. Ponatinib is an oral tablet available as 15 mg and 45 mg; it has Health Canada approval with conditions for 45 mg once daily.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

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 developed the T3151 mutation after TKI therapy.[2]

The study had a total of 449 patients receiving ponatinib:

- 270 in chronic phase (CP), with 214 patients (84%) resistant to dasatinib or nilotinib and 40 patients (16%) with unacceptable side effects to dasatinib or nilotinib.
- 85 in accelerated phase (AP), with 74 patients (92%) resistant to dasatinib or nilotinib and 6 patients (8%) with unacceptable side effects to dasatinib or nilotinib.
- 62 in blast phase (BP), with 59 patients (97%) resistant to dasatinib or nilotinib and 2 patients (3%) with unacceptable side effects to dasatinib or nilotinib.
- 32 in Ph+ ALL, with 27 patients (90%) resistant to dasatinib or nilotinib and 2 (7%) with unacceptable side effects to dasatinib or nilotinib.

Resistant or unacceptable side effects to dasatinib or nilotinib at any time, this includes but is not limited to, failure to achieve a MaHR within three (AP/BP-CML) or one month (Ph+ ALL) of initiation of therapy. They are further defined in Section 6.3.2.1.a. The median age of patients was 60, 60, 53, and 62 years in the CP, AP, BP, and Ph+ ALL groups, respectively. The majority of patients had an ECOG PS of 0 (60%) or 1 (33%). Ninety-three percent of patients had ≥2 drugs for prior TKI therapy and 58% of patients had ≥3 drugs. The median time on prior TKI therapy was 4.6 months (range of 0.1-13.3). The median duration of treatment was 12.8 months (range 1 day to >24.8 months). The median relative dose intensity was 0.84.

Efficacy

Major cytogenetic response (MCyR) was the primary outcome for patients with CP-CML. Major hematologic response (MaHR) was the primary outcome for patients with AP-CML, BP-CML, and Ph+ ALL patients. Secondary endpoints included response (hematologic, cytogenetic, and molecular), time to response, and duration of response. For the main data analysis of PACE, the median follow-up was 15 months (range of <1 to 25).

CP-CML patients:

MCyR at any time within the first 12 months was reached in 56% (95%CI: 50-62) of patients with CP-CML. Of those who had a response to treatment, the median time to a MCyR was 2.8 months (range: 1.6-11.3) and the median duration of a MCyR was not reached. A sustained response of at least 12 months was seen in 91% of patients who had a MCyR.

AP-CML and BP-CML patients:

MaHR by 6 months was reached by 55% (95%CI: 44-66) of patients with AP-CML and 31% (95%CI: 20-44) of patients with BP-CML. Of those who had a response to treatment, the median time to a MaHR was 3 weeks (range: 2-25 weeks) for AP-CML patients and 4.1 weeks (range: 1.7-16.1) for BP-CML patients. The median duration of a MaHR was 12 months and 5 months for patients with AP-CML and BP-CML, respectively. Sustained responses of at least 12 months were seen in 48% and 42% of patients with AP-CML and BP-CML, respectively.

Ph+ ALL patients:

MaHR was seen in 41% (95%CI: 24-59) of patients with Ph+ ALL. Of those who had a response to treatment, the median time to a MaHR was 2.9 weeks (range: 1.6-24) and the median duration was 3 months. A sustained response of at least 12 months was estimated to be 8%.

Efficacy results for patients in the PACE study

	MCyR/MaHR, % (95%CI)	**Median time to MCyR/MaHR, range**	**Median duration of MCyR/MaHR, months**	**Sustained response, %**
CP-CML (n=270)	56 (50-62)	2.8 months (1.6-11.3)	Not Reached	91
AP-CML (n=85)	55 (44-66)	3 weeks (2-25)	12 months	48
BP-CML (n=62)	31 (20-44)	4.1 weeks (1.7-16.1)	5 months	42
Ph+ ALL (n=32)	41 (24-59)	2.9 weeks (1.6-24)	3 months	8

Quality of life was not measured in the PACE study.

Harms

There were 57 (13%) deaths during the study or within 30 days after treatment was discontinued, causes of death included progressive disease (29 patients) and adverse events (28 patients). Five deaths were attributable to ponatinib and due to pneumonia, myocardial infarction, fungal pneumonia, gastric hemorrhage, or cardiac arrest.

The most common non-hematologic grade 1 and 2 adverse events (AEs) were rash (34%), dry skin (32%), and abdominal pain (22%). Rates of grade 3 or 4 AEs were similar across all patient groups (CP-CML, AP-CML, BP-CML, and Ph+ ALL). Serious non-fatal treatment-emergent serious AEs included arterial thromboembolic and arterial stenosis events. At the original data cut-off date, 41 (9%) of patients experienced an arterial event of all grades.

Fifty-five percent of patients had a dose reduction and 73% of patients had at least one dose interruption. For all cohorts, a dose reduction was recommended by the manufacturer in October 2013. The most common reasons for study discontinuation were progressive disease (21%) and adverse events (15%).

1.2.2 Additional Evidence

pCODR received input on ponatinib from one patient advocacy group (Chronic Myelogenous Leukemia Society of Canada). Provincial Advisory Group input was obtained from nine of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. No supplemental issues were identified during the development of the review.

1.2.3 Interpretation and Guidance

While the majority of patients with CML/ALL do well on first and second-generation TKIs, a small number of patients will not benefit from treatment with current TKIs. These patients include those who develop mutations (e.g. T3151 mutations) that are resistant to these agents, those who fail on at least two second-generation TKIs, or those who progress to advanced disease while on a TKI. Treatment options for these patients include allogeneic hematopoietic cell transplantation and palliative treatment with hydroxyurea.

Although there is a lack of long-term data on the risks and benefits of ponatinib, the Clinical Guidance Panel felt that early adoption of ponatinib was justified given the urgent clinical need of the highly selected group of patients.

Effectiveness

Responses (MCyR and MaHR) to ponatinib were observed for all subgroups of patients enrolled in the PACE study. MCyR was observed for 56% of patients with CP-CML. Ninety-one percent of patients with CP-CML who achieved this endpoint remained in a MCyR at the end of the first year of treatment. MaHR was observed for 55% of patients with AP-CML and 31% of patients with BP-CML. MaHR was observed in 41% of patients with Ph+ ALL.

At the primary data cut-off, median overall survival (OS) was not reached for patients with CP-CML and AP-CML, 12-month OS rates were 94% and 86%, respectively. The median OS for patients with BP-CML was 6.9 months with a 12-month OS rate of 31%. The median OS for patients with Ph+ ALL was 9.0 months with a 12-month OS rate of 47%.

There have been no comparisons of ponatinib compared to other agents for treating patients with CML/ALL, however ponatinib should not be an alternative to other TKIs but as a last-resort option for patients who would otherwise be treated with palliative intent.

Safety

Ponatinib is associated with a relatively high rate of grade 3 and 4 hematological adverse events including neutropenia and thrombocytopenia. Non-hematological grade 3 and 4 adverse events included increased lipase, pancreatitis, abdominal pain, and rash. Concerns have been raised about the high rates of arterial and venous occlusive events among patients treated with ponatinib. Recurrent events are common among patients who experience one of these events and who choose to remain on ponatinib. Among patients who experience an arterial event, 95% had one or more risk factor for atherosclerotic disease. It is anticipated this risk will be mitigated by restricting the ability to prescribe ponatinib to specifically-trained physicians with expertise in managing CML and the specific side effects of ponatinib.

1.3 Conclusions

The Clinical Guidance Panel (CGP) concluded that there is net clinical benefit for select patients with CML/ALL with ponatinib. Patients with CML who would benefit from this agent include those who are not candidates for hematopoietic cell transplantation and who 1) develop a T315I mutation, 2) are resistant or intolerant to two currently-available second generation TKIs, or 3) progress to advanced disease on a TKI. Benefit was seen with ponatinib in all phases of CML and in Philadelphia-positive ALL. The CGP felt that treatment with this agent should be available to all patients with Philadelphia-positive leukemia regardless of stage and prior therapy, who 1) develop T315I mutations, 2) are resistant or intolerant to two or more second generation TKIs, or 3) progress to advanced disease while on treatment with a TKI. The Panel based this conclusion on the results of a large phase II open-label study showing a high rate of clinically-meaningful responses in this group of patients. Although serious safety concerns have been identified the panel felt that the risks of treatment with ponatinib were justified given the lack of alternative treatments. The panel was unable to consider quality of life given the lack of data from the study. In reaching this conclusion the panel considered that:

- The ability to prescribe ponatinib should be restricted to physicians who have received specific training in its use. The side effect profile of ponatinib differs from that of other agents used to treat Philadelphia-positive leukemias and special care is required to address cardiovascular risk factors for patients receiving this drug. Such Risk Evaluation and Mitigation Programs have been successfully established for other drugs.
- There is currently no data on the optimal starting dose for ponatinib, however there is evidence for CP-CML that dose can reduced after initial response to as low as 15 mg daily with a decrease in adverse events.
- Decreasing the dose of ponatinib to the lowest dose possible to achieve the target benefit may improve the side effect profile of this agent. Newer guidelines for the use of ponatinib have recommended such dosage adjustments.
- It is unlikely that indications for ponatinib will broaden substantially given the adverse effect profile of this drug. Indication creep could be addressed through a carefully designed Risk Evaluation and Mitigation Program.
- An indirect study comparison of ponatinib and other TKIs is not appropriate given the different patient populations, lines of therapy, and small sample sizes in the available studies.

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 ponatinib (Iclusig) for Chronic Myeloid Leukemia/Acute Lymphoblastic Leukemia. 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.cadth.ca/pcodr.

This Clinical Guidance is based on: a systematic review of the literature regarding ponatinib (Iclusig) 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 is fully reported in Sections 6. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on ponatinib (Iclusig) and a summary of submitted Provincial Advisory Group Input on ponatinib (Iclusig) are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

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 5,890 cases will be diagnosed in the United States in 2014, and CML will be responsible for approximately 800 deaths.[3] There were 447 cases of CML diagnosed in Canada in 2006, the most recent year for which there are incidence data.[4] ALL represents about 20% of all leukemias in adults.[5] Ph+ ALL is associated with a particularly poor prognosis despite development in TKI therapies, with a worse prognosis than other forms of ALL.

In the past, without treatment or with previous chemotherapy using busulfan or hydroxyurea, overall survival was approximately 3 to 5 years. Allogeneic stem cell transplantation resulted in cure of 70-80% of patients treated in chronic phase, but this treatment was limited to younger patients and those with available donors, and thus limited to less than 25% of the population. 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.[6]

The use of oral tyrosine kinase inhibitors (TKIs) targeting the BCR-ABL kinase represents the standard of care for patients with newly diagnosed CP CML and Ph+ ALL. 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.[7] However, 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. The second generation TKIs dasatinib and nilotinib have a much smaller spectrum of resistance mutations, but neither are able to overcome the T315I mutation. Both of these agents produce similar rates of major molecular response (MMR) and have similar progression-free and overall survival when used as second-line therapies.

Current treatment recommendations of the European Leukemia Network are that imatinib, nilotinib or dasatinib are 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.

Current treatment options for Ph+ ALL, similar to CML, include the TKIs imatinib and dasatinib. In Canada, none of the TKIs are approved for use in Ph+ ALL following failure on dasatinib or in patients with the T315I mutation. Most patients with ALL who cannot be rescued with currently available TKI therapies would be treated with allotransplant or supportive care.

Ponatinib was rationally designed to fit into the ATP binding domain of mutant forms of BCR-Abl, and is known to bind firmly even in the presence of mutations such as T315I that are associated with resistance to first and second-generation TKIs. Serious toxicity of ponatinib includes elevation of pancreatic enzymes, pancreatitis, dermatitis and fatigue. Hematological toxicity includes grade 3 and grade 4 cytopenias.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effectiveness of ponatinib (Iclusig) 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.

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 open label, phase 2, single arm, ongoing study was found for this review (PACE study). Characteristics of the study's design can be found in Table 5. The study included CML or PH+ ALL patients who were resistant or intolerant to imatinib, dasatinib or nilotinib including patients who developed the T3151 mutation after TKI therapy.[2] A total of N=449 patients were included in this study. There were 270 chronic phase CML patients, 85 accelerated phase CML patients, 62 blast phase CML patients and 32 PH+ ALL patients.[2] The median age of patients was 60 years. Sixty percent of patients had an ECOG performance status (ECOG PS) 0, 33% had an ECOG PS 1 and 8% had an ECOG PS 2. Ninety three percent of patients had two or prior TKIs and 58% had three or more previous TKIs. Resistance to TKIs was seen in 88% of patients and intolerance in 12% and unspecified in 1% of patients.[2]

The PACE study commenced in September 2010. Ponatinib was administered orally in a 45 mg tablet taken once daily. The manufacturer of ponatinib issued a dose reduction recommendation on October 10, 2013. For CP-CML patients who have achieved a MCyR, the dose should be reduced to 15 mg/day, for CP-CML patients who have not already achieved MCyR the dose should be reduced to 30 mg/day and for advanced-phase patients the dose should be reduced to 30 mg/day.[8]

At the January 6, 2014 analysis, the median follow-up was 27.9 months (range 0.1-39.5 months) and 38% of patients (50% were CP-CML) were still ongoing in the study. The most common reasons for study discontinuation were progressive disease (21%) and adverse events (15%).[9]

The results for cytogenetic, hematologic and molecular responses are listed in Table 1 below.

CP CML

The primary outcome for CP CML patients was major cytogenetic response (MCyR) at any time within the first 12 months. This was reached by 56% of CP-CML patients (95% confidence interval [CI], 50 to 62).[2] In CP CML patients who had a response to treatment, the median time to a MCyR was 2.8 months (range, 1.6 to 11.3), and the duration ranged from 1 day to over 19.4 months since the median was not reached. The estimated rate of a sustained response in patients who had a MCyR of at least 12 months was 91% (95% CI, 85 to 95).[2] Data as of January 6, 2014 shows that a MCyR was seen in 59% of CP-CML patients.[9]

AP CML

In patients who had accelerated phase CML (AP-CML) the major hematologic response (MaHR) by 6 months was 55% (95% CI, 44 to 66). This was the primary endpoint for the group. At the January 6, 2014 update, 61% of AP-CML patients had a MaHR.[9] The median time to a MaHR was 3 weeks (range, 2 to 25 weeks), and it lasted from 1 month to over 21 months, the median being 12 months. A sustained response for 12 months was estimated to be 48%.[2]

BP CML

In patients who had blast phase CML (BP-CML), the MaHR by 6 months was 31% (95% CI, 20 to 44) and this was the primary endpoint for this group. The median time to a MaHR in patients with BP CML was 4.1 weeks (range, 1.7-16.1 weeks), and it lasted from 1 month to over 20 months, the median being 5 months. A sustained response for 12 months was estimated to be 42%.[2]

Ph+ ALL

In patients with Ph-positive ALL (Ph+ ALL), a MaHR was seen in 41% (95% CI, 24 to 59) of patients. In patients with Ph+ ALL, the median time to a MaHR was 2.9 weeks (range, 1.6 to 24) and it lasted for 2 to over 14 months, with the median being 3 months. A sustained response for 12 months was estimated to be 8%.[2]

Table 1: Hematologic, Cytogenetic and Molecular responses for Chronic Phase CML patients

	CP CML 12 months [10] N=267 (%)	CP CML Jan 2014 update[9] N=267 (%)	AP CML patients[10] N= 83	BP CML[2] N= 62	Ph+ ALL[2] N=32
CHR *	250 (93.6)	NR	NR	NR	NR
MaHR[§]	NA	NA	46 (55.4)	(31)	(41)
Any CyR[‖]	180 (67.4)	NR	46 (55.4)	NR	NR
MCyR	149** (55.8)	158 (59)	32 (38.5)	(23)	(47)
CCyR	142 (53)	142 (53)	20 (24.0)	(18)	(38)
PCyR	25 (9.3)	NR	12 (14.4)	NR	NR
MMR[§§]	91 (34.0)	102 (38)	13(15.6)	NR	NR
MR^4	56 (20.9)	68 (26)	4 (6)	NR	NR
$MR^{4.5}$	39 (14.6)	53 (20)	4 (6)	NR	NR

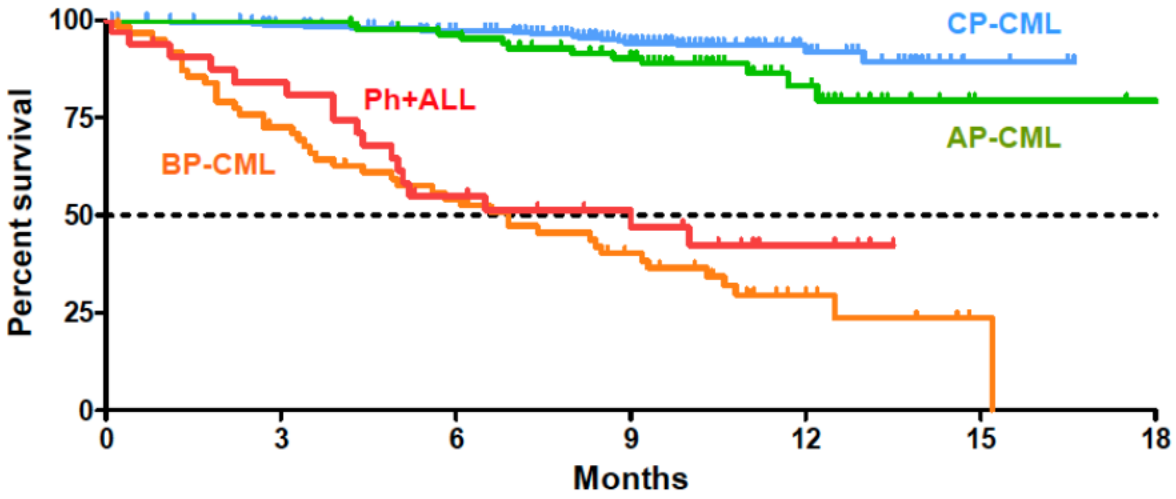
Abbreviations: CHR=complete hematologic response; CCyR=complete cytogenetic response; MaHR=major hematologic response; MCyR (CCyR + PCyR)=major cytogenetic response; MMR =major molecular response = MR3 only + MR4 only +MR4.5; MR^4 Either detectable transcripts ≤0.01% BCR-ABL[IS] or undetectable BCR-ABL transcripts in cDNA with ≥10,000 ABL transcripts, in peripheral blood as measured by RT-qPCR; $MR^{4.5}$ Either detectable transcripts ≤0.0032% BCR-ABL[IS] or undetectable BCR-ABL transcripts in cDNA with ≥32,000 ABL transcripts, in peripheral blood as measured by RT-qPCR; NA=not applicable; NR= not reported; PCyR=partial cytogenetic response;

* The CHR rate includes patients maintaining or achieving CHR on study. CP-CML patients with CHR at baseline: R/I N=89, T315I N=24.
§Patients missing baseline bone marrow blasts and those entering the study in MaHR are counted as non-responders in the analysis of MaHR; 14 AP-CML patients entered the study in MaHR, and 1 AP-CML patient had missing baseline bone marrow blasts.
||Any CyR=CCyR + PCyR + minor CyR + minimal CyR
**CP-CML patients who entered the study in PCyR had to achieve CCyR to meet the criteria for MCyR. In the R/I and T315I cohorts, 39 and 13 patients entered the study in
§§Molecular responses were measured in peripheral blood.

There were several pre-specified subgroup analyses in CP and AP CML patients that were done to demonstrate the effect of clinical factors on response rates. In patients who had taken fewer previous tyrosine kinase inhibitors, were younger, and had a shorter interval between diagnosis and enrolment in the study, higher response rates were observed.[10]

Overall survival for the Pace study can be seen in Figure 1.

Figure 1: Overall survival for the PACE study from the April 27, 2012 data cut off[11]



For all cohorts a dose reduction was recommended by the manufacturer on October 10, 2013.[9] According to an analysis of the dose intensity-safety relationship in the PACE study, it was determined that "after adjusting for covariates, the overall dose intensity is significantly associated with an increased risk of vascular occlusion, with an odds ratio of approximately 1.6 for each 15 mg increase."[12] Maintenance on lower doses showed that in the CP CML group efficacy was not lost on lower doses. Table 13 in section 6.

Adverse Events

The January 6, 2014 update showed that the following AEs occurred in more than 20% of patients: thrombocytopenia 44%; abdominal pain 42%; rash 41%; constipation 37%; headache 37%; dry skin 35%; fatigue 29%; pyrexia 29%; nausea 28%; arthralgia 28%; hypertension 26%; neutropenia 25%;anemia 22%; myalgia 21%; diarrhea 21%; vomiting 21%; increased lipase 21%.[9]

Serious non-fatal treatment-emergent serious adverse events

Serious non-fatal treatment-emergent serious adverse events in ≥2% of patients can be seen in Table 2. Arterial thromboembolic and arterial stenosis events were prominent in the

study. These consisted of cardiac, central nervous system, and peripheral arterial events. The 120-day safety update with a data cut-off of 23 July 2012 showed that 51 (11%) of patients had an ischemic event of any grade and 34 patients experienced a serious ischemic event.[11] Twenty-four patients had arterial stenosis. A revascularization procedure was necessary in 21 patients.[11]

Serious hemorrhagic events took place in 19 patients (4%). The central nervous system was the site in 10 patients and gastrointestinal in 6 patients. Most of these events were associated with severe thrombocytopenia.[11] Treatment-emergent infections that were serious were seen in 15% of the patients, with the most serious being pneumonia, sepsis, and cellulitis.[11] Another of the serious adverse events (SAE) was pancreatitis. This was likely to occur early during treatment and was mostly reversible as the majority of cases resolved within 1 week.[2] Hypertension was experienced by eight (2%) patients as a SAE that needed urgent clinical intervention. Out of the eight patients, three did not have a prior history of hypertension.[11]

Congestive heart failure (CHF) was another SAE. In the PACE study the risk of CHF was considered serious in 4% of patients. Nine patients who had CHF or decreased ejection fraction had dose modifications and treatment was discontinued in 3 patients.[11] Pacemakers for symptomatic bradyarrhythmias were required in three patients.[11]

The site investigators felt that the following percentages of events were possibly related to ponatinib treatment: cardiovascular, (2.2%), cerebrovascular (0.7%), and peripheral vascular (1.6%).[2]

Table 2: Nonfatal treatment-emergent serious adverse events in ≥2% of patients[11]

Event	April 27 2012 data N
Cardiovascular disorders	
Arterial ischemic event	27 (6%)
Myocardial infarction or worsening coronary artery disease	18 (4%)
Stroke or TIA	7 (2%)
Peripheral arterial disease	4 (1%)
Hemorrhage	19 (4%)
CNS hemorrhage	10 (2%)
Gastrointestinal hemorrhage	6 (1%)
Cardiac failure	17 (4%)
Effusions (includes pericardial effusion, pleural effusion, and ascites)	10 (2%)
Atrial fibrillation	9 (2%)
Hypertension	8 (2%)
Venous thromboembolism	8 (2%)
Gastrointestinal disorders	
Pancreatitis	23 (5%)
Abdominal pain	16 (4%)
Blood and lymphatic system disorders	
Febrile neutropenia	13 (3%)
Thrombocytopenia	12 (2%)
Anemia	12 (2%)
Infections	
Pneumonia	21 (5%)

Sepsis	10 (2%)
General	
Pyrexia	14 (3%)

Deaths

There were 57 (13%) deaths during the study or within 30 days after treatment was discontinued. The cause of death was progressive disease (29 patients) and adverse event (28 patients).[11]

Five deaths were attributable to ponatinib; one patient with CP-CML had pneumonia, another had a myocardial infarction; one patient with AP-CML had fungal pneumonia, one patient with BP-CML had a gastric hemorrhage and one patient with Ph+ ALL had a cardiac arrest.[2]

As of February 2, 2015 there were an additional two deaths being attributable to ponatinib.[13]

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

2.1.5 Summary of Supplemental Questions

Critical Appraisal of an Indirect Comparison of Ponatinib and Second-Generation Tyrosine Kinase Inhibitors (bosutinib, dasatinib, and nilotinib)

The comparative efficacy of ponatinib and second-generation tyrosine kinase inhibitors (TKIs) for best response rates in patients with CML or ALL was indirectly assessed using descriptive forest plots and Bayesian analysis. The main limitation with the naïve ITC is that it compared response rates between several single-arm studies without adjustments. Any differences may be due to differences between studies with respect to known patient or disease characteristics (e.g. age, co-morbidities, and co-interventions) or due to unknown factors that differ between study populations. It is unknown how much the difference between trials affects the estimated response rates. Therefore, any conclusions drawn from this naïve indirect comparison regarding the comparative clinical effectiveness between ponatinib and second-generation TKIs should be interpreted with caution.

See section 7.1 for more information.

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, symptoms of CML, which includes constant fatigue, weight loss, low blood counts, loss of energy, shortness of breath along with joint and muscle pain have a significant impact on the overall quality of life. While there are several treatments classified as tyrosine kinase inhibitors (TKIs) that are available to CML patients, these treatments have a myriad of side effects and managing them can be a challenge for many patients. Chronic

Myelogenous Leukemia Society of Canada (CMLSC) reported that patients' expectations for ponatinib is that it will result in fewer hospital visits, and although managing side effects is an ongoing challenge, patients can, to some degree, manage a fairly normal lifestyle as it would offer them a chance to control BCR-ABL, the causative factor in CML, and would therefore would extend their lives significantly. Respondents who have experience with ponatinib reported that they responded well to the drug and that their hematological and molecular response while on ponatinib improved significantly. However, respondents also noted side effects, such as, dry eyes, constipation, fatigue and muscle pain were difficult to manage, and that they needed better help with managing these side effects. Recognizing the side-effects, CMLSC submits that ponatinib could play an important role and benefit for a minority of CML patients in which current therapy is not effective (i.e., due to a mutation such as T315I) or who do not respond to current therapy. In addition, ponatinib may also be important with helping patients regain response and time for a suitable bone marrow donor to be located.

PAG Input

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.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of ponatinib:

Clinical factors:

- New drug with severe toxicities to monitor
- Long-term data on benefits versus risks of treatment

Economic factors:

- Cost of drug

2.2 Interpretation and Guidance

Burden of Illness and Need

Approximately 450 new cases of Chronic Myelogenous Leukemia are diagnosed in Canada every year. While the majority of these patients are expected to do very well with the first- and second-generation tyrosine kinase inhibitors (TKI) already available, a small number of patients will not benefit from treatment with these medications. This group consists of patients who develop mutations that are resistant to these agents, such as the T315I BCR-Abl mutation, those who fail on at least two second-generation TKIs, or who progress to advanced disease while on a TKI. Treatment options for this group of patients include allogeneic hematopoietic cell transplantation (available to the few younger patients with suitable donors) and palliative treatment with hydroxyurea. The Clinical Guidance Panel estimates that only ten patients with CML presenting in chronic phase would require treatment with ponatinib each year in Canada.

Efficacy

Patients (n=449) with Philadelphia chromosome-positive leukemias who were resistant or intolerant to nilotinib or dasatinib, who had unacceptable toxicity to these agents, or who developed the T315I mutation after any tyrosine kinase inhibitor therapy were treated with ponatinib in a single-arm phase II study. Patients had received extensive prior therapy and had been treated with tyrosine kinase inhibitors for a median of 4.6 (range 0.1 – 13.3) years. More than half of CML and 38% of Ph+ ALL patients had received three or more previously approved tyrosine kinase inhibitors. The overwhelming majority of patients (88%) had experienced resistance to nilotinib or dasatinib prior to enrollment in this study. The median follow-up of patients on this study was 15 months.

Responses to ponatinib were observed in all subgroups of patients enrolled on this study. Among patients with chronic-phase CML, 56% of patients experienced a major cytogenetic response (the primary endpoint for this group), with responses being seen more commonly in patients with T315I mutations. Cytogenetic responses were sustained, with 91% of patients who achieved this endpoint remaining in a major cytogenetic response at the end of the first year of treatment. The primary endpoint for patients with advanced (accelerated- or blast-phase) CML was a major hematological response after six months of treatment. This endpoint was reached in 55% of patients with accelerated-phase and 31% of patients with blast-phase CML. Responses were sustained for at least one year in 73% of responding accelerated-phase patients and their rate of progression-free survival was 55%. Among patients with Philadelphia-positive ALL the rate of major hematologic response was 41% with 38% of these patients achieving complete cytogenetic response. No single BCR-Abl mutation was associated with resistance to ponatinib.

At the primary data cut off, median overall survival was not reached for the CP and AP-CML groups, 12-month OS rates were 94% and 86%. The median OS for the BP-CML group was 6.9 with a 12-month OS rate of 31% and the median OS for the Ph+ ALL group was 9.0 months with a 12-month OS rate of 47%.

Safety

Treatment with ponatinib is associated with a relatively high rate of grade 3 – 4 hematological adverse events. Grade 3 – 4 neutropenia and thrombocytopenia were observed in 14% and 32% of chronic-phase, 26% and 33% of accelerated-phase and 18% and 26% of blast-phase patients, respectively. Non-hematological grade 3 – 4 adverse events included increased lipase or pancreatitis, abdominal pain or rash. Rates of serious adverse events were similar for patients with Ph+ ALL. Concern has been raised over the high rate of arterial and venous occlusive events that has been observed among patients treated with ponatinib. Cardiovascular, cerebrovascular and/or peripheral arterial occlusion was seen in 7.1%, 3.6% and 4.9% of patients in this study. Recurrent events are common among patients who experience one of these events and who choose to remain on ponatinib. Among patients who experienced an arterial event, 95% had one or more risk factor for atherosclerotic disease. It is anticipated that this risk will be mitigated by restricting the ability to prescribe ponatinib to a relatively small group of specifically-trained physicians with expertise in the management of CML and the specific side effects of this drug.

Limitations

Despite being the largest study to date in this group of patients, this study has a number of limitations that may have implications for the adoption of ponatinib for clinical use. These

include the lack of long-term data on the risks and benefits of treatment with ponatinib. This limitation is common to all new drugs that enter clinical use shortly after completion of early-phase studies and the panel felt that early adoption of ponatinib was justified given the urgent clinical need of the highly selected group of patients who need it. There have been no comparisons of ponatinib to other agents used to treat patients with CML/ALL, and this lack of a control group makes it difficult to estimate the magnitude of the clinical benefit patients may experience. Ponatinib, however, is not to be positioned as an alternative to other TKIs but as an agent of last-resort for patients who otherwise would largely be treated with palliative intent. In the face of such an active agent it is difficult to justify a study that would randomize patients to receive palliative/supportive care, and it is highly doubtful that phase III studies of ponatinib will be carried out in this setting. Finally, this study does not report on quality of life.

2.3 Conclusions

The Clinical Guidance Panel (CGP) concluded that there is net clinical benefit for select patients with CML/ALL with ponatinib. Patients with CML who would benefit from this agent include those who are not candidates for hematopoietic cell transplantation and who 1) develop a T315I mutation, 2) are resistant or intolerant to two currently-available second generation TKIs, or 3) progress to advanced disease on a TKI. Benefit was seen with ponatinib in all phases of CML and in Philadelphia-positive ALL. The CGP felt that treatment with this agent should be available to all patients with Philadelphia-positive leukemia regardless of stage and prior therapy, who 1) develop T315I mutations, 2) are resistant or intolerant to two or more second generation TKIs, or 3) progress to advanced disease while on treatment with a TKI. The Panel based this conclusion on the results of a large phase II open-label study showing a high rate of clinically-meaningful responses in this group of patients. Although serious safety concerns have been identified the panel felt that the risks of treatment with ponatinib were justified given the lack of alternative treatments. The panel was unable to consider quality of life given the lack of data from the study. In reaching this conclusion the panel considered that:

In reaching this conclusion the panel considered that:

- The ability to prescribe ponatinib should be restricted to physicians who have received specific training in its use. The side effect profile of ponatinib differs from that of other agents used to treat Philadelphia-positive leukemias and special care is required to address cardiovascular risk factors for patients receiving this drug. Such Risk Evaluation and Mitigation Programs have been successfully established for other drugs.
- There is currently no data on the optimal starting dose for ponatinib, however there is evidence for CP-CML that dose can reduced after initial response to as low as 15 mg daily with a decrease in adverse events.
- Decreasing the dose of ponatinib to the lowest dose possible to achieve the target benefit may improve the side effect profile of this agent. Newer guidelines for the use of ponatinib have recommended such dosage adjustments.
- It is unlikely that indications for ponatinib will broaden substantially given the adverse effect profile of this drug. Indication creep could be addressed through a carefully designed Risk Evaluation and Mitigation Program.
- An indirect study comparison of ponatinib and other TKIs is not appropriate given the different patient populations, lines of therapy, and small sample sizes in the available studies.

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 or symptoms due to splenic enlargement. Initial laboratory results demonstrate a high white blood cell (WBC) with large numbers of granulocyte precursors and an increased platelet count. Acute Lymphoblastic Leukemia (ALL) is an aggressive hematological malignancy characterized by the excessive production of immature lymphoblasts. Like CML, symptoms include fatigue, anemia and enlarged lymph nodes, liver and/or 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+). Ph+ chromosomal abnormality occurs in approximately 20-30% of adult patients with ALL.[14] The protein produced by this fusion gene is a constitutively active tyrosine kinase resulting in the continuous activation of other cell cycle regulatory proteins and unrestrained bone marrow proliferation. Since the introduction of tyrosine kinase inhibitors for Ph+ hematological disorders the BCR-Abl kinase has been the key therapeutic target in the treatment of CML and BCR-Abl-expressing ALL. 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.[3] There were 447 cases of CML diagnosed in Canada in 2006, the most recent year for which there are incidence data.[4] 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).

ALL is the most common form of childhood leukemia and represents about 20% of all leukemias in adults.[5] Ph+ ALL is associated with a particularly poor prognosis despite development in TKI therapies, carrying a worse prognosis than other forms of ALL. 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 patients 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.[6] Interferon is rarely used anymore and usually indicated for women who are pregnant or trying to become pregnant.

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 and Ph+ ALL. 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.[7] 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.[15] The starting dose of imatinib is 400mg daily; comparisons of this dose to high-dose imatinib (800mg/day) showed similar rates of complete cytogenetic and major molecular response at 1 year, with fewer side effects.[16]

With additional follow up of patients treated with TKIs for CP CML, response criteria have been refined, and are summarized in Table 3.[17]

Table 3: Response Criteria

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. Mutations to the ATP binding site of BCR-Abl, which is the site of contact of tyrosine kinase inhibitors active in these diseases, are associated with drug resistance and a high risk of progression. While some binding site mutations may preserve the activity of alternative TKIs the T315I mutation is associated with universal resistance to first and second generation drugs. The second generation TKIs dasatinib and nilotinib have a much smaller spectrum of resistance mutations, but neither are able to overcome the T315I mutation. Both of these agents produce similar rates of MMR and have similar progression-free and overall survival when used as second-line therapies. The T315I mutation is more likely to occur in ALL or BP that has become resistant to other drugs, particular dasatinib. Survival is shorter with the T315I mutation given the lack of effective treatment options.

Dasatinib and nilotinib have been compared to imatinib as initial therapy for CP CML. Nilotinib 300 mg twice daily was compared to imatinib 400 mg once daily and resulted in a significantly higher rate of CCyR after 1 and 2 years (80% vs 65%, and 87% vs 77%), a significantly higher rate of MMR after 1 year (50% vs 27%) and 3 years (73% vs 53%).[18] 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%).[19] 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, however, there is brand and generic imatinib and approval for these vary from province to province. Funding for dasatinib and nilotinib also varies from province to province. This results in a heterogeneous approach to primary therapy across the country. Bosutinib, a newer second-generation TKI, is an option for patients with CP/AP-CML who are intolerant to other drugs, have failed dasatinib and/or nilotinib and have no obvious mutation present to make other drugs viable. Current treatment options for Ph+ ALL, similar to CML, include the TKIs imatinib and dasatinib. In Canada, none of the TKIs are approved for use in Ph+ ALL following failure on dasatinib or in patients with the T315I mutation. Most patients with ALL who cannot be rescued with currently available TKI therapies would be treated with allotransplant or supportive care.

Currently available options in Canada for patients with CML/ALL

- CP-CML without T315I mutation: dasatinib; nilotinib; SCT; hydroxyurea*; interferon
- CP-CML with T315I mutation: SCT
- AP-CML (without or with T315I mutation): SCT; hydroxyurea*
- BP-CML (without or with T315I mutation): hydroxyurea*
- Ph+ALL without T315I mutation: SCT; vincristine/prednisone*
- Ph+ ALL with T315I mutation: SCT

SCT=stem cell transplant is an option if in remission; *Best supportive care

Ponatinib is a novel tyrosine kinase inhibitor with activity against wild-type and mutant BCR-Abl, as well as a large number of other targets such as c-kit, FMS-like tyrosine kinase-3 (FLT-3) and FGFR1-derived fusion tyrosine kinases. Ponatinib was rationally designed to fit into the ATP binding domain of mutant forms of BCR-Abl, and is known to bind firmly even in the presence of mutations such as T315I that are associated with resistance to first and second-generation TKIs. Serious toxicity of ponatinib includes elevation of pancreatic enzymes, pancreatitis, dermatitis and fatigue; arterial events including cardiovascular, cerebrovascular and peripheral vascular have been reported. Hematological toxicity includes grade 3 and grade 4 cytopenias.

Regular monitoring, using the above criteria to inform testing for resistance mutations or the presence of acquired cytogenetic abnormalities (e.g. loss of chromosome 7, 7q- and others), is recommended and treatment with a second generation TKI initiated in the event of treatment failure. In addition to the presence of a mutation that may predict for reduced efficacy of a second-line agent, 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 exacerbating significant co-morbidities are very much needed in the treatment of CML and ALL.

3.3 Evidence-Based Considerations for a Funding Population

Ponatinib is indicated for the treatment of adult patients with chronic phase, accelerated phased, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom other tyrosine kinase inhibitor therapy is not appropriate, including CML or Ph+ ALL that is T315I mutation positive or where there is prior TKI resistance or intolerance. T315I mutation testing is typically completed when patients are not responding to initial treatment of CML or ALL. These patients are heavily pre-treated and ponatinib can provide benefit to patients who are resistant or were not tolerant to previous TKIs.

3.4 Other Patient Populations in Whom the Drug May Be Used

None identified.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

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

CMLSC periodically surveys CML patients on a regular basis regarding issues about treatment access, quality of life, level of understanding/comprehension of CML in general. CMLSC also hosts three on-line chat forums. These other sources of information provide timely information on the concerns of the CML patient community in general. As it relates to ponatinib, CMLSC used several channels to reach out to patients, which included paid advertising through Facebook online community and emailing CML patients registered on CMLSC's website. CMLSC also reached out to CML clinician experts in Canada by providing them with an information sheet that they may hand out to their CML patients who were either currently taking ponatinib or have had an experience with ponatinib. In addition, CMLSC canvassed input from international patients, including from the U.S and the U.K. who had experience with ponatinib.

For the purposes of the ponatinib patient submission, CMLSC obtained general information from the online survey for CML patients. CMLSC also conducted one-on-one interviews with 10 respondents who specifically had experienced with ponatinib.

From a patient perspective, symptoms of CML, which includes constant fatigue, weight loss, low blood counts, loss of energy, shortness of breath along with joint and muscle pain have a significant impact on the overall quality of life. While there are several treatments classified as tyrosine kinase inhibitors (TKIs) that are available to CML patients, these treatments have a myriad of side effects and managing them can be a challenge for many patients. CMLSC reported that patients' expectations for ponatinib is that it will result in fewer hospital visits, and although managing side effects is an ongoing challenge, patients can, to some degree, manage a fairly normal lifestyle as it would offer them a chance to control BCR-ABL, the causative factor in CML, and would therefore would extend their lives significantly. Respondents who have experience with ponatinib reported that they responded well to the drug and that their hematological and molecular response while on ponatinib improved significantly. However, respondents also noted side effects, such as, dry eyes, constipation, fatigue and muscle pain were difficult to manage, and that they needed better help with managing these side effects. Recognizing the side-effects, CMLSC submits that ponatinib could play an important role and benefit for a minority of CML patients in which current therapy is not effective (i.e., due to a mutation such as T315I) or who do not respond to current therapy. In addition, ponatinib may also be important with helping patients regain lost response and buy time for a suitable bone marrow donor to be located.

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

According to CMLSC, the aspect that patients with chronic myeloid leukemia (CML) stated that is important to control is the appropriate targeting of the BCR-ABL, a constitutively active tyrosine kinase, which is the causative factor in CML.

CMLSC believes that as long as the BCR-ABL oncogene is well targeted, and results in significantly decrease, control or eradication of the mutation, then patients can expect to live a normal life span.

CMLSC reported that the symptoms of CML, which includes constant fatigue, weight loss, low blood counts, loss of energy, shortness of breath along with joint and muscle pain have a significant impact on the overall quality of life. The impact of these symptoms on a day-to-day life means that CML patients have to create a new normal which can be incredibly difficult. As an example, CML patients report on the limitations and challenges on the need to refocus their key objectives for their day-to-day living, such as, how to manage routine household chores, and re-evaluating work life balance.

4.1.2 Patients' Experiences with Current Therapy for Chronic Myeloid Leukemia

CMLSC reported that there are several treatments classified as tyrosine kinase inhibitors (TKIs) that are available to CML patients, including imatinib, dasatinib, nilotinib and bosutinib. These drugs are taken orally, outside of the hospital setting. For most patients one or another of these currently available drugs work rather well at controlling BCR-ABL, which is the causative oncogene in CML.

CMLSC indicated that TKIs have a myriad of side effects and managing them can be a challenge for many patients. The side effects of TKI include: diarrhea, constipation, joint and muscle pain, severe fatigue, low esteem, anxiety attacks, edema, water retention and high blood pressure. For some patients cardiovascular problems such as peripheral arterial occlusive disease are caused. For other patients there could be problems such as pleural effusions. Because these patients are being treated with oral cancer therapy, the role of managing these side effects falls to the haematologist oncologist, where in other cancer types patients being treated with drugs provided as part of the health care system these side effects would be managed by oncology nurses.

Because the idea of drug cessation is still relatively new, once patients understand that this can be a viable goal of treatment for CML, CMLSC reported that patients are willing to consider the side effects listed above as acceptable. As it relates specifically to ponatinib, CMLSC indicated that patients taking this drug generally have failed all other available therapies, and as such, these patients would be willing to withstand some degree of side effects to ensure the best response, and as long as they know they are being well managed by their healthcare team.

CMLSC noted the hardships with accessing treatment. While many patients are accessing the treatments through patient access programs provided by the pharmaceutical company; these patients are followed by nurses who are working for the pharmaceutical companies. Although drug treatments are mostly reimbursed on a provincial level they still must be purchased them through local specialty pharmacies, with the exception of B.C. and Alberta who provide the drugs directly to the patients from the hospital pharmacy. Because drugs are currently not considered to be part of the health care system, some patients do not have adequate insurance to cover the high cost of the drug. Moreover, CMLSC suggested that younger patients have faced prejudice in the workplace as employers see their cost of providing insurance and drug coverage to their employees increasing significantly to cover the cost of the drugs.

CMLSC believes that optimal response to therapy is very critical for patients if treatment cessation is to be considered. CMLSC indicated that as long as patients can achieve a good response to therapy, such as, major molecular response (MMR) or molecular response (MR) of 4.5 or better, after several years of therapy, patients may be considered for a trial of drug cessation. For a minority of CML patients controlling and/or eradicating BCR-ABL is a challenge either because of a

mutation that is not addressed by current therapies or for other unknown factors. CMLSC stated that if the BCR-ABL oncogene is not controlled then the prognosis for the patient is very poor. CMLSC submits that ponatinib could play an important role for the subset of patients who are deemed poor responders to current therapy by offering them a chance to control BCR-ABL and would extend their lives significantly, with a more or less good quality of life when all things are considered. In addition, for some patients, the use of ponatinib will buy time for their healthcare team to locate a good bone marrow donor, as it may be inevitable that some patients on ponatinib may eventually need a bone marrow transplant.

4.1.3 Impact of Chronic Myeloid Leukemia and Current Therapy on Caregivers

CMLSC did not specifically interview caregivers for this submission.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Ponatinib

CMLSC reported that patients' expectations for ponatinib is that it will result in fewer hospital visits, and although managing side effects is an ongoing challenge, patients can, to some degree, manage a fairly normal lifestyle.

In addition to the above, for a minority of CML patients in which current therapy is not effective (i.e., due to a mutation such as T315I) or who do not respond to current therapy, it is expected that these patient subsets may benefit from using ponatinib.

Ponatinib may also be important with helping patients regain lost response and buy time for a suitable bone marrow donor to be located. CMLSC received a response from a patient noting that ponatinib was used prior to bone marrow transplant and played a significant role in improving the patient's chance of a successful bone marrow transplant. This respondent is a patient who is post-transplant and disease free.

CMLSC noted that CML patients recognized that there are potential risks associated with ponatinib. Generally, patients taking ponatinib are advised about the risks of cardiovascular effects and are followed specifically by a cardio oncology program. Most CML patients, however, will be followed through a cardio oncology program as this is a concern for all TKIs and not just ponatinib.

CMLSC conducted one-on-one interviews with 10 respondents who specifically had experiences with ponatinib.

It was reported that respondents responded well to ponatinib and that their hematological and molecular response while on ponatinib improved significantly. Respondents reported side effects, such as, dry eyes, constipation, fatigue and muscle pain were difficult to manage and patients need better help with managing these side effects. It was reported that these patients will likely stay on ponatinib for a very long time.

CMLSC noted that these side effects could seem trivial in the scheme of things. Because these side effects are constant and ongoing without relief and are not at all of a transient nature, CMLSC indicated that over time these side effects could become debilitating.

CMLSC submits that ponatinib will dramatically change the prognosis for patients who respond to it. Patients who are not responding to current treatment or who have been diagnosed with a T315I mutation should have the benefit of the option of trying this drug in order to help increase their prognosis for survival.

4.3 Additional Information

Not applicable.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of ponatinib:

Clinical factors:

- New drug with severe toxicities to monitor
- Long-term data on benefits versus risks of treatment

Economic factors:

- Cost of drug

Please see below for more details and other factors.

5.1 Factors Related to Comparators

CML

The current treatment of CML is nilotinib, dasatinib, or imatinib. PAG noted the ponatinib is a treatment option for CML patients who have the T3151 mutation. However, PAG is requesting clarity on the comparative efficacy and safety of all the tyrosine kinase inhibitors available for treatment CML, specifically for patients with T3151 mutation. PAG noted the ponatinib data is only short-term from a single-arm, phase 2 trial available at this time and expressed concerns for long-term safety.

ALL

The current treatment for ALL is imatinib in the first-line setting and dasatinib in the second-line setting.

5.2 Factors Related to Patient Population

PAG noted that the number of patients with CML or ALL is very small and ponatinib is another treatment option available. Ponatinib would fill an unmet need for patients who are resistant to other treatments. These are enablers.

There is the potential for indication creep where ponatinib would be used in other lines therapy, which would be a barrier. However, given the black box warnings for severe adverse events, ponatinib may be the last treatment of choice.

5.3 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 available for dosage adjustments.

5.4 Factors Related to Implementation Costs

PAG noted that healthcare providers are familiar with tyrosine kinase inhibitors, although ponatinib has different and severe side effects that will require more rigorous monitoring. It is unclear at this time whether Health Canada will mandate a monitoring program for ponatinib as the Food and Drug Administration has done.

5.5 Factors Related to Health System

PAG noted that ponatinib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration 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.

5.6 Factors Related to Manufacturer

PAG noted the high cost of ponatinib and the same price applied to both tablet strengths would also be a barrier.
In the U.S., ponatinib is distributed in bulk bottles. PAG has concerns if ponatinib is not in unit dosing packaging in Canada, pharmacy personnel would need to take extra pre-cautions on handling of cytotoxics and/or pharmacies may not want to dispense a portion of a bulk bottle. In addition, PAG has concerns if ponatinib is dispensed at a local pharmacy, the appropriate patient counselling and monitoring may not be readily available.

Given that the Food and Drugs Administration had temporarily suspended distribution of ponatinib due to significant adverse events and then re-authorized distribution with black box warnings and a Risk Evaluation and Mitigation Strategy program, PAG has expressed concerns with the long-term safety and what Health Canada's approved indication and restrictions may be.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness of ponatinib (Iclusig) 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.

No supplemental questions were identified.

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 ponatinib 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.	chronic phase, accelerated phase, or blast phase 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 prior TKI resistance or intolerance.	Oral ponatinib 45mg once daily	Best supportive care No comparator in the case of single arm studies Stem cell transplants Interferon Hydroxycarbamide or *hydroxyurea* Hyper-CVAD	OS PFS Hematologic Response Cytogenic Response Molecular Response Duration of response Time to response **Quality of Life** **Grade 3 or 4 Adverse events** Emergent toxicity-peripheral vascular disease, lipid abnormalities. Other mutations Line of treatment
ALL = acute lymphoblastic leukemia; CML = chronic myeloid leukemia; Hyper-CVAD = cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate and cytarabine; OS = Overall survival; Ph+ = Philadelphia chromosome positive; PFS = Progression free survival; RCT = Randomized clinical 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-) with in-process records & daily updates via Ovid; EMBASE (1980-) via

Ovid; The Cochrane Central Register of Controlled Trials (2010, Issue 2) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were [ponatinib - iclusig] and [chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic 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 year. Retrieval was limited to the English language.

The search is considered up to date as of July 2, 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 [Include other conferences as per the guidance provided in S2 on tumour type, e.g. ESMO, ASH, SABCS] 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 the 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.

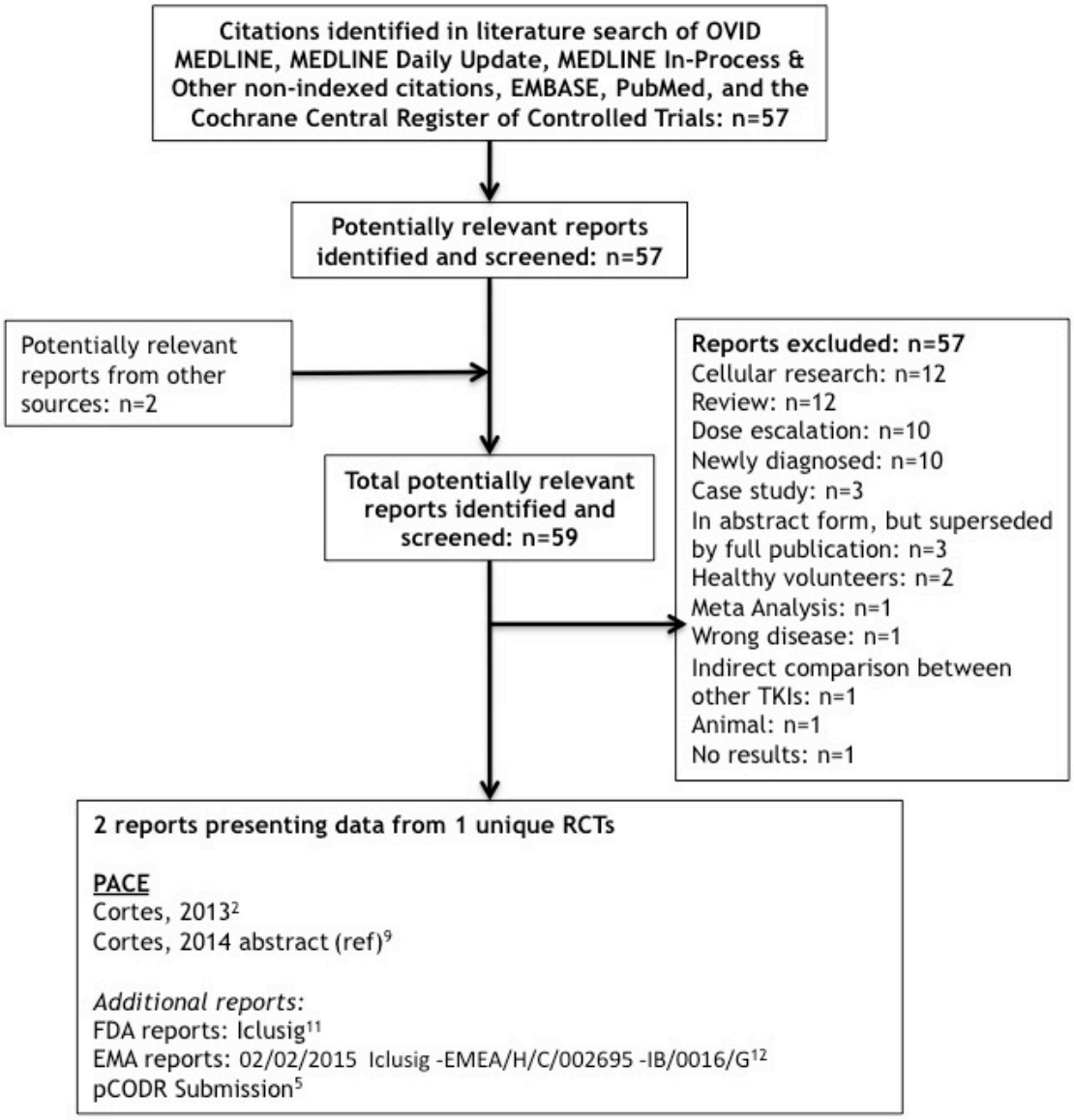
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided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

6.3 Results

6.3.1 Literature Search Results

Of the 56 potentially relevant reports identified, 2 studies were included in the pCODR systematic review and 51 studies were excluded. Studies were excluded because they were cellular research,[20-29] review,[30-41] Dose Escalation,[42-51] newly diagnosed,[52-61] case study,[62-64] found in abstract form, but superseded by full publication,[65-67] healthy volunteers,[68,69] meta-analysis,[70] wrong disease,[71] indirect comparison between TKIs,[72] and animal[73].

Figure 2: QUOROM Flow Diagram for Inclusion and Exclusion of studies



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

6.3.2 Summary of Included Studies

Provide a brief statement summarizing the number and type of included studies.

6.3.2.1 Detailed Trial Characteristics

Table 5: Summary of Trial characteristics of the included Study[2,74]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
NCT01207440 **PACE** Phase 2, single arm, open label study N=449 Chronic phase CML N=270 Accelerated Phase CML N=85 Blast Phase CML N=62 PH + ALL N=32 66 centres in 14 countries including: Australia, Belgium, Canada, France, Germany, Italy, Korea, Netherlands, Singapore, Spain, Sweden, United Kingdom and the United States of America **Study Start date:** Sept 2010 **Estimated Study Completion Date:** October 2020 **Funded by:** ARIAD Pharmaceuticals, Inc.	**Inclusion Criteria:** • Previously treated with and developed resistance or intolerance to dasatinib or nilotinib, or developed the T3151 mutation after any TKI therapy including imatinib • ≥18 years old • ECOG performance status ≤2 • Normal pancreatic function • QTcF interval ≤450 ms for males and ≤470 ms for females • Adequate renal and hepatic function • Minimum life expectancy of ≥3 months • Provide written informed consent • Negative pregnancy test and agree to use effective form of contraception **Exclusion Criteria:** • Received prior TKI within 7 days to first dose of ponatinib • Received other listed therapies in time frame prior to starting study drug • Not recovered from adverse events from prior treatments. • Taking medications associated with torsades de pointes • Previously treated with ponatinib • Underwent stem cell transplant <60 days prior to receiving first dose of ponatinib • On-going graft versus-host disease • Require concurrent treatment with immunosuppressive agents • Active Central Nervous System disease • Significant or active cardiovascular disease • Significant bleeding disorder • History of pancreatitis or alcohol abuse • Have uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL) • Major surgery 14 days prior to first dose • Have ongoing or active infection • Have malabsorption syndrome or other gastrointestinal illness that could affect absorption of ponatinib	Ponatinib 45 mg tablet taken orally once daily	**Primary Outcomes:** • Major cytogenetic response (MCyR) for chronic phase CML patients • Major Hematologic Response (MaHR) for accelerated and blast phase CML patients and Ph+ ALL patients **Secondary Outcomes:** **For chronic phase patients:** • Hematologic responses: CHR • Cytogenetic responses: confirmed MCyR • Molecular responses: major molecular response MMR **For accelerated and blast phase CML and Ph+ ALL patients:** • Cytogenetic responses: CCyR, PCyR, confirmed MCyR; and • Molecular responses: MMR. **For all patients:** • Time to response, duration of response, progression free survival, and overall survival, safety and tolerability.

September 2010

October 2020

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
	• Diagnosed with another primary malignancy in the past 3 years • Pregnant or lactating • Suffer from any other condition or illness that would compromise safety		
[Abbreviations] ALL = acute lymphoblastic leukemia; CML = chronic myeloid leukemia; CCyR = Complete cytogenetic response; ECOG = Eastern Cooperative Oncology Group; MaHR = Major hematologic response; MCyR = Major cytogenetic response; ms = milliseconds; PCyR = Partial cytogenetic response; Ph+ = Philadelphia chromosome positive; QTcF = Fredericia's formula; TKI = tyrosine kinase inhibitor			

a) Trials

One open label, phase 2, single arm, ongoing study was found for this review. Characteristics of the study's design can be found in Table 5. The study included CML or PH+ ALL patients who were resistant or intolerant to imatinib, dasatinib or nilotinib including patients who developed the T3151 mutation after TKI therapy.[2]

The primary outcome in the study for chronic phase (CP) patients was a major cytogenic response (MCyR) at any time within the first 12 months. A MCyR is defined as a complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR).[10] CP patients who start the study already in PCyR must achieve CCyR in order to be considered as achieving a MCyR.[10] If patients do not respond by 12 months they will be categorized as non-responders.

The primary outcome for patients in the accelerated phase (AP) of CML at the start of the study is major hematologic response (MaHR). This is defined as a complete hematologic response (CHR) or no evidence of leukemia (NEL). The MaHR will be confirmed by a peripheral blood complete blood count (CBC) and differential no earlier than 28 days. If patients do not respond by 6 months then they will be categorized as non-responders.[10]

The primary outcome for patients in blast phase (BP) of CML or a Philadelphia chromosome positive (Ph+) at the time of study entry is a MaHR consisting of CHR or NEL. A peripheral CBC and differential will confirm this no earlier than 28 days.[10]

The secondary end point for CP CML patients is a CHR confirmed in a time period greater than 28 days after starting treatment.[2] Secondary outcomes for patients in accelerated and blast phase CML and Ph+ ALL are a CCyR, PCyR, or MCyR. Secondary outcomes for all groups of patients are: major molecular response, time to response, duration of response, progression free survival, overall survival and safety.[2]

Table 6: Inclusion Criteria

To be labeled as dasatinib or nilotinib resistant, CP patients must have met one of the following criteria: [10]	• No cytogenetic response (>95% Ph+) or failure to achieve CHR three months after initiation of therapy, • Less than a minor cytogenetic response (>65% Ph+) six months after the initiation of therapy, less than a PCyR (>35% Ph+) 12 months after initiation of therapy, • The development of new BCR-ABL kinase domain mutations in the absence of CCyR at any time after the initiation of therapy, • The development of new clonal evolution in the absence of CCyR at any time afte the initiation of therapy, • The loss of any cytogenetic response [from complete (0%), partial (1% to 35%), minor (36% to 65%), minimal (66% to 95%) to a response at least 1 grade worse] confirmed in at least 2 consecutive analyses separated by at least 4 weeks at any time after the initiation of therapy, • Progression of disease (to AP or BP) at any time after the initiation of therapy.
To be labeled as dasatinib or nilotinib resistant, AP patients must have met one of the following criteria: [10]	• Failure to achieve a MaHR three months after the initiation of therapy, • The loss of a MaHR confirmed in at least 2 consecutive analyses separated by at least 4 weeks at any time after the initiation of therapy, • The development of new BCR-ABL kinase domain mutations in the absence of a MaHR at any time after the initiation of therapy.
To be labeled as dasatinib or nilotinib resistant, BP patients must have met one of the following criteria: [10]	• Failure to achieve a MaHR one months after the initiation of therapy, • The loss of a MaHR confirmed in at least 2 consecutive analyses separated by at least 1 week at any time after the initiation of therapy, • The development of new BCR-ABL kinase domain mutations in the absence of a MaHR at any time after the initiation of therapy.
Philadelphia chromosome positive patients were labeled as resistant to dasatinib or nilotinib if: [12]	• They failed to achieve either a MaHR by 1 month, • Had the loss of MaHR at any time, • Developed a kinase domain mutation in the absence of a MaHR
Non-hematologic intolerance to dasatinib or nilotinib for all cohorts of patients is defined as: [10]	• Patients with grade 3 or 4 toxicity while on therapy, or with persistent grade 2 toxicity, unresponsive to optimal management including dose adjustments (unless dose reduction is not considered in the best interest of the patient if response is already suboptimal) in the absence of a CCyR for CP–CML patients or MaHR for AP-CML, BP-CML or Ph+ ALL patients.
Hematologic intolerance was define as: [10]	• Patients with grade 3 or 4 toxicity (absolute neutrophil count [ANC] or platelets) while on therapy that is recurrent after dose reduction to the lowest doses recommended by manufacturer (80 mg QD for dasatinib; 400 mg QD for nilotinib) in the absence of a CCyR for CP-CML patients or MaHR for AP-CML, BP-CML or Ph+ ALL patients.
CML and ALL patients were eligible for the study if they had the T315I mutation, specifically: [10]	• Patients with T315I mutation after any TKI need not have been treated with dasatinib or nilotinib; • Patients with T315I in CP must have less than a CCyR (>0% Ph+); • Patients with T315I in AP, BP, or Ph+ ALL must have less than a MaHR; • Patients with any history of T315I mutation will be eligible for study participation. However, only those patients who carry a T315I mutation that is detected by direct sequencing in a pre-treatment blood sample using the study's central laboratory will be analyzed in the T315I subset.

Patients in CP-CML had response assessments that were completed every 3 months. Patients with AP-CML, BP-CML, or Ph+ ALL had response assessments completed at the end of cycle 1 (each cycle was 28 days), cycle 2, and every 2 months thereafter.[2]

In the PACE study, the planned sample sizes of the cohorts were estimated to rule out pre-specified null response rates with the use of 95% confidence intervals.[2] The rates of major cytogenetic response, major hematologic response, complete hematologic response, and major molecular response were calculated using two-sided, exact 95% confidence intervals. The Kaplan-Meier method was used to estimate the duration of response, progression-free survival, and overall survival. Subgroup comparisons used Fisher's exact test.[2] Power was calculated based on effect size and ranged from 78% to ≥98%.[10]

b) Populations

A total of N=449 patients were included in this study. There were 270 chronic phase CML patients, 85 accelerated phase CML patients, 62 blast phase CML patients and 32 PH+ ALL patients. The study baseline patient demographics can be seen in Table 7.

Table 7: Patient characteristics[2]

	CP CML N=270 (%)	AP CML N=85 (%)	BP CML N=62 (%)	PH+ ALL N=32 (%)	Total N=449 (%)
Age- median (range) years	60 (18-94)	60 (23-82)	53 (18-74)	62 (20-80)	59 (18-94)
Age- ≥ 65 years, n	101 (37)	27 (32)	14 (23)	13 (41)	155 (35)
ECOG PS, n					
0	189 (70)	47 (55)	20 (32)	11 (34)	267 (60)
1	77 (29)	31 (37)	22 (35)	17 (53)	147 (33)
2	4 (1)	7 (8)	19 (31)	4 (13)	34 (8)
Prior TKI therapy*					
≥2 drugs	252 (93)	80 (94)	59 (95)	26 (81)	417 (93)
≥3 drugs	161 (60)	51 (60)	37 (60)	13 (41)	262 (58)
Number of prior approved TKIs					
1	19 (7)	5 (6)	3 (5)	6 (19)	33 (7)
2	98 (36)	33 (39)	22 (35)	14 (44)	167 (37)
3	141 (52)	44 (52)	34 (55)	12 (38)	231 (51)
4	12 (4)	3 (4)	3 (5)	0	18 (4)
Median time (range) on prior TKI* years	5.4 (0.4-13.3)	5.1 (0.3-12.1)	2.0 (0.1-11.6)	1.2 (0.1-8.2)	4.6 (0.1-13.3)
Prior approved TKI					
Imatinib	261 (97)	84 (99)	58 (94)	27 (84)	430 (96)
Dasatinib	217 (80)	70 (82)	58 (94)	30 (94)	375 (84)
Nilotinib	184 (68)	56 (66)	41 (66)	13 (41)	294 (65)
Bosutinib	24 (9)	5 (6)	4 (6)	0	33 (7)
Resistant or unacceptable side effects to dasatinib or nilotinib at any time § ¶					
Resistance ‖	214 (84)	74 (92)	59 (97)	27 (90)	374 (88)
Unacceptable side effects only †	40 (16)	6 (8)	2 (3)	2 (7)	50 (12)
Not specified	2 (1)	0	0	1 (3)	3 (1)
Cytogenetic status at enrolment,					
Complete cytogenetic response **	0	1 (1)	3 (5)	2 (6)	6 (1)
Partial cytogenetic response §§	53 (20)	1 (1)	3 (5)	8 (25)	65 (14)

	CP CML N=270 (%)	AP CML N=85 (%)	BP CML N=62 (%)	PH+ ALL N=32 (%)	Total N=449 (%)
Less than partial cytogenetic response	215 (80)	80 (94)	51 (82)	20 (62)	366 (82)
Missing or < 20 metaphases examined	2 (1)	3 (4)	5 (8)	2 (6)	12 (3)
Best response to most recent regimen containing dasatinib or nilotinib ¶					
MaHR or better¶¶	NA	17 (21)	9 (15)	13 (43)	NR
MCyR or better||	66 (26)	12 (15)	7 (11)	8 (27)	NR
MMR	8 (3)	2 (2)	1 (2)	5 (17)	NR

*Includes imatinib, nilotinib, dasatinib and bosutinib and investigational TKIs. Previous investigational TKIs received by at least 1% of patients are radotinib (2%). Bafetinib (2%), DCC-2036 (2%) and XL228 (2%)
§ To be eligible for enrollment patients with unacceptable side effects had to have active disease
¶ Percentages were calculated according to the number of patients who received previous dasatinib, nilotinib: 256 with CP-CML, 80 with AP-CML, 61 with BP-CML and 30 with PH+ ALL
| Patients with resistance to one TKI and unacceptable side effects to another were classified as having resistance
† Patients may have had resistance to or unacceptable side effects of TKIs other than dasatinib or nilotinib.
** Patients who had a CCyR at study entry were classified as not having a cytogenetic response during study
§§ Patients who had a partial cytogenetic response at study entry and then had a complete cytogenetic response were considered as having a MCyR
¶¶ This category includes a MaHR, PCyR, CCyR and MMR
|| This category includes a PCyR, CCyR and MMR

c) Interventions

Ponatinib was administered orally in a 45 mg tablet taken once daily. Dose modifications were not necessary for grade 1 and 2 adverse events (AEs) except for pancreatitis and QTcF prolongation. However, if the AEs were unmanageable patients could have a delay in their dose. Grade 3 and 4 AEs were managed by a dose delay or a dose modification.[10] The median duration of treatment was 12.8 months (range 1 day to >24.8 months). The median relative dose intensity was 0.84.[2] Fifty five percent of patients had a dose reduction, with the median time to dose reduction at 2.3 months (range 1 day to 19 months). Seventy three percent of patients had at least one dose interruption.[11] The manufacturer of Ponatinib issued a dose reduction recommendation on October 10, 2013. For CP-CML patients who have achieved a MCyR, the dose should be reduced to 15 mg/day, for CP-CML patients who have not already achieved MCyR the dose should be reduced to 30 mg/day and for advanced-phase patients the dose should be reduced to 30 mg/day.[8] As of April 7, 2014, 44% of patients had their dose reduced and 36% were maintained on their prior dose. Only a few patients did not have their doses reduced.[9]

d) Patient Disposition

Patients were enrolled in the study from September 2010 to October 2011. There were 449 patients in total: 203 with CP-CML; 64 with CP-CML and the T3151 mutation; 65 with AP-CML; 18 with AP-CML and the T3151 mutation; 48 with BP-CML or Ph + ALL; and 46 with CP-CML or Ph+ ALL and the T3151 mutation. There were 5 patients (3 who had CP-CML and 2 with CP-CML) that had a history of the T315I mutation. These patients were enrolled and treated but were not assigned to a cohort since the T315I mutation was not established at baseline and the patients had not received nilotinib or dasatinib. Therefore, these patients were excluded from the efficacy population.[2]

At the time of the November 9, 2012 analysis which was used for the main PACE publication, the median follow-up was 15 months (range, <1 to 25), and 222 patients (49%) were still receiving treatment. The minimum follow-up was 12 months. The most common causes for study discontinuation were: progressive disease (7% of patients with chronic-phase CML and 37% of patients with accelerated and blast phase); adverse events (13% of patients with chronic-phase CML and 12% of patients with accelerated and blast phase).[2]

At the January 6, 2014 analysis, the median follow-up was 27.9 months (range 0.1-39.5 months) and 38% of patients (50% were CP-CML) were still ongoing in the study.[9] The most common reasons for study discontinuation were progressive disease (21%) and adverse events (15%).[9]

e) Limitations/Sources of Bias

This study was a single arm open label phase 2 study and therefore there was no comparator. Since there is no comparative evidence for ponatinib, the efficacy of ponatinib versus current treatments is uncertain. In addition, there were no independent assessments in this study, which would have helped to minimize bias in the reporting of results. ARIAD Pharmaceuticals, Inc. was the sponsor of the study and the main PACE publication had help from a medical writer funded by ARIAD Pharmaceuticals, Inc.[2]

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Efficacy outcomes for Chronic Phase CML

The primary outcome for the PACE study was major cytogenetic response (MCyR) by 12 months in chronic phase CML (CP-CML) patients. The MCyR was 56% (95% confidence interval [CI], 50 to 62). This includes a response of 51% in patients with resistance to or unacceptable side effects of dasatinib or nilotinib and 70% in patients with the T315I mutation.[2] In patients who had a response to treatment, the median time to a MCyR was 2.8 months (range, 1.6 to 11.3), and the duration ranged from 1 day to over 19.4 months since the median was not reached. The estimated rate of a sustained response in patients who had a MCyR of at least 12 months was 91% (95% CI, 85 to 95).[2]Data as of January 6, 2014 shows that a MCyR was seen in 59% of CP-CML patients. This includes a response of 55% in patients with resistance to or unacceptable side effects of dasatinib or nilotinib and 72% for patients with the T315I mutation.[9]

A complete cytogenetic response (CCyR) was seen in 46% of patients with CP-CML. This included 40% of patients with resistance to or unacceptable side effects of dasatinib or nilotinib and 66% of patients with the T315I mutation.[2]

Data as of January 6, 2014 shows a CCyR was seen in 53% of patients with CP-CML. This included 48% of patients with resistance to or unacceptable side effects of dasatinib or nilotinib and 70% of patients with the T315I mutation.[9]

A major molecular response (MMR) was seen in 34% of patients. This included 27% of patients with resistance to or unacceptable side effects of dasatinib or nilotinib and in 56% of patients with the T315I mutation.[2] Moreover, a deeper molecular response "(a transcript ratio of BCR-ABL to ABL of 0.0032% or less [with the ratio expressed as a percentage on the International Scale], referred to as a molecular response 4.5)"[2] was seen in 15% of patients. This included 12% of patients with resistance to or unacceptable[2] side effects of dasatinib or nilotinib and 23% of patients with the T315I mutation.[2] Data as of January 6, 2014 shows

that a MMR was seen in 38% of patients. This included 32% of patients with resistance to or unacceptable side effects of dasatinib or nilotinib and in 58% of patients with the T315I mutation.[9] A deeper molecular response was seen in 20% of patients. This included 16% of patients with resistance to or unacceptable side effects of dasatinib or nilotinib and 33% of patients with the T315I mutation.[9]

Table 8: Hematologic, Cytogenetic and Molecular responses for Chronic Phase CML patients

	Chronic phase CML 12 months[10]			Chronic phase CML January 2014 update[9]		
Chronic phase CML	R/I N=203 (%)	T3151 N=64 (%)	Total N=267 (%)	R/I N=203 (%)	T3151 N=64 (%)	Total N=267 (%)
CHR *	192 (95)	58 (91)	(94)	NR	NR	NR
MaHR§	NA	NA	NA	NA	NA	NA
Any CyR||	128(63)	52 (81)	NR	NR	NR	NR
MCyR	104 (51)**	45 (70)**	(56)	112 (55)	46 (72)	158 (59)
CCyR	82 (40)	42 (66)	(46)	97 (48)	45 (70)	142 (53)
PCyR	22 (11)	3 (5)	NR	NR	NR	NR
MMR§§	55 (27)	36 (56)	(34)	65 (32)	37 (58)	102 (38)
MR^4	34 (17)	22 (34)	NR	43 (21)	25 (39)	68 (26)
$MR^{4.5}$	24 (12)	15 (23)	NR	32 (16)	21 (33)	53 (20)
Median time (range) to MCyR	2.8 (1.8-11.3)	2.8 (1.6-10.9)	NR	NR	NR	NR

Abbreviations: CCyR=complete cytogenetic response; CHR=complete hematologic response; MaHR=major hematologic response; MCyR (CCyR + PCyR)=major cytogenetic response; MMR =major molecular response = MR3 only + MR4 only +MR4.5; MR^4 Either detectable transcripts ≤0.01% BCR-ABL[IS] or undetectable BCR-ABL transcripts in cDNA with ≥10,000 ABL transcripts, in peripheral blood as measured by RT-qPCR; $MR^{4.5}$ Either detectable transcripts ≤0.0032% BCR-ABL[IS] or undetectable BCR-ABL transcripts in cDNA with ≥32,000 ABL transcripts, in peripheral blood as measured by RT-qPCR; NA=not applicable; NR= not reported; PCyR=partial cytogenetic response; R/I=resistant or intolerant

* The CHR rate includes patients maintaining or achieving CHR on study. CP-CML patients with CHR at baseline: R/I N=89, T315I N=24.

§Patients missing baseline bone marrow blasts and those entering the study in MaHR are counted as non-responders in the analysis of MaHR; 14 AP-CML patients entered the study in MaHR, and 1 AP-CML patient had missing baseline bone marrow blasts.

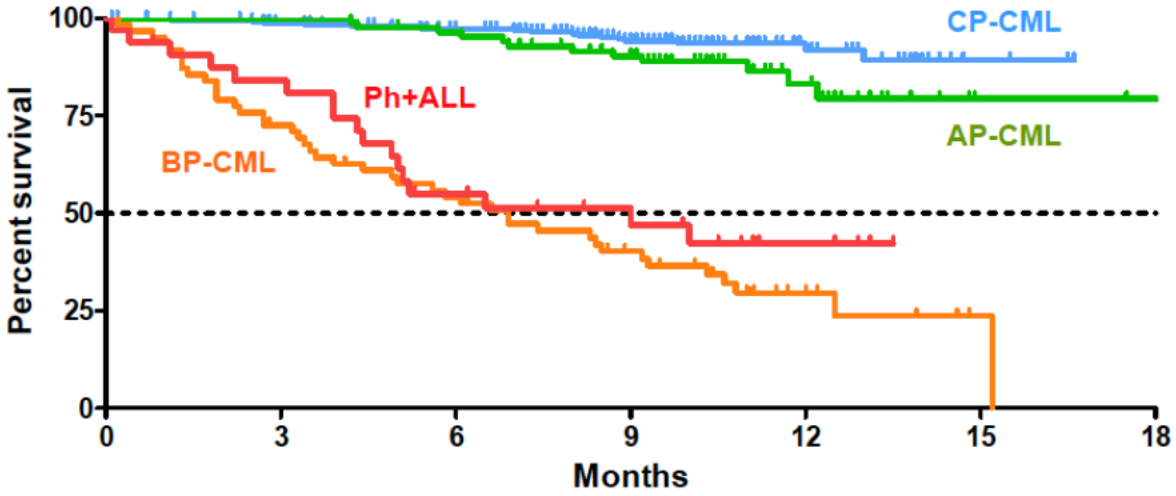
||Any CyR=CCyR + PCyR + minor CyR + minimal CyR

**CP-CML patients who entered the study in PCyR had to achieve CCyR to meet the criteria for MCyR. In the R/I and T315I cohorts, 39 and 13 patients entered the study in PCyR, respectively. The MCyR rates for these patients were 64% and 92% for R/I and T315I, respectively, and 71% overall.

§§Molecular responses were measured in peripheral blood.

In patients who had CP-CML the estimated rate of progression-free survival (PFS) was 80% and the estimated rate of overall survival (OS) was 94%.[2] The median OS was not evaluable and the 12 month overall survival rate was 94% as seen in Figure 1.[11] Data as of January 6, 2014, shows the estimated rate of MCyR duration was 87%. The estimated rate of PFS was 67% and the estimated rate of OS was 86%.[9] In addition, there were three patients with CP-CML who had progressed to AP-CML or BP-CML and there were two additional patients with a history for this state, who developed AP-CML.[2]

Figure 1: Overall survival for the PACE study from the April 27, 2012 data cut off[11]



In the CP-CML group, there were several pre-specified subgroup analyses that were done to demonstrate the effect of clinical factors on response rates. In patients who had taken fewer previous tyrosine kinase inhibitors (Table 9), were younger, and had a shorter interval between diagnosis and enrolment in the study, higher response rates were observed.[2] Even through higher response rates were seen in the T315I group compared to those in the resistance to or unacceptable side effects of dasatinib or nilotinib groups, a post hoc multivariate analysis demonstrated that T315I was not a significant predictor of a MCyR. There were other factors in the chronic phase T315I mutation group such as higher dose intensity and younger age that explained the higher response rates.[2]

Table 9: Response according to previous therapy in chronic phase CML patients[10]

Variable	All patients		Patients with resistance or unacceptable side effects		T3151 mutation	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
One previously approved TKI*						
MCyR§	19†	79(54-94)	4	50 (7-93)	12	83 (52-98)
CCyR		74 (49-91)		50 (7-93)		75 (43-95)
MMR		47 (24-71)		0		67 (35-90)
Two previously approved TKIs*						
MCyR§	98	67 (57-76)	68	63 (51-75)	30	77 (58-90)
CCyR		56 (46-66)		49 (36-61)		73 (54-88)
MMR		36 (26-46)		28 (18-40)		53 (34-72)
Three previously approved TKIs*						
MCyR§	141	45 (37-54)	119	44 (35-53)	22	55(32-76)
CCyR		39 (31-48)		37 (28-46)		50(28-72)
MMR		33 (26-42)		29 (21-38)		55 (32-76)
Four previously approved TKIs*						
MCyR§	12	58 (28-85)	12	58 (28-85)		
CCyR		25 (5-57)		25 (5-57)		
MMR		8 (0.2-38)		8 (0.2-38)		

* Patients may have received other non-approved TKIs
§ A major cytogenetic response consists of a partial cytogenetic response plus a complete cytogenetic response
† This category includes 3 patients who were not assigned to a cohort. They were T3151 negative at baseline and had not previously received dasatinib or nilotinib, but they have received imatinib.

Accelerated-Phase CML

In patients who had accelerated phase CML (AP-CML) the major hematologic response (MaHR) by 6 months was 55% (95% CI, 44 to 66). This was the primary endpoint for the AP-CML group. At the January 6, 2014 update, 61% of AP-CML patients had a MaHR, 62% in the resistant or intolerant group and 61% in the T315I group.[9] In the 2012 analysis, a MCyR was visible in 39% of patients in this group. Of them, 24% had a CCyR, and 16% had a MMR. The median time to a MaHR was 3 weeks (range, 2 to 25 weeks), and it lasted from 1 month to over 21 months, the median being 12 months. A sustained response for 12 months was estimated to be 48%.[2] "The median time to a major cytogenetic response was 3.7 months (range, 0.8 to 9.7), and the estimated rate of a sustained response of at least 12 months was 73%".[2] The results can be seen in Table 10.

At 12 months, in patients who had AP-CML the estimated rate of PFS was 55% (median 18 months) and the estimated rate of OS was 44%.[2] The median OS was not evaluable and the 12 month OS rate was 86%.[11] This can be seen in Figure 2. The estimated two-year rate of PFS was 39% and the estimated rate of OS was 72% at the January 6, 2014 analyses.[9]

Table 10: Hematologic, Cytogenetic and Molecular responses for Accelerated Phase CML patients[10]

	R/I N=65 (%)	T3151 N=18 (%)	Total N=83(%)
CHR	NA	NA	NA
MaHR[§]	37 (57)	9 (50)	(55)
Any CyR[‖]	34 (52)	12 (67)	NR
MCyR	22 (34)	10 (56)	(39)
CCyR	14 (22)	6 (33)	(24)
PCyR	8 (12)	4 (22)	NR
MMR[§§]	9 (14)	4 (22)	(16)
MR^4	4 (6)	0	NR
$MR^{4,5}$	4 (6)	0	NR
Median time (range) to MCyR (CP) or MaHR (AP, BP, Ph+ ALL) for all responders, months	0.7 (0.4-3.7)	0.6 (0.5-5.8)	NR

CHR=complete hematologic response; NA=not applicable; NR= not reported; MaHR=major hematologic response; MCyR (CCyR + PCyR)=major cytogenetic response; CCyR=complete cytogenetic response; PCyR=partial cytogenetic response; MMR =major molecular response = MR3 only + MR4 only +MR4.5; R/I=resistant or intolerant
§Patients missing baseline bone marrow blasts and those entering the study in MaHR are counted as non-responders in the analysis of MaHR; 14 AP-CML patients entered the study in MaHR, and 1 AP-CML patient had missing baseline bone marrow blasts.
‖Any CyR=CCyR + PCyR + minor CyR + minimal CyR
§§Molecular responses were measured in peripheral blood.

A similar scenario that was seen in CP-CML was seen in the AP-CML group as patients who received fewer previous TKIs showed higher response rates.[2] This can be seen in Table 11.

Table 11: Response by prior therapy for accelerated phase CML[10]

Response by number of prior TKIs*	Total	R/I	T3151
One previously approved TKI	N=5	N=1	N=3
MaHR	80%	100%	67%
MCyR	100%	100%	100%
CCyR	80%	100%	67%
MMR	40%	0	33%
Two previously approved TKIs	N=33	N=26	N=6
MaHR	61%	65%	33%
MCyR	42%	35%	67%
CCyR	30%	23%	50%
MMR	24%	19%	33%
Three previously approved TKIs	N=44	N=35	N=9
MaHR	50%	49%	56%
MCyR	30%	29%	33%
CCyR	16%	17%	11%
MMR	11%	11%	11%
Four previously approved TKIs	N=3	N=3	N=0
MaHR	67%	67%	-
MCyR	67%	67%	-
CCyR	33%	33%	-
MMR	0%	0%	-

* Patients may have received other anti-cancer agents or investigational TKIs. This table includes two patients who were unassigned to a cohort (T3151- negative at baseline and did not receive prior dasatinib or nilotinib)

Blast-Phase CML and Ph-Positive ALL

In patients who had blast phase CML (BP-CML), the MaHR by 6 months was 31% (95% CI, 20 to 44). This was the primary endpoint for the BP-CML group. At the January 6 2014 analysis, the MaHR was still 31% for the whole group and 32% in the resistant and intolerant group and 29% in the T315I mutation group.[9] In the 2012 analysis, a MCyR was visible in 23% of patients in this group and a CCyR was seen in 18% of patients. In BP-CML patients who had a response, the median time to a MCyR was 1.9 months (range, 0.9 to 5.5). A sustained response for 12 months was estimated to be 66%.[2]

In patients with Ph-positive ALL (Ph+ ALL), a MaHR was seen in 41% (95% CI, 24 to 59) of patients.[2] At the January 6, 2014 analysis, the MaHR was still 41% for the whole group, 50% in the resistant and intolerant group and 36% in the T315I mutation group.[9]In the 2012 analysis, a MCyR was seen in 47% of patients and a CCyR was seen in 38%.[2] The median time to a MaHR in patients with BP CML was 4.1 weeks (range, 1.7-16.1 weeks), and it lasted from 1 month to over 20 months, the median being 5 months. A sustained response for 12 months was estimated to be 42%.[2] In patients with Ph+ ALL, the median time to a MaHR was 2.9 weeks (range, 1.6 to 24) and it lasted for 2 to over 14 months, with the median being 3 months. A sustained response for 12 months was estimated to be 8%. In Ph+ ALL patients, a MCyR was seen in a median time of 1 month (range, 0.9 to 3.7), and this lasted for 3.7 months. A sustained response for 12 months was estimated to be 32%. %.[2] These results can be seen in Table 12.

At 12 months, in patients who had BP-CML the rate of PFS was 19% (median 4 months). The median OS was 6.9 months (95% CI, 3.9-9.3) and the 12 month overall survival was 31%.[11] This can be seen in Figure 2. The estimated 2-year PFS rate at the January 6, 2014 data analysis was 18% for both the BP-CML and Ph+ ALL groups.[9]

At 12 months, in patients who had Ph+ ALL the rate of PFS was 7% (median 4 months).[2] The median OS was 9.0 months (95% CI, 4.4 to not evaluable) and the 12 month OS rate was 47%.[11] this can be seen in figure 2. The estimated 2 year PFS at the January 6, 2014 data analysis was 11% [9] and the estimated rate of OS was slightly higher than PFS for the Ph+ group.

Table 12: Hematologic, Cytogenetic and Molecular responses 12 months for Blast Phase CML and Ph+ ALL

	Blast phase CML[2]			Ph+ ALL[2]			Blast phase CML/ Ph+ ALL combined[10]	
	R/I N=38 (%)	T3151 N=24 (%)	Total N=62 (%)	R/I N=10 (%)	T3151 N=22(%)	Total N=32 (%)	R/I N=48 (%)	T3151 N=46 (%)
CHR *	NA	NA	NA	NA	NA	NA	NA	NA
MaHR§	(32)	(29)	(31)	(50)	(36)	(41)	17 (35) ¶	15 (33) †
Any CyR||	NR	NR	NR	NR	NR	NR	19 (40)	20 (43)
MCyR	(18)	(29)	(23)	(60)	(41)	(47)	13 (27)	16 (35)
CCyR	(16)	(21)	(18)	(50)	(32)	(38)	11 (23)	12 (26)
PCyR	NR	NR	NR	NR	NR	NR	2 (4)	4 (9)
Median time (range) to MCyR (CP) or MaHR (AP, BP, Ph+ ALL) for all responders, months	NR	NR	NR	NR	NR	NR	0.9 (0.5-5.5)	0.8 (0.4-1.9)

CHR=complete hematologic response; NA=not applicable; NR = not reported; MaHR=major hematologic response; MCyR (CCyR + PCyR)=major cytogenetic response; CCyR=complete cytogenetic response; PCyR=partial cytogenetic response; R/I=resistant or intolerant

§Patients missing baseline bone marrow blasts and those entering the study in MaHR are counted as non-responders in the analysis of MaHR; 14 AP-CML patients entered the study in MaHR, and 1 AP-CML patient had missing baseline bone marrow blasts.

¶The MaHR rate for R/I BP-CML patients was 12/38 (32%); the MaHR rate for R/I Ph+ ALL patients was 5/10 (50%).

†The MaHR rate for T315I BP-CML patients was 7/24 (29%); the MaHR rate for T315I Ph+ ALL patients was 8/22 (36%).

||Any CyR=CCyR + PCyR + minor CyR + minimal CyR

For all cohorts a dose reduction was recommended by the manufacturer on October 10, 2013.[9] According to an analysis of the dose intensity-safety relationship in the PACE study, it was determined that "after adjusting for covariates, the overall dose intensity is significantly associated with an increased risk of vascular occlusion, with an odds ratio of approximately 1.6 for each 15 mg increase."[12] Therefore, a reduction in dose is predicted to reduce the risk of vascular occlusive events. Nevertheless, the analysis proposed that a "carry over" effect in patients with high doses may be in place and that it will take several months before a dose reduction becomes visible in risk reduction.[12] Table 13 shows the maintenance of response in relation to dose decreases. Efficacy was not lost on lower doses.

Table 13: Maintenance of response in CP-CML patients who achieved MCyR or MMR at 45mg dose (April 7 2015) [12]

	Achieved MCyR at 45 mg (N=87)		Achieved MMR at 45 mg (N=63)	
	Number of patients	**Maintained MCyR**	**Number of patients**	**Maintained MMR**
No dose reduction	23	18(78%)	18	11(61%)
Dose reduction to 30mg only	25	24 (96%)	13	11 (85%)
≥ 90 day reduction at 30mg	21	20 (95%)	8	9 (89%)
≥ 180 day reduction at 30mg	11	10 (89%)	5	4 (80%)
≥ 360 day reduction at 30mg	5	4 (80%)	2	1 (50%)
Any dose reduction to 15mg	39	39 (100%)	32	30 (94%)
≥ 90 day reduction at 15mg	32	32 (100%)	27	26 (96%)
≥ 180 day reduction at 15mg	10	10(100%)	6	6 (100%)
≥ 360 day reduction at 15mg	6	6 (100%)	3	3 (100%)

Mutation status

The most common BCR-ABL mutations in the study population were T315I (29%), F317L (8%), E255K (4%), F359V (4%), G250E (3%), E255V (2%), Y253H (2%) and V299L (2%).[11] Higher response rates were seen in patients with CP-CML regardless of mutation status.[2] At the time of the November 2012 analysis, there was no single BCR-ABL mutation conferring resistance to ponatinib in CP-CML patients.[2] In AP-CML patients, high response rates were seen in patients with BCR-ABL mutations, including those with the T315I mutation, and among those without BCR-ABL mutations. However no single mutation conferring resistance to ponatinib was observed. In BP CML and Ph+ ALL patients, once again, no single mutation was related with resistance to ponatinib. Nevertheless, the attainment of greater than two mutations in the same BCR-ABL allele was occasionally seen in patients with an unsustained major hematologic response.[2]

Quality of Life

Quality of Life was not assessed as part of this trial as a secondary outcome.[74] This was confirmed with the manufacturer.

Harms Outcomes

Adverse Events

From the Cortes 2013 paper, the most common non-hematologic grade 1 and 2 adverse events (AEs) were rash (34%), dry skin (32%), and abdominal pain (22%). The most common hematologic AEs were thrombocytopenia (in 37% of patients), neutropenia (in 19%), and anemia (in 13%).[2] The January 6, 2014 update showed that the following AEs occurred in more than 20% of patients: thrombocytopenia 44%; abdominal pain 42%; rash 41%; constipation 37%; headache 37%; dry skin 35%; fatigue 29%; pyrexia 29%; nausea 28%; arthralgia 28%; hypertension 26%; neutropenia 25%;anemia 22%; myalgia 21%; diarrhea 21%; vomiting 21%; increased lipase 21%.[9] The frequency of thrombocytopenia, neutropenia and anemia occurred more frequently in patients with BP-CML and Ph+ ALL followed by AP-CML, and then CP-CML.[11] For patients without and with arterial thrombotic events, the OS estimate at 2 years was 86% for both groups. The MCyR was 69% in patients with a serious arterial thrombotic event and 53% in patients without.[9] A list of cumulative adverse events through to February 2015 can be seen in table 14.

Table 14: Cumulative adverse events through February 2015[75]

Event*	Chronic-Phase CML (N = 270)		Accelerated-Phase CML (N = 85)		Blast-Phase CML (N = 62)		Ph-Positive ALL (N = 32)	
	Any Grade	*Grade 3 or 4*	*Any Grade*	*Grade 3 or 4*	*Any Grade*	*Grade 3 or 4*	*Any Grade*	*Grade 3 or 4*
Number of patients (percent)								
Rash†	112 (42)	10 (4)	29 (34)	3 (4)	15 (24)	2 (3)	6 (19)	1 (3)
Dry skin	109 (40)	9 (3)	21 (25)	1 (1)	11 (18)	1 (2)	7 (22)	0
Abdominal pain	79 (29)	20 (7)	15 (18)	4 (5)	6 (10)	1 (2)	6 (19)	2 (6)
Headache	68 (25)	7 (3)	11 (13)	0	7 (11)	1 (2)	4 (13)	0
Lipase increased	66 (24)	29 (11)	13 (15)	11 (13)	8 (13)	7 (11)	3 (9)	2 (6)
Fatigue	54 (20)	4 (2)	17 (20)	1 (1)	7 (11)	2 (3)	3 (9)	0
Constipation	55 (20)	5 (2)	12 (14)	1 (1)	3 (5)	0	6 (19)	1 (3)
Myalgia	48 (18)	3 (1)	16 (19)	0	8 (13)	0	2 (6)	0
Arthralgia	49 (18)	6 (2)	16 (19)	2 (2)	8 (13)	0	1 (3)	0
Nausea	42 (16)	0	10 (12)	0	13 (21)	0	1 (3)	0
Alanine aminotransferase increased	40 (15)	11 (4)	14 (17)	2 (2)	6 (10)	2 (3)	2 (6)	1 (3)
Pancreatitis	20 (7)	18 (7)	7 (8)	5 (6)	3 (5)	2 (3)	0	0
Hypertension	53 (20)	16 (6)	11 (13)	5 (6)	2 (3)	2 (3)	1 (3)	1 (3)
Aspartate aminotransferase increased	30 (11)	6 (2)	12 (14)	3 (4)	5 (8)	1 (2)	2 (6)	1 (3)
(blood) Amylase increased	19 (7)	8 (3)	6 (7)	3 (4)	3 (5)	2 (3)	1 (3)	0
Gamma-glutamyl transferase increased	17 (6)	7 (3)	8 (9)	3 (4)	2 (3)	2 (3)	0	0
Dyspnoea	21 (8)	6 (2)	7 (8)	0	4 (7)	1 (2)	0	0
Cardiac failure	3 (1)	2 (1)	3 (4)	2 (2)	2 (3)	2 (3)	0	0
Hematologic events								
Thrombocytopenia	111 (41)	86 (32)	38 (45)	30 (35)	17 (27)	16 (26)	3 (9)	2 (6)
Neutropenia	47 (17)	40 (15)	25 (29)	25 (29)	14 (23)	11 (18)	4 (13)	4 (13)
Anemia	30 (11)	16 (6)	18 (21)	11 (13)	14 (23)	13 (21)	5 (16)	4 (13)
Decreased white-cell count	11 (4)	7 (3)	7 (8)	5 (6)	0	0	1 (3)	1 (3)
Pancytopenia	2 (<1)	2 (1)	3 (4)	2 (2)	3 (5)	3 (5)	0	0
Febrile neutropenia	1 (<1)	1 (<1)	2 (2)	2 (2)	2 (3)	2 (3)	2 (6)	2 (6)

Data extraction date: 02 FEB 2015.
* Treatment-related adverse events were defined as events that the site investigators deemed to have a possible, probable, or definite relationship to ponatinib. Listed are the treatment-related adverse events that were reported in at least 10% of the patients, along with any incidence of grade 3 or 4 events in more than 1% of the total study population.
† Rash includes erythematous and papular rash.

Note: Patients may have more than 1 AE per Preferred Term. At each level of patient summarization, a patient was counted once for the most severe event. AEs were classified according to MedDRA (Medical Dictionary for Regulatory Activities)v 16.0 and graded according to CTCAE v 4.0. Clinically synonymous terms have been recoded to single MedDRA preferred terms.

Abbreviations: ALL = Acute lymphoblastic leukemia, AP = accelerated phase, BP = blast phase, CML = Chronic myeloid leukemia, CP = chronic phase, N and n = number of patients, Ph = Philadelphia chromosome

Serious non-fatal treatment-emergent serious adverse events

Serious non-fatal treatment-emergent serious adverse events in ≥2% of patients can be seen in Table 15. Arterial thromboembolic and arterial stenosis events were prominent in the study. These consisted of cardiac, central nervous system, and peripheral arterial events. As of the original data cut-off date of 27 April 2012, 41 (9%) of patients in the study experienced an arterial event. Twenty-seven of these patients had a serious ischemic event. The 120-day safety update with a data cut-off of 23 July 2012 demonstrated an increase in the number of arterial events.

Fifty one (11%) of patients had an ischemic event of any grade and 34 patients experienced a serious ischemic event.[11]The median time to develop any serious ischemic event was 5.8 months. Nevertheless, serious myocardial and central nervous system ischemic events happened sooner (median time to event (TTE) of 5.3 and 5.7 months) compared to peripheral arterial events (median TTE of 6.7 months).[11] Twenty-four patients had arterial stenosis. A revascularization procedure was necessary in 21 patients (16 patients with coronary revascularization, 4 patients with peripheral arterial revascularization, and 1 patient with cerebrovascular revascularization).

Arterial stenosis that occurs in major arteries that supply the central nervous system was found in four patients: bilateral middle cerebral artery (1 patient); right internal cartoid artery stenosis, right vertebral and basilar (1 patient); carotid artery supraclinoid (1); vertebral and subclavian artery (1 patient).[11] Multiple-site or recurrent arterial occlusive or thromboembolic events were seen in 13 patients.[11] Univariate analysis of baseline factors associated with any grade or serious arterial occlusive or thromboembolic events showed a significant (P<0.01) association with age, time from first diagnosis, prior arterial ischemia or any vascular procedure, diabetes, and hypertension.

The risks for serious adverse arterial ischemic events were: increasing age (p=0.001), greater than 5 years from first diagnosis (p=0.012), a history of diabetes (p<0.001) or a prior arterial ischemic event or vascular procedure (p< 0.001), and hypertension (p=0.003).[11] A post-hoc subset analysis of patients with CP-CML and AP-CML showed that at dose levels of 15 mg, 30 mg, 45 mg, and 60 mg, arterial ischemic events took place at all the levels. In this subset, the overall serious ischemic risk was 18% (9/49), and it corresponded to a median duration of exposure of 26 months.[11]

Table 15: Nonfatal treatment-emergent serious adverse events in ≥2% of patients[11]

Event	April 27 2012 data N
Cardiovascular disorders	
Arterial ischemic event	27 (6%)
Myocardial infarction or worsening coronary artery disease	18 (4%)
Stroke or TIA	7 (2%)
Peripheral arterial disease	4 (1%)
Hemorrhage	19 (4%)
CNS hemorrhage	10 (2%)
Gastrointestinal hemorrhage	6 (1%)
Cardiac failure	17 (4%)
Effusions (includes pericardial effusion, pleural effusion, and ascites)	10 (2%)
Atrial fibrillation	9 (2%)
Hypertension	8 (2%)

Event	April 27 2012 data N
Venous thromboembolism	8 (2%)
Gastrointestinal disorders	
Pancreatitis	23 (5%)
Abdominal pain	16 (4%)
Blood and lymphatic system disorders	
Febrile neutropenia	13 (3%)
Thrombocytopenia	12 (2%)
Anemia	12 (2%)
Infections	
Pneumonia	21 (5%)
Sepsis	10 (2%)
General	
Pyrexia	14 (3%)

Serious adverse events

Serious hemorrhagic events took place in 19 patients (4%). The central nervous system was the site in 10 patients and gastrointestinal in 6 patients. Most of these events were associated with severe thrombocytopenia. However, some serious hemorrhages were seen in patients with mild thrombocytopenia (platelet count ≥ 100 x 10^9/L).[11] Treatment-emergent infections that were serious were seen in 15% of the patients, with the most serious being pneumonia, sepsis, and cellulitis.[11]

Another of the serious adverse events (SAEs) was pancreatitis. This also was likely to occur early during treatment. The median time to first onset was 14 days and 69% of cases occurred in the first month and 17% took place in the second month. Pancreatitis was mostly reversible as the majority of cases resolved within 1 week.[2] Twenty-three patients had a serious pancreatic adverse event and there were no deaths due to pancreatitis.[11] Hypertension was experienced by eight (2%) patients as a SAE that needed urgent clinical intervention. Out of the eight patients, three did not have a prior history of hypertension.[11]

Congestive heart failure (CHF) was another SAE. In the PACE study the risk of CHF was considered serious in 4% of patients. Nine patients who had CHF or decreased ejection fraction had dose modifications and treatment was discontinued in 3 patients.[11] "The median time-to-onset for clinical cardiac failure (excludes echocardiogram findings) was 153 days. The median time-to-onset for all cardiac failure (includes echocardiogram findings) was 85 days."[11] Pacemakers for symptomatic bradyarrhythmias were required in three patients.[11]

The site investigators felt that the following percentages of events were possibly related to ponatinib treatment, cardiovascular, (2.2%), cerebrovascular (0.7%), and peripheral vascular (1.6%).[2]

From the 2014 update serious cardiovascular adverse events were seen in 7% of the patients, serious cerebrovascular events were seen in 5% of patients and serious peripheral vascular events were seen in 4% of patients.[9] Patients who received a high dose of ponatinib, were older and had cardiovascular risk factors which were associated with a high likelihood of developing SAEs.[9]

More than half of patients with CP-CML had at least one serious adverse event; a greater proportion of patients with AP-CML, Ph+ ALL, and BP-CML had at least one serious adverse event.

Deaths

There were 57 (13%) deaths during the study or within 30 days after treatment was discontinued. The cause of death was progressive disease (29 patients) and adverse event (28 patients). Deaths due to adverse events can be seen in Table 16. These do not include deaths from progressive disease.[11]

Table 16: Deaths on study or within 30 days after discontinuation[11]

MedDRA Preferred Term	N	Cohort
Infections		
Septic shock	1	AP CML
Septic shock	2	Ph+ ALL
Sepsis	2	BP CML
Pneumonia	2	CP CML
Pneumonia - fungal	1	AP CML
Pneumocystis jiroveci pneumonia	1	CP CML
Enterocolitis infectious	1	BP CML
Cardiac disorders		
Acute myocardial infarction	1	CP CML
Cardiac failure	1	BP CML
Cardiac failure congestive	1	CP CML
Cardiac failure congestive	1	BP CML
Cardiopulmonary failure	1	Ph+ ALL
Cardiac arrest	2	CP CML
Cardiac arrest	1	Ph+ ALL
Nervous system		
Haemorrhage intracranial	2	BP CML
Haemorrhagic cerebral infarction	1	CP CML
Ischaemia	1	Ph+ ALL
Subdural Haematoma	1	CP CML
General disorders		
Multi organ failure	2	BP CML
Pyrexia	1	AP CML
Gastrointestinal disorders		
Gastritis haemorrhagic	1	BP CML
Metabolism and Nutrition		
Dehydration	1	BP CML

Five deaths were attributable to ponatinib; one patient with CP-CML had pneumonia, another had a myocardial infarction; one patient with AP-CML had fungal pneumonia, one patient with BP-CML had a gastric hemorrhage and one patient with Ph+ ALL had a cardiac arrest.[2] As of February 2, 2015 there were an additional two deaths attributable to ponatinib.[13]

6.4 Ongoing Trials

Seven ongoing clinical trials were found through clinicaltrials.gov.[76-82]

Table 17: Ongoing trials

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
Ponatinib as Second Line Therapy for Patients With Chronic Myeloid Leukemia in Chronic Phase Resistant or Intolerant to Imatinib[76]			
Study NCT01746836 Open-label, single arm, phase II trial. Start date: January 2013 Expected completion date: January 2019 Last verified in February 2015 – ongoing, but not recruiting patients. Estimated enrolment: 50 Sponsor: M.D. Anderson Cancer Center Ariad Pharmaceuticals	**Inclusion Criteria:** • Diagnosis of Ph-positive CML in chronic phase. • Failure to or intolerance to imatinib, dasatinib, or nilotinib as frontline therapy. • Age >/= 18 years. • ECOG performance of 0-2. • Adequate end organ function tests. • Reliable telephone access to receive calls. • Women of pregnancy potential must practice an effective method of birth control during the study and have a negative pregnancy test. • Patients should have discontinued therapy with imatinib, dasatinib or nilotinib or other anti-leukemia therapy (except hydroxyurea), at least 48 hours prior to start of study therapy and recovered from any toxicity due to these therapies to at least grade 1. **Exclusion Criteria:** • Prior therapy with other BCR-ABL-targeted TKIs (e.g., bosutinib). • NYHA cardiac class 3-4 heart disease. • Cardiac Symptoms • Active, uncontrolled psychiatric disorders including. • Patients with uncontrolled hypertension. • Patients with history of pancreatitis. • Patients in accelerated or blast phase, or patients who have ever been documented to be in blast phase CML, are excluded. • Patients who have received more than one FDA-approved TKI for CML, or any investigational, non-FDA approved TKI.	Ponatinib 30 mg tablet taken orally once daily	Primary Outcome Measures: • Major cytogenetic response (MCyR) With Second Line Ponatinib Therapy • Complete Hematologic Remission (CHR) – • Time to Toxicity
Ponatinib as Initial Therapy for Patients With Chronic Myeloid Leukemia in Accelerated Phase[77]			
Study NCT01570868 Open-label, single arm, phase II trial. Start date: April 2012 Expected completion date: April 2016 Last verified in February 2015 – currently recruiting patients. Estimated enrolment: 80	**Inclusion Criteria:** • Diagnosis of Ph-positive CML with accelerated phase. • Patients must have received no or minimal prior therapy, defined as </=1 month of prior IFN-α (with or without ara-C) and/or an FDA-approved tyrosine kinase inhibitor (e.g, dasatinib, nilotinib). Prior use of hydroxyurea or anagrelide is allowed with no limitations. • Age >/=18 years • ECOG performance of 0-2. • Adequate end organ function tests.	Ponatinib 30 mg tablet taken orally once daily	Primary Outcome Measures: • Complete Cytogenetic Response (CCyR) **Secondary Outcome Measures:** • Time to Toxicity

Ponatinib as Second Line Therapy for Patients With Chronic Myeloid Leukemia in Chronic Phase Resistant or Intolerant to Imatinib[76]			
Sponsor: M.D. Anderson Cancer Center Ariad Pharmaceuticals	• Women of pregnancy potential must practice an effective method of birth control during the study and have a negative pregnancy test. **Exclusion Criteria:** • NYHA cardiac class 3-4 heart disease • Cardiac Symptoms. • Patients with active, uncontrolled psychiatric disorders including. • Patients with uncontrolled hypertension. • Patients with history of pancreatitis. • Patients in late chronic phase (i.e., time from diagnosis to treatment >6 months), or blast phase are excluded.		
A Phase 1/2 Multi-center, Open-label Study of Ponatinib in Japanese Patients With Chronic Myeloid Leukemia (CML) Who Have Failed Dasatinib or Nilotinib or Ph+ Acute Lymphoblastic Leukemia (ALL) Who Have Failed Prior Tyrosine Kinase Inhibitors (TKIs)[78]			
Study NCT01570868 Open-label, single arm, phase 1/2 trial. Start date: August 2012 Expected completion date: July 2018 Last verified in August 2014 – Ongoing but not recruiting patients. Estimated enrolment: 40 Sponsor: Ariad Pharmaceuticals	**Inclusion Criteria:** • Patients must have CML in any phase (CP, AP, or BP of any phenotype) or Ph+ ALL. • Be resistant, or intolerant, to either dasatinib or nilotinib for CML or at least one TKI for Ph+ ALL. • Must be ≥ 18 years old. • Provide written informed consent. • ECOG performance status ≤ 2. • Minimum life expectancy of 3 months or more. • Adequate end organ function tests. • Normal QT interval • A negative pregnancy test. • Patients who are of childbearing potential must use an effective form of contraception. **Exclusion Criteria:** • Received TKI therapy within 7 days prior to receiving the first dose of ponatinib, or have not recovered (> grade 1) from adverse events • Received other therapies as per protocol. • Underwent autologous or allogeneic stem cell transplant < 60 days prior to receiving the first dose of ponatinib; any evidence of ongoing graft versus-host disease (GVHD) or GVHD requiring immunosuppressive therapy. • Take medications that are known to be associated with Torsades de Pointes. • Require concurrent treatment with immunosuppressive agents. • Have previously been treated with ponatinib. • Patients with CP-CML are excluded if they are in CCyR. • Patients with CP-CML are excluded if a baseline BM aspirate adequate for conventional cytogenetic analysis with 20 metaphases examined is not available. • Patients with AP-CML, BP-CML, or Ph+ ALL are excluded if they are in MaHR.	Phase 1 30 mg dose of ponatinib taken orally once daily for at least the first 6 patients. If no dose-limiting toxicities are observed, the next patients will receive 45 mg dose of ponatinib taken orally once daily. Once the recommended dose is confirmed, all patients may receive the recommended dose, at the investigators' discretion. Phase 2 Recommended dose of ponatinib as determined in the dose escalation phase. In addition, 3 patients will receive 15 mg dose once daily for 8 days for PK testing. These PK patients may be allowed to receive the recommended dose after PK testing is complete, at the investigators' discretion.	Primary Outcome Measures: • Phase 1: Safety of recommended dose of oral ponatinib • Phase 2: Major cytogenetic response (MCyR) • Phase 2: Major hematologic response (MaHR) • Secondary Outcome Measures: • Pharmacokinetic (PK) parameters of maximum plasma concentration (Cmax), time of maximum concentration (tmax), area under the time-concentration curve (AUC), and elimination half-life (t1/2) • Hematologic responses • Cytogenetic responses • Molecular responses • Response time • Survival follow-up

Ponatinib as Second Line Therapy for Patients With Chronic Myeloid Leukemia in Chronic Phase Resistant or Intolerant to Imatinib[76]			
	• Patients with AP-CML, BP-CML, or Ph+ ALL are excluded if a baseline BM aspirate adequate for cell count and differential report is not available. • Have active central nervous system (CNS) disease. • Have significant or active cardiovascular disease, specifically including, but not restricted to. • Have a significant bleeding disorder. • Have a history of pancreatitis or alcohol abuse. • Have uncontrolled hypertriglyceridemia. • Have malabsorption syndrome or other gastrointestinal illness that could affect absorption of orally administered ponatinib. • Have been diagnosed with another primary malignancy within the past 3 years. • Are pregnant or lactating. • Underwent major surgery. • Have HIV, HBV or HCV.		
Expanded Access Program of Ponatinib (AP24534) for Patients With Refractory Chronic Myeloid Leukemia or Ph+ Acute Lymphoblastic Leukemia[79]			
Study NCT01592136 Open-label, single arm, phase 1/2 trial. Start date: May 2012 Expected completion date: not listed Last verified in January 2013 – Estimated enrolment: Not stated Sponsor: Ariad Pharmaceuticals	**Inclusion Criteria:** • CP-CML and AP-CML patients previously treated with and resistant or intolerant to imatinib, dasatinib and nilotinib or those who developed the T315I mutation after any TKI therapy. BP-CML and Ph+ ALL patients previously treated with and resistant or intolerant to imatinib and dasatinib or those who developed the T315I mutation after any TKI therapy. • Patients must be ≥ 18 years old. • Provide written informed consent. • ECOG) performance status ≤ 2. • Patients must agree to effective contraception. • **Exclusion Criteria:** • Are eligible for an ongoing and accessible clinical trial of ponatinib • Have not adequately recovered from AEs due to agents previously administered • Require concurrent treatment with immunosuppressive agents. • Have previously been treated with ponatinib. • Have significant or active cardiovascular disease, specifically including, but not restricted to: • Have abnormal QTcF . • Have a significant bleeding disorder. Have a history of pancreatitis or alcohol abuse • Have elevated amylase or lipase at entry. • Have inadequate hepatic function. • Have inadequate renal function or serum creatinine. • Have uncontrolled hypertriglyceridemia or triglycerides at entry. • Have malabsorption syndrome or other gastrointestinal illness that could affect absorption of orally administered ponatinib.	ponatinib 45 mg orally as a single dose once daily	Until disease progression, unacceptable toxicity, or withdrawal of consent

Ponatinib as Second Line Therapy for Patients With Chronic Myeloid Leukemia in Chronic Phase Resistant or Intolerant to Imatinib[76]			
	• Women who are pregnant or lactating. • Underwent major surgery within 14 days prior to the first dose of ponatinib. Have HIV, HBV or HCV.		
Phase II Study of Combination of Hyper-CVAD and Ponatinib in Patients With Philadelphia (PH) Chromosome Positive and/or BCR-ABL Positive Acute Lymphoblastic Leukemia (ALL)[80]			
Study NCT01424982 Open-label, phase 2 trial. Start date: October 2011 Expected completion date: October 2016 Last verified in April 2015 – Currently recruiting patients Estimated enrolment: 60 Sponsor: M.D. Anderson Cancer Center Ariad Pharmaceuticals	**Inclusion Criteria:** • Previously untreated Ph-positive ALL [either t(9;22) and/or bcr-abl positive] (includes patients initiated on first course of hyper-CVAD before cytogenetics known); b) Previously treated Ph-positive ALL, after 1-2 courses of chemotherapy with or without other TKIs 1) If they achieved CR, they are assessable only for event-free and overall survival, or 2) If they failed to achieve CR, they are assessable for CR, event-free, and overall survival • Age >/= 18 years • ECOG Performance status </= 2. • Adequate organ function tests. • Patients who are fertile must use an effective form of contraception. • Adequate cardiac function. • Signed informed consent **Exclusion Criteria:** • Active serious infection • History of acute pancreatitis within 1 year of study or history of chronic pancreatitis • History of alcohol abuse • Uncontrolled hypertriglyceridemia • Active secondary malignancy. • Active Grade III-V cardiac failure. • Clinically significant, uncontrolled, or active cardiovascular disease. • Patients currently taking drugs that cause Torsades de Pointes • Taking any medications or herbal supplements that are known to be strong inhibitors of CYP3A4 within at least 14 days before the first dose of ponatinib • Prior history of treatment with ponatinib • Treatment with any investigational antileukemic agents or chemotherapy agents in the last 7 days before study entry, unless full recovery from side effects • Pregnant and lactating women. • History of significant bleeding disorder. • Patients with documented significant pleural or pericardial effusions.	Arm 1 Hyper-CVAD and Ponatinib 45 mg orally daily days 1-14 for Course 1 then 30 mg daily other odd courses. Arm 2 Methotrexate + Cytarabine + Ponatinib 30mg day Maintenance chemotherapy with vincristine, Ponatinib 30 mg by mouth daily as tolerated and 15 mg by mouth daily in patients who have achieved complete molecular response and prednisone for approximately 24 months.	Primary Outcome Measures: • Participants' Median Event-Free Survival (EFS)
Optimizing Ponatinib USe (OPUS). A GIMEMA Phase 2 Study of the Activity and Risk Profile of Ponatinib, 30 mg Once Daily, in Chronic Myeloid Leukemia (CML) Chronic Phase (CP) Patients Resistant to Imatinib[81]			
Study NCT02398825 Open-label, single arm, phase 2 trial.	**Inclusion Criteria:** • Cytogenetic and/or molecular confirmed diagnosis of Ph+ and/or BCR-ABL1+ CML • Age ≥ 18 years	Ponatinib is given orally 30 mg daily, with dose adjustment to 15 mg daily once a	Primary Outcome Measures: • Major cytogenetic response

Ponatinib as Second Line Therapy for Patients With Chronic Myeloid Leukemia in Chronic Phase Resistant or Intolerant to Imatinib[76]			
Start date: June 2015 Expected completion date: June 2020 Last verified in March 2015 – Not yet recruiting patients Estimated enrolment: 78 Sponsor: Gruppo Italiano Malattie EMatologiche dell'Adulto	• Chronic phase CML • Prior treatment with imatinib, any dose • Resistance to imatinib, • For females of childbearing potential, a negative pregnancy test and must use effective form of contraception • Signed written informed consent • Willingness and ability to comply with scheduled visits and study procedures. **Exclusion Criteria:** • Accelerated or blastic phase CML • Patients previously treated with nilotinib or dasatinib • Patients with the T315I mutation • History of acute pancreatitis within 1 year of study or history of chronic pancreatitis or of alcohol abuse • Patients with history of acute myocardial infarction (AMI), unstable angina or coronary heart disease (CHD), congestive heart failure, cerebrovascular events (CVE) (stroke or transitory ischemic attack), or peripheral artery occlusive disease (PAOD) • Compelled to take medications that are known to be associated with Torsades de Pointes and/or with significant QTc prolongation • Any condition or illness that, in the opinion of the Investigator, would compromise patient safety or interfere with the evaluation of the drug	BCR-ABL1 level minor or equal to 0.1% (MMR) has been achieved and confirmed in the next test, 4 weeks apart. A return to prior, 30 mg, dose is due in case of return of BCR-ABL1 transcripts level to > 1%. Dose adjustments for toxicity are detailed in the protocol.	• Major Cytogenetic Response if Ph pos metaphases < 35% • Complete (CCyR) if Ph pos metaphases 0 or FISH BCR-ABL1 nuclei minor or equal to 1% • Partial (PCyR) if Ph pos metaphases 1-34% • Minor (mCyR) if Ph pos metaphases 35-65% Minimal or none (min/none CyR) if Ph pos metaphases > 65% **Secondary Outcome Measures:** • Number of Cardiovascular, hypertension, pancreatic Adverse Events (AEs) • Number of patients achieving Complete Cytogenetic Response (CCyR) • Number of patients achieving major molecular response • Number of patients with failure-free survival • Number of patients with progression-free survival and overall survival • Number of patients in event-free survival • Quality of Life
Front-line Treatment of Philadelphia Positive (Ph+)/BCR-ABL Positive Acute Lymphoblastic Leukemia (ALL) With AP24534 (Ponatinib), a New Potent Tyrosine Kinase Inhibitor (TKI). A Phase II Exploratory Multicentric Study in Patients More Than 60 Years Old or Unfit for a Program of Intensive Chemotherapy and Stem Cell Transplantation.[82]			
Study NCT01641107 Open-label, single arm, phase 2 trial. Start date: October 2014 Expected completion date: November 2019 Last verified in January 2015 – Currently recruiting patients Estimated enrolment: 44	**Inclusion Criteria:** • To be classified as having Ph+ ALL, patients must have >20% blasts in bone marrow at the time of diagnosis and no prior history of CML. • Patients with previously untreated Ph+ and/or BCR/ABL + ALL: • Adequate organ function tests. • A negative pregnancy test. • Fertile patients must use an effective form of contraception. • Signed written informed consent. **Exclusion Criteria**	Ponatinib at a dose of 45 mg/day for 6 weeks (defined as one course) for 8 courses, same dose and schedule, for a total of 48 weeks.	Primary Outcome Measures: • Proportion of patients who are in Complete Hematological Response (CHR). **Secondary Outcome Measures:** • The rate of Complete Hematological Response (CHR). • The rate of complete Cytogenetic Response (CgR).

Ponatinib as Second Line Therapy for Patients With Chronic Myeloid Leukemia in Chronic Phase Resistant or Intolerant to Imatinib[76]			
Sponsor: Gruppo Italiano Malattie EMatologiche dell'Adulto	• WHO performance status ≤ 50% (Karnofsky) or ≥ 3 (ECOG). • Active HBV or HCV hepatitis, or AST/ALT ≥ 2.5 x ULN and bilirubin ≥ 1.5 x ULN. • History of acute pancreatitis within 1 year of study or history of chronic pancreatitis. • History of alcohol abuse. • Ongoing or active infections. • Uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL). • Clinically significant, uncontrolled, or active cardiovascular disease, • Uncontrolled hypertension • Taking medications that are known to be associated with Torsades de Pointes. • Taking any medications or herbal supplements that are known to be strong inhibitors of CYP3A4 within at least 14 days before the first dose of ponatinib. • Creatinine level > 2.5mg/dl or Glomerular Filtration Rate (GFR) < 20 ml/min or proteinuria > 3.5 g/day. • Anything that may significantly alter the absorption of study drugs. • Patients who are currently receiving treatment with any of the medications listed in protocol. • Patients who have received any investigational drug ≤ 4 weeks. • Patients who have undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy. • Patients who are pregnant or breast feeding • Patients with a history of another primary malignancy that is currently clinically significant or currently requires active intervention. • Patients unwilling or unable to comply with the protocol.		• Complete (CCgR) if Ph pos 0 • Partial (PCgR) if Ph pos 1-34% • Minor (mCgR) if Ph pos 35-65% • Minimal or none (min/none CgR) if Ph pos > 65% • Duration of Complete Cytogenetic Response (CCgR). • The rate of Complete Molecular Response (CMoIR). • Complete if by RT-Q-PCR the BCR-ABL: ABL ratio is below 0.01, with a sensitivity of at least 30,000 molecules of ABL. • The rate of major molecular response. • Major (MMolR) if by RT-Q-PCR the BCR-ABL • Duration of Complete molecular response (CMR). • Type and number of BCR-ABL kinase domain mutations. • Percentage of relationships between the response and the biomarkers. • Event Free Survival. • Overall survival • Failure Free Survival

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of Ponatinib (Iclusig) for Chronic Myeloid Leukemia/Acute Lymphoblastic Leukemia:

- Critical Appraisal of an Indirect Comparison of Ponatinib and Second-Generation Tyrosine Kinase Inhibitors (bosutinib, dasatinib, and nilotinib)

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Critical Appraisal of an Indirect Comparison of Ponatinib and Second-Generation Tyrosine Kinase Inhibitors (bosutinib, dasatinib, and nilotinib)

7.1.1 Objective

The manufacturer submitted supporting evidence of a naïve indirect treatment comparison (ITC) of ponatinib versus other treatments in current use (bosutinib, dasatinib, and nilotinib), in order to evaluate the relative effectiveness of these therapies in the CML/ALL population.[X] This section of this report provides a summary and critical appraisal of the methods and findings of this naïve ITC.

7.1.2 Findings

The comparative efficacy of tyrosine kinase inhibitor (TKI) treatments in the third-line setting for chronic-phase CML after failure of second-generation TKIs was analyzed in a naïve ITC reported by Lipton et al.[83] The literature search strategies and selection criteria used to identify these studies were reported in the publication. All studies had to have at least 10 patients who were either CML or Ph+ ALL and were resistance/intolerant to at least one previous second-generation TKI. The included studies were then screened to identify those which included patients with CP-CML.

The naïve ITC was based on five single-arm trials (one phase III, three phase II, and one phase I) and seven observational studies (four prospective observational and three retrospective observational studies). Overall, 586 patients from 12 treatment arms were included in the analysis, 134 (23%) patients were treated with ponatinib.

Table 18. Summary of studies used for indirect comparison as per Lipton et al.

Publications	Intervention, dose	Study design	Response end point
Cortes (PACE)	Ponatinib, 45 mg qd	Phase II single arm	% patients achieving MCyR
Cortes (Phase I)	Ponatinib, escalating doses	Phase I single arm	% Patients achieving each response grade
Khoury	Bosutinib, 500 mg/day	Phase II single arm	Best cumulative response
Giles	Nilotinib, 400 mg bid	Phase II single arm	% patients achieving MCyR
Nicolini	Nilotinib, 400 mg bid	Phase III single arm	% patients achieving CHR, MCyR, CCyR
Garg	Nilotinib, NR	Retrospective observational	Cumulative response
Quintas-Cardama	Dasatinib, 70; 120; or 140 mg bid	Prospective observational	Best response
Garg	Dasatinib, NR	Retrospective observational	Cumulative response

Publications	Intervention, dose	Study design	Response end point
Garcia-Gutierrez	Dasatinib or nilotinib	Prospective observational	Probability of achieving CHR and CCyR
Ibrahim	Dasatinib or nilotinib	Prospective observational	30-month cumulative incidence of MCyR, CCyR, and MMR
Russo Rossi	Dasatinib or nilotinib	Prospective observational	Best response
Cortes	Bafeteinib or bosutinib or dasatinib or nilotinib	Retrospective observational	Best response

The authors indicated that an adjusted indirect comparison was not suitable given the absence of randomized controlled trials and the considerable heterogeneity in the design between studies. A naïve indirect comparison of the data was conducted in the form of forest plots depicting reported best response rates (MCyR and CCyR) in the individual studies. In the forest plot, node size was determined by the number of patients in the study arm and the line length represented the derived confidence intervals.

For each treatment, response probabilities were synthesized to estimate the overall response probability with 95% credible interval (Crl).Response probabilities for ponatinib were estimated using individual patient data from the PACE study and published phase I data for patients who had received two prior TKIs. A Markov chain Monte Carlo Bayesian analysis was used to obtain estimates of the probabilities of treatment response. It was later determined that the response to ponatinib was nominally higher than other treatments and the probability of ponatinib providing the best response compared to other treatments was estimated. This was modelled using a binomial likelihood with fixed treatment effects estimated for each individual treatment. No prior assumptions about the efficacy of each individual treatment was made and the probability that ponatinib provided the best response was estimated from the joint posterior distribution of the treatment effects. There was insufficient data to perform random effect analyses.

A sensitivity analysis was also conducted to compare response to ponatinib in patients without the T315I mutation to second-generation TKIs in all patients.

Comparative Efficacy

Efficacy data from each individual study were presented in the ITC. The proportion of patients in each trial achieving CCyR or MCyR after failure of at least one second-generation TKI and derived 95% confidence intervals were plotted. Visually, the results suggest ponatinib provides nominally higher response probability in terms of CCyR and MCyR.

Table 19. Response Rates by Included Study

Publications, drug	N	T3151 Mutation (%)	MCyR (%)	CCyR (%)
Cortes (PACE), ponatinib	91	24	69	58
Cortes (Phase I), ponatinb	43	29	72	65
Khoury, bosuitinib	118	6	39	22
Giles, nilotinib	37	11	43	24
Nicolini, nilotinib	218	NR	41	28
Garg, nilotinib	9	0	NR	11
Quintas-Cardama, dasatinib	4	9	NR	0
Garg, dasatinib	16	9	NR	31
Garcia-Gutierrez, dasatinib or nilotinib	31	NR	NR	29
Ibrahim, dasatinib or nilotinib	26	NR	50	35
Russo Rossi, dasatinib or nilotinib	68	NR	NR	21

NR=not reported

When studies were pooled by treatment used with the choice of dasatinib or nilotinib pooled separately from the dasatinib-only and nilotinib-only studies, estimated probabilities of achieving CCyR with a second-generation TKI ranged from 22 to 26%. The probability of achieving CCyR was estimated to be more than double (60%, 95%CrL: 52-68) and probability of achieving MCyR was estimated to be higher (0.70, 97%Crl: 0.62-0.77) with ponatinib than second-generation TKIs. The probability of ponatinib providing a higher response rate than all included studies was estimated at 0.99 and 0.97 for CCyR and MCyR, respectively.

Studies with ponatinib were the only studies to report response by T315I status, results suggest the probabilities of response to ponatinib were slightly higher in the T3151 mutation status than in the all-patient analysis.

Table 20. Results of naïve ITC: Probability of CCyR and MCyR by Treatment

Treatment	Probability of CCyR P (95%Crl)	Probability of MCyR P (95%Crl)
All studies and patients		
Ponatinib	0.60 (0.52-0.68)	0.70 (0.62-0.77)
Bosutinib	0.22 (0.15-0.29)	0.29 (0.21-0.38)
Dasatinib	0.24 (0.09-0.45)	-
Nilotinib	0.26 (0.21-0.32)	0.41 (0.35-0.47)
Bafetinb, bosutinib, dasatinib or nilotinib	0.24 (0.10-0.41)	-
Dasatinib or nilotinib	0.25 (0.18-0.32)	0.50 (0.31-0.69)
Probability ponatinib response is higher	0.99	0.97
Non-T315I patients		
Ponatinib	0.52 (0.41-0.62)	0.64 (0.54-0.73)
Probability ponatinib response in non-T315I is higher than response to any second-generation TKI in all-patient population	0.98	9.90

Crl=Credible interval

Limitations

The main limitation with this naïve ITC is that it compared response rates between several single-arm studies without adjustments. Any differences may be due to differences between studies with respect to known patient or disease characteristics (e.g. age, co-morbidities, and co-interventions) or due to unknown factors that differ between study populations.

Although the publication report the information sources, search strategy, study selection process, and data extraction, for the included studies, an assessment of the validity or quality of those studies included was not reported by Lipton et al. Of note, there was heterogeneity in the study designs, patient characteristics, clinical characteristics, and data reporting. Brief descriptions of the patient and trial characteristics were provided; however, the lack of in-depth reporting made it difficult to determine whether the baseline patient characteristics and trial characteristics were similar between trials. The naïve ITC did not examine baseline characteristics which may identify differential treatment responses, however this was not possible given the aggregated nature of the data in the included studies.

Many of the included observational studies had small sample sizes and wide confidence intervals; the largest data sets were from the ponatinib and bosutinib trials. A naïve ITC does not allow for adjustment for cross-trial differences or extrapolation of outcomes beyond the observed trial period. The ITC did not include safety data and efficacy was measured by MCyR and CCyR. In addition, the quality of the ITC was further compromised by the lack of comparators in the trials.

The quality of the manufacturer-submitted indirect comparison was assessed according to the recommendations of the International Society for Pharmacoeconomics and Outcomes Research

(ISPOR) Task Force on Indirect Treatment Comparisons.[84] Details and commentary for each of the relevant items identified by the ISPOR group are provided in Table 21.

Table 21. Appraisal of the Indirect Comparison Analyses using ISPOR Criteria

ISPOR Checklist Item	Details and Comments
1. Are the rationale for the study and the objectives stated clearly?	• The rationale for conducting an indirect comparison analysis and the study objectives were clearly stated.
2. Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• Details regarding the literature search, study selection and data extraction were provided. • Quality assessment of included studies was not provided.
3. Are the outcome measures described?	• N/A, commonly accepted definitions for MCyR and CCyR
4. Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• Descriptive analyses of forest plots were used for the naïve indirect comparisons. • A narrative description of the methodology was reported, however an in depth description of the synthesis of response probabilities was not reported. • Description and justification of the methods/models was provided.
5. Are sensitivity analyses presented?	• For patients without the T315I mutation
6. Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• A table with trial characteristics of all included studies was provided. There were no data presented on the definition of responses. The eligibility criteria for individual trials were not presented. • Table with raw data by study and treatment were provided for the naïve indirect comparison.
7. Does the study describe an assessment of model fit? Are competing models being compared?	• N/A
8. Are the results of the evidence synthesis presented clearly?	• The results of the analysis were clearly reported for each outcome measure including point estimates and 95% credible intervals as a measure of uncertainty.
9. Sensitivity/scenario analyses	• Scenario analysis was reported.

7.1.3 Summary

The comparative efficacy of ponatinib and second-generation tyrosine kinase inhibitors (TKIs) for best response rates in patients with CML or ALL was indirectly assessed using descriptive forest plots and Bayesian analysis. The main limitation with the naïve ITC is that it compared response rates between several single-arm studies without adjustments. Any differences may be due to differences between studies with respect to known patient or disease characteristics (e.g. age, co-morbidities, and co-interventions) or due to unknown factors that differ between study populations. It is unknown how much the difference between trials affects the estimated response rates. Therefore, any conclusions drawn from this naïve indirect comparison regarding the comparative clinical effectiveness between ponatinib and second-generation TKIs should be interpreted with caution.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Hematology 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 ponatinib (Iclusig) for Chronic Myeloid Leukemia/ Acute Lymphoblastic 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.cadth.ca/pcodr).

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. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

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.

The Hematology 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.cadth.ca/pcodr). 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. Literature Search via OVID Platform.

Ovid MEDLINE (R), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily Update, Ovid EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL).

1. *chronic myeloid leukemia/
2. (chronic adj3 (myeloid or myelogenous) adj3 leuk?emia).ti,ab.
3. 1 or 2
4. 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/
5. ponatinib.ti.
6. iclusig.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw, tn, dm, mf, dv, nm, kf, px, rx, an, ui]
7. 5 or 6
8. *acute lymphoblastic leukemia/
9. 3 or 8
10. 4 and 9
11. 7 and 10
12. remove duplicates from 11
13. limit 12 to english language
14. limit 13 to humans

2. Literature Search via PubMed

1. ponatinib OR iclusig
2. Chronic myeloid leukemia
3. publisher [sb]
4. 1 and 2
5. 3 and 4

3. 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: ponatinib OR iclusig

Select International Agencies:

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

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

Search terms: ponatinib OR iclusig

Conference Abstracts:

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

Search terms**:** ponatinib OR iclusig

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

Search terms: ponatinib OR iclusig

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