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Comparative Efficacy of Tyrosine Kinase Inhibitor Treatments in the Third-Line Setting, for Chronic-Phase Chronic Myelogenous Leukemia after Failure of Second-Generation Tyrosine Kinase Inhibitors.

Lipton JH\textsuperscript{1}, Bryden P\textsuperscript{2}, Sidhu MK\textsuperscript{3}, Huang H\textsuperscript{4}, McGarry LJ\textsuperscript{4}, Lustgarten S\textsuperscript{4}, Mealing S\textsuperscript{2}, Woods B\textsuperscript{2}, Whelan J\textsuperscript{2}, Hawkins N\textsuperscript{2}

\textsuperscript{1}Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; \textsuperscript{2}ICON Health Economics; Oxford, UK; \textsuperscript{3}ICON Health Economics; Morristown, NJ, USA; \textsuperscript{4}ARIAD Pharmaceuticals, Inc.; Cambridge MA, USA

Correspondence: Manpreet Sidhu, ICON Health Economics, 161 Madison Avenue Suite 205, Morristown NJ 07960; e-mail: Manpreet.sidhu@iconplc.com

Running head: CP-CML: comparative efficacy after 2G-TKI failure

Highlights

- We compared the efficacy of ponatinib and 2G-TKIs in CP-CML after ≥1 prior 2G-TKI.
- Relevant studies were identified by systematic review.
- Estimated response to 2G-TKI was 22-26\% vs 60\% (95\%CI 52-68\%) with ponatinib.
- Probability of response was greater with ponatinib than with a further 2G-TKI.
Abstract

We compared the efficacy of ponatinib and second-generation tyrosine kinase inhibitors (2G-TKIs: bosutinib, dasatinib, and nilotinib) in chronic phase CML resistant/intolerant to ≥1 prior 2G-TKI. Estimated probabilities of CCyR with 2G-TKI ranged from 22% to 26%, compared with 60% (95% CrI 52-68%) with ponatinib. The estimated probability of ponatinib providing higher response rate than all other included treatments was 99% (CCyR) and 97% (MCyR). Use of further 2G-TKI may provide limited benefit in CP-CML patients resistant/intolerant to prior 2G-TKI treatment. Compared with 2G-TKIs, ponatinib is estimated to provide substantially higher probability of achieving CCyR and MCyR; safety was not compared.

100 words

Key Words

CML
Ponatinib
Second generation tyrosine kinase inhibitor
Response
Systematic review

Abbreviations

2G, second-generation; CML, chronic myelogenous leukemia; CP, chronic phase; CrI, credible interval; CCyR, complete cytogenetic response; MCyR, major cytogenetic response; R/I, resistant/intolerant; TKI, tyrosine kinase inhibitor
1. Introduction

Despite major advances in treatment, resistance and intolerance (R/I) to tyrosine kinase inhibitor (TKI) therapy continue to be significant challenges in the management of chronic phase (CP) chronic myelogenous leukemia (CML). Patients who are R/I to first-line TKI treatment with imatinib are generally treated with a second-generation TKI (2G-TKI), e.g. nilotinib, dasatinib, or bosutinib. Although 2G-TKIs show good efficacy in patients R/I to imatinib, with reported complete cytogenetic response (CCyR) rates of 40–60% [1], at least half of patients receiving dasatinib or nilotinib in the second line experience R/I to these agents over the course of treatment [2-4], and 48-month follow-up data with second-line bosutinib report a 40% incidence of R/I. For patients who experience R/I to 2G-TKIs, treatment options were previously limited to sequential treatment with another 2G-TKI, stem cell transplant, or clinical trials. Because large randomized studies in this setting are few, no TKI is specifically indicated for treatment of CML after failure of both first- and second-generation TKIs. Sequential treatment with 2G-TKIs, although common, may be associated with decreasing clinical response with increasing lines of treatment after failure of a previous 2G-TKI [5]. Newer pharmacologic treatments may provide additional options for patients in this setting.

Ponatinib, a third-generation TKI, is a potent pan-BCR-ABL inhibitor designed to bind with high affinity to both wild-type and mutant BCR-ABL [6]. It is effective in vitro and in vivo against all clinically relevant mutations including the T315I mutation [7], against which no other currently licensed TKI is effective [8]. No single mutation conferring resistance to ponatinib at therapeutic doses has been characterized in CML to date [9]. Although ponatinib has demonstrated clinical efficacy, continuing analyses of the PACE trial of ponatinib in 2013 showed that the cumulative incidence of arterial thrombotic events increased with longer treatment duration [10]. Dasatinib and nilotinib have also been reported to be associated with an increased risk of lung and arterial pathologies, respectively [1].

As more is learned about the potential for late toxicity from long-term treatment with TKIs [1], understanding the relative efficacy of the available agents in later treatment lines has become increasingly important for clinical decision-making. Among the R/I patient population the overall prognosis is poor, and these patients will likely die from their underlying leukemia. Even though overall survival in newly-diagnosed CP-CML has generally increased, patients with advanced disease and patients resistant to prior therapy face a much poorer prognosis and higher likelihood of CML-related death. The median failure-free survival of CP patients
receiving their third line of therapy is 20 months, and drops to 3-5 months in patients with advanced disease [11]. Among refractory patients, those with the T315I mutation have been shown to have a worse prognosis than those without the mutation. CP-CML patients with the T315I mutation have a median overall survival of <2 years post detection of T315I mutation; patients with advanced disease have a median OS of <5 months post detection [12]. For patients for whom two prior lines of therapy have failed, CML is the main investigator-reported cause of death in more than 70% of cases, compared with approximately 7% who die of treatment-related causes [13, 14]. The potential benefit that patients could receive by effective treatment of their refractory leukemia continues to exceed the potential risk for adverse events associated with treatment; therefore, efficacy is likely to remain the paramount consideration in resistant patients.

Assessment of the relative efficacy of available treatment options is needed in order to weigh the risks and benefits of alternative treatment strategies in individual R/I patients. The current study evaluated the comparative efficacy of ponatinib and 2G-TKIs after failure of at least one previous 2G-TKI in patients with CP-CML using data from clinical trials and other published studies.

2. Methods

2.1 Systematic review

To identify relevant clinical trials, a systematic literature review was conducted in MEDLINE, EMBASE, and the Cochrane Libraries (publication dates 2002–2012), and in the abstracts of the American Society of Hematology, American Society of Clinical Oncology, and European Hematology Association conferences (2008–2012). Studies were included if they were randomized controlled trials, single-arm trials, or observational studies (either retrospective or prospective); enrolled 10 or more adult patients in each arm; and presented results for patients with CML or Philadelphia chromosome-positive acute lymphoblastic leukemia who were R/I to prior treatments. No restriction was applied with respect to therapy dose due to incomplete reporting of doses in the available studies. The included studies were then screened again to identify those conducted in patients with CP-CML who were R/I to at least one previous 2G-TKI (Figure 1). In the case of multiple publications from the same study, the publication with the largest patient accrual and/or longest follow-up period was used. Study and patient characteristics were abstracted, as were rates of major (MCyR) and complete (CCyR) cytogenetic response.
2.2 Statistical methods

Measures of cytogenetic response were chosen for synthesis because they are more widely reported than measures of molecular response. Moreover, cytogenetic response by 12 months to treatment with 2G-TKIs has been shown to predict longer-term survival [15]. Only data in CP-CML were analyzed.

**Naïve indirect comparison of response:** The absence of randomized controlled trials and the considerable heterogeneity in design between studies meant that the data were not suitable for an adjusted indirect comparison. We therefore performed a naïve indirect comparison of the data in the form of forest plots depicting reported best response rates (MCyR and CCyR) in individual studies. Node size was determined by the number of patients in the study arm, and line length represented the derived confidence intervals. The time period for reporting response was unspecified in all but one study; responses were therefore plotted regardless of timing. Response probabilities for ponatinib were estimated using individual patient data from the phase 2 PACE study [16, 17] and published phase 1 study data [18]. For the PACE study, only patients who had received two prior TKIs were included in the analysis in order to provide an appropriate comparison to the 2G-TKI studies, which were conducted in patients receiving third-line treatment.

**Synthesis of response probabilities:** In addition to descriptive analyses, we synthesized probabilities of MCyR and CCyR from individual studies, and estimated the overall response probability with 95% credible interval (CrI) for each treatment. A Markov chain Monte Carlo Bayesian analysis was used to obtain estimates of the probability of response to treatment. After determining that the response to ponatinib was nominally higher than the response to any 2G-TKI treatment, we examined the uncertainty around this conclusion by estimating the probability of ponatinib providing the best response. Response was modeled using a binomial likelihood with fixed treatment effects estimated for each individual treatment. Vague priors were given for treatment effects on the log-odds scale ($N[0,1000]$), i.e. no prior assumption was made regarding the relative efficacy of the treatments. The probability that ponatinib provides the highest response of all the treatments included in the analysis was estimated from the joint posterior distribution of the treatment effects. There were insufficient data to perform random effects analyses.

**Sensitivity analysis:** The primary analysis included all patients regardless of T315I mutation status. A sensitivity analysis compared response to ponatinib in patients without the T315I mutation with response to 2G-TKIs in all patients.
3. Results

3.1 Systematic review

After de-duplication of multiple publications from the same study, 12 clinical trials and observational studies were identified from the systematic review that met the inclusion criteria in the post-2G-TKI setting (Figure 1). The treatments represented were the 2G-TKIs bosutinib, dasatinib and nilotinib; the protein translation inhibitor omacetaxine; and ponatinib (Table 1). Use of bafetinib was also reported in a very small number of patients. Four studies reported treatment with any one of two or three different 2G-TKIs. Twelve studies were included in the analysis (the study of omacetaxine was excluded because the analysis was intended as a comparison between TKIs, and Garg et al. [11] was treated as two studies because it contributed two different treatment arms). Overall, 586 patients from 12 treatment arms were included in the analysis (134 for ponatinib and 452 treated with a 2G-TKI).

The included studies consisted of five single-arm trials and seven observational studies (Table 1). No randomized controlled trials were identified. All studies reported use of 2G-TKIs as third line or later; no second-line studies were identified. All studies reported CCyR and seven reported MCyR. Median age ranged from 49 to 58 years where reported. One study reported response at a specified time point; for the others the time of reported response was unspecified. Median duration of follow-up ranged from 9 to 49 months. T315I mutation status was unreported in five of the ten 2G-TKI trials; in the others, the proportion of patients with known T315I mutation ranged from 0% to 11%. In contrast, 29% and 24% of patients in the ponatinib trials (phase 1 [18] and PACE [17], respectively) had the T315I mutation. Only the ponatinib studies reported results by T315I status.

3.2 Comparative efficacy

The proportion of patients in each study achieving CCyR or MCyR (where reported) after failure of at least one 2G-TKI is shown in Table 2 and plotted with derived 95% confidence intervals in Figures 2 and 3. Visual inspection suggests that ponatinib provides a nominally higher response probability in terms of both CCyR and MCyR, although a number of the studies examined have small sample sizes with wide credible intervals.

When studies were pooled by treatment(s) used, with studies allowing a choice of dasatinib or nilotinib pooled separately from the dasatinib-only and nilotinib-only studies, estimated
probabilities of achieving CCyR with a 2G-TKI ranged from 22% to 26% (Table 3). The probability of achieving CCyR with ponatinib was estimated to be more than double, at 60% (95% CrI 52–68%). The estimated probability of MCyR was also substantially higher with ponatinib (0.70 [95% CrI 0.62–0.77]) than with 2G-TKIs (probability range 0.29–0.50). The probability of ponatinib providing a higher response rate than all other included treatments was estimated at 0.99 or CCyR and 0.97 for MCyR.

As only the ponatinib studies reported response by T315I status, ponatinib was the only treatment for which response probabilities for patients known to be without T315I could be calculated. Probabilities of response to ponatinib in the subgroup of patients without the T315I mutation (n=99) were slightly lower than in the all-patients analysis (0.52 [95% CrI 0.41–0.62] and 0.60 [95% CrI 0.52–0.68] for CCyR and MCyR, respectively). The probability that ponatinib provides a higher response rate in non-T315I patients than that provided by all the other agents in the all-patients population was estimated at 98% for CCyR and 90% for MCyR.

4. Discussion

Our review of studies of the efficacy of third-line TKI treatment indicates that sequential use of 2G-TKIs is of limited value for most patients with CML who have experienced failure of prior 2G-TKIs: probabilities of complete cytogenetic response range from 22% to 26% across the 2G-TKIs examined. Patients with CP-CML R/I to second-line treatment with 2G-TKI therapies are estimated to be more than twice as likely to achieve CCyR if treated with ponatinib (60% probability of CCyR) rather than with a further 2G-TKI. Based on the available data, we estimate that ponatinib has a >90% likelihood of providing a higher treatment response in this setting than any of the 2G-TKIs examined; therefore, sequential use of 2G-TKIs in patients R/I to a previous 2G-TKI is likely to be a suboptimal treatment strategy. The analysis focused on efficacy only and did not include toxicity data. Of note, the efficacy results as analyzed are likely to take into account any dose changes that may have occurred.

Our analysis presents both the reported response estimates derived from the respective studies as well as synthesized estimates generated using Bayesian inference. Analogous to more traditional statistical methods, Bayesian methods are used to quantify the degree of belief that observed differences are due to chance. The technique used generates a distribution of values by repeated random sampling, and has the advantage of not relying on large-sample approximations. A further advantage of the Bayesian approach is that results have simple interpretation in terms of probability (i.e. “>90% probability of higher response
with ponatinib”) rather than generating a point estimate and confidence intervals (“95% of
intervals so generated will contain the true value”). Bayesian analysis has the disadvantage
of relying on prior probability assumptions, and, as with all statistical techniques, cannot
correct for unmeasured bias in the source data.

To our knowledge, ours is the first study to systematically examine the literature in order to
evaluate the efficacy of this sequential treatment approach. Optimal response in this setting
has not yet been defined, but treatment guidelines recommend considering alternative
therapies in patients who do not achieve cytogenetic or molecular response to dasatinib or
nilotinib at 3, 6, or 12 months after the failure of two prior TKIs [27]. As yet, limited data are
available on treatment responses with third-line treatment in patients R/I to one or more
previous 2G-TKIs. The major trials of nilotinib and dasatinib in previously treated patients are
in the second-line setting among patients R/I to imatinib; there are no pivotal trials of these
agents in third line. The largest data sets in this third-line population come from the ponatinib
[16, 18] and bosutinib [19] trials, and from a subgroup analysis of the ENACT study that
examined nilotinib in patients who had previously experienced failure of second-line
dasatinib [22]. As the populations in the 2G-TKI studies were predominantly receiving third-
line treatment, and the number of prior therapy lines is generally recognized as a modifier of
treatment effect in CML, we limited the sample from the PACE trial of ponatinib to those
patients who had received two prior TKIs (91 of 270 patients with CP-CML).

We note that ponatinib is known to be the only TKI effective against the T315I mutation [7,
8], and the ponatinib trials contained a greater proportion of patients with T315I (29% in the
Phase 1 trial [18] and 24% in PACE [17]) than the studies of other treatments (where this
was reported). In addition, patients with the T315I mutation in the ponatinib studies had a
better treatment response than the overall study population, although confidence intervals
overlapped and a multivariate analysis found that the presence of T315I was not a predictor
of response [17]. Therefore, to ensure that our results were not biased by the inclusion of
patients with T315I, we conducted analyses in the subset of ponatinib-treated patients
without T315I to confirm that the higher likelihood of response extends to this group. The
estimated 97% probability that the likelihood of response to ponatinib in patients without
the T315I mutation is higher than that estimated for other agents in a mixed (T315I and non-
T315I) population appears to confirm that ponatinib’s superior probability of response is not
driven solely by its status as the only agent effective against T315I. Rather, it suggests that
patients R/I to a previous 2G-TKI may be more likely to respond to ponatinib than another
agent regardless of their mutation status.

We were unable to examine other baseline patient characteristics that may predict
differential treatment response. As with any literature -based systematic review, our
analyses are limited by the lack of patient-level data and our reliance on the reporting of outcomes in the publications, which generally did not stratify efficacy outcomes by patient demographic or clinical characteristics. Because this analysis focuses on patients in the third line, we would expect most patients to have significant pretreatment and to be resistant to at least one of their prior therapies, and therefore relatively homogenous in these respects; however we were not able to test the relative efficacy of treatments in patient subgroups.

Our study is subject to a number of additional limitations related to the available data. Because survival with current treatments in CP-CML is higher than in most cancers, the use of progression-free and overall survival – study outcomes common in oncology research – may not demonstrate differences in treatment outcomes over the limited clinical trial period. For this reason, surrogate endpoints based on cytogenetic response are used to capture efficacy differences between treatments in CML, and thus were the focus of our analysis. Clinical data have shown that achievement of CCyR is predictive of increased survival [28-30] and long-term modeling studies have shown that patients who achieve this endpoint may be expected to have a near normal life expectancy [31], suggesting that achievement of CCyR is an important predictor of treatment benefit.

We note also that a non-TKI treatment, the protein elongation inhibitor omacetaxine, is approved in some countries for the treatment of CP-CML R/I to two or more TKIs [32]. An analysis of a subset of 69 CP-CML patients who were resistant to two or more approved TKIs, from two phase 2 studies of omacetaxine, reported that MCyR occurred in 13 patients (19%) [33]. This is similar to the range of response probabilities found in our analysis of 2G-TKI studies in this setting.

As noted, there are no large randomized trials in this setting. With the exception of the ENACT subanalysis and the phase 2 bosutinib study, the literature on 2G-TKIs after previous 2G-TKI failure is restricted to observational studies or studies with limited patient numbers. Furthermore, there is considerable heterogeneity in terms of study design, and definition and reporting of end points. Owing to limitations in the descriptive data available, we were not able to examine the effect of differences in study design and baseline patient characteristics on observed treatment response in a univariate fashion, or to conduct random effects analyses. Although patient characteristics, such as disease duration and extent of prior non-TKI therapy, may affect treatment outcomes, it is unlikely that baseline differences are driving the differences in predicted response given the broadly similar inclusion criteria across the studies. Resistance versus intolerance to prior TKI therapy is predictive of outcomes in earlier therapy lines; however, data to classify patients by reason for failure was not generally reported in the later-line studies used for this analysis.
Moreover, when we explored this issue by comparing outcomes among the approximately 12% of PACE patients intolerant to their most recent line of therapy versus those who were resistant, we found no difference in response to therapy. Nevertheless, these limitations suggest that the analyses presented here should be regarded as exploratory (although indicative of the potential for ponatinib in CP-CML patients who have experienced failure of at least one 2G-TKI), and should be confirmed with a large randomized trial.

The population of patients R/I to one or more 2G-TKIs is likely to grow as the number of patients treated with, and over time experiencing failure of, these agents accumulates. Thus, it is important to formulate evidence-based strategies to optimize outcomes for these patients. In the light of emerging concerns over the safety of ponatinib and other TKIs in the long-term treatment of CML, more careful assessment of the risk–benefit for individual patients will be required when making treatment decisions. This will necessitate better screening for co-morbidities, careful monitoring for potential serious problems (particularly vascular problems), and tight management of conditions that may increase risk. However, efficacy is likely to remain the paramount consideration in patients with treatment-resistant disease, especially for those who do not have the option of allogeneic stem cell transplant. The overall risk-benefit assessment for treatments available for R/I patients must heavily weight the ability of the treatment to control the patient’s underlying leukemia by rapidly achieving clinically meaningful responses that are as deep and durable as possible and ultimately prolong survival.

5. Conclusions

Based on the available data and given the limitations of our analysis, ponatinib is predicted to provide superior efficacy compared with sequential 2G-TKI therapy in patients R/I to a prior 2G-TKI.

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Authorship contributions

Lipton JH: study design and interpretation of data. Bryden P: statistical analysis. Sidhu MK: study design, collection and interpretation of data, writing manuscript. Huang H: study design, interpretation of data, writing manuscript. McGarry LJ: study design, interpretation of data, writing manuscript. Lustgarten S: study design, interpretation of data. Mealing S: statistical analysis, collection and interpretation of data. Woods B: study design, statistical analysis, interpretation of data. Whelan J: collection and interpretation of data, writing manuscript. Hawkins N: study design, statistical analysis. All authors critically reviewed the manuscript.

Disclosure of Conflicts of Interest

JHL: honoraria, membership of an entity’s board of directors or advisory committees, research funding and speakers bureau (ARIAD Pharmaceuticals, Inc, Bristol-Myers Squib, Novartis Pfizer); HH, LJM, and SL are employees of ARIAD Pharmaceuticals, Inc; PB, MKS, BW, SM, JW, and NH have all received research funding from ARIAD Pharmaceuticals, Inc.
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[32] Teva Pharmaceuticals USA Inc. SYNBRIO Prescribing Information, 10/2012.

### Tables

#### Table 1. Studies included in the analysis

<table>
<thead>
<tr>
<th>Study publication</th>
<th>Intervention (dose)</th>
<th>Study design</th>
<th>Response end point as described in publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khoury (2012) [19]</td>
<td>Bosutinib (500 mg/day)</td>
<td>Phase II single arm</td>
<td>Best cumulative response</td>
</tr>
<tr>
<td>Quintas-Cardama (2007) [20]</td>
<td>Dasatinib (70, 120, or 140 mg bid)</td>
<td>Prospective observational</td>
<td>Best response</td>
</tr>
<tr>
<td>Giles (2010) [21]</td>
<td>Nilotinib (400 mg bid)</td>
<td>Phase II single arm</td>
<td>% patients achieving MCyR</td>
</tr>
<tr>
<td>Nicolini (2009) [22]</td>
<td>Nilotinib (400 mg bid)</td>
<td>Phase III single arm</td>
<td>% patients achieving CHR, MCyR, CCyR</td>
</tr>
<tr>
<td>Cortes (PACE) (2013) [16, 17]</td>
<td>Ponatinib (45 mg qd)</td>
<td>Phase II single arm</td>
<td>% patients achieving MCyR</td>
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<tr>
<td>Cortes (Phase I) (2012) [18]</td>
<td>Ponatinib (escalating doses)</td>
<td>Phase I single arm</td>
<td>% patients achieving each response grade</td>
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<tr>
<td>Garcia-Gutierrez (2012) [23]</td>
<td>Dasatinib OR nilotinib (NR)</td>
<td>Prospective observational</td>
<td>Probability of achieving CHR and CCyR</td>
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<tr>
<td>Russo Rossi (2011) [24]</td>
<td>Dasatinib OR nilotinib (NR)</td>
<td>Prospective observational</td>
<td>Best response</td>
</tr>
<tr>
<td>Cortes (2011) [25]</td>
<td>Bafetinib OR bosutinib OR dasatinib OR nilotinib (NR)</td>
<td>Retrospective observational</td>
<td>Best response</td>
</tr>
</tbody>
</table>

*Counted as separate studies as efficacy results were stratified by intervention.

Bid, twice daily; CCyR, complete cytogenetic response; CHR, complete hematologic response; MCyR, major cytogenetic response; MMR, major molecular response; NR, not reported; qd, once daily.
### Table 2. Response rates, follow-up period, and mutation status

<table>
<thead>
<tr>
<th>Study publication, drug</th>
<th>N*</th>
<th>Median follow-up (months)</th>
<th>T3151 mutation (%)</th>
<th>MCyR</th>
<th>CCyR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khoury (2012)[19], bosutinib</td>
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<td>29</td>
<td>6</td>
<td>30</td>
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<td>Quintas-Cardama (2007)[20], dasatinib</td>
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<td>9</td>
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<td>0</td>
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<tr>
<td>Garg (2009)[11], dasatinib</td>
<td>16</td>
<td>13</td>
<td>9</td>
<td>-</td>
<td>31</td>
</tr>
<tr>
<td>Giles (2010)[21], nilotinib</td>
<td>37</td>
<td>12</td>
<td>11</td>
<td>43</td>
<td>24</td>
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<td>Nicolini, (2009)[26], nilotinib</td>
<td>218</td>
<td>-</td>
<td>-</td>
<td>41</td>
<td>28</td>
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<tr>
<td>Garg (2009)[11], nilotinib</td>
<td>9</td>
<td>13</td>
<td>0</td>
<td>-</td>
<td>11</td>
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<tr>
<td>Cortes (PACE) (2012), ponatinib</td>
<td>91**</td>
<td>15.3</td>
<td>24</td>
<td>69</td>
<td>58</td>
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<tr>
<td>Cortes (Phase I) (2013)[17], ponatinib</td>
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<td>19.4</td>
<td>29</td>
<td>72</td>
<td>65</td>
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<tr>
<td>Garcia-Gutierrez (2012)[23], dasatinib or nilotinib</td>
<td>31</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td>29</td>
</tr>
<tr>
<td>Ibrahim (2010)[13], dasatinib or nilotinib</td>
<td>26</td>
<td>22</td>
<td>-</td>
<td>50</td>
<td>35</td>
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<tr>
<td>Russo Rossi (2011)[24], dasatinib or nilotinib</td>
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<td>14</td>
<td>-</td>
<td>-</td>
<td>21</td>
</tr>
<tr>
<td>Cortes (2011)[25] bafetinib, bosutinib, dasatinib, or nilotinib</td>
<td>29</td>
<td>49</td>
<td>-</td>
<td>-</td>
<td>24</td>
</tr>
</tbody>
</table>

*Number of patients meeting criteria for inclusion in the analysis (chronic phase chronic myelogenous leukemia; failure of previous second-generation tyrosine kinase inhibitor).

**Only patients who had received 2 prior tyrosine kinase inhibitors were included.

# N=68 reporting only CP patients, which is different from the published N=82, but relevant for this CP-only patient group, all the CCyR occurred within the CP population.

-, not reported. CCyR, complete cytogenetic response; CP, chronic phase; MCyR, major cytogenetic response.
Table 3. Synthesized treatment-specific probabilities of CCyR and MCyR, post 2G-TKI, as third line

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Probability of response (CCyR)</th>
<th>Probability of response (MCyR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All studies, all patients</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bosutinib</td>
<td>0.22 (95% CrI 0.15–0.29)</td>
<td>0.29 (95% CrI 0.21–0.38)</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>0.24 (95% CrI 0.09–0.45)</td>
<td>-</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>0.26 (95% CrI 0.21–0.32)</td>
<td>0.41 (95% CrI 0.35–0.47)</td>
</tr>
<tr>
<td>Bafetinib, bosutinib, dasatinib or nilotinib</td>
<td>0.24 (95% CrI 0.10–0.41)</td>
<td>-</td>
</tr>
<tr>
<td>Dasatinib or nilotinib</td>
<td>0.25 (95% CrI 0.18–0.32)</td>
<td>0.50 (95% CrI 0.31–0.69)</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>0.60 (95% CrI 0.52–0.68)</td>
<td>0.70 (95% CrI 0.62–0.77)</td>
</tr>
<tr>
<td>Probability ponatinib response is highest</td>
<td>0.99</td>
<td>0.97</td>
</tr>
<tr>
<td><strong>Non-T315I patients†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ponatinib</td>
<td>0.52 (95% CrI 0.41–0.62)</td>
<td>0.64 (95% CrI 0.54–0.73)</td>
</tr>
<tr>
<td>Probability ponatinib response in non-T315I is higher than response to any 2G-TKI in all-patient population</td>
<td>0.98</td>
<td>0.90</td>
</tr>
</tbody>
</table>

*Studies using the same treatment/choice of treatments were pooled, and all CP patients were included regardless of T315I status. †Only the ponatinib studies reported results by T315I status: this analysis compares ponatinib-treated patients without T315I with the all-patients population (regardless of T315I status) from the 2G-TKI studies.

CCyR, complete cytogenetic response; MCyR, major cytogenetic response; 2G-TKI, second-generation tyrosine kinase inhibitor; CP, chronic phase; CrI, credible interval.
Figure legends and footnotes

Figure 1. PRISMA diagram of study search and selection.
CML, chronic myelogenous leukemia; CP, chronic phase; 2G, second generation; R/I, resistant/intolerant; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukemia.

Figure 2. Proportion of patients with chronic phase chronic myelogenous leukemia achieving complete cytogenetic response, after second-generation tyrosine kinase inhibitor treatment, in third line setting.

[Footnote] Node size represents patient numbers; line signifies derived 95% confidence interval. Unless specified, responses are for all patients, regardless of T315I status; the non-T315I subgroup from the ponatinib studies is also shown.

Figure 3. Proportion of patients with chronic phase chronic myelogenous leukemia achieving major cytogenetic response, after second-generation tyrosine kinase inhibitor treatment, in third line setting.

[Footnote] Node size represents patient numbers; line signifies derived 95% confidence interval. Unless specified, responses are for all patients, regardless of T315I status; the non-T315I subgroup from the ponatinib studies is also shown.
Figures

Figure 1.
Figure 2.

- Bafetinib, bosutinib, dasatinib or nilotinib
  - Cortes, 2011
  - Bosutinib
  - Khoury, 2012
  - Dasatinib
  - Garg, 2009
  - Quintas-Cardama, 2007
- Dasatinib or nilotinib
  - Garcia-Gutierrez, 2012
  - Ibrahim, 2010
  - Rossi, 2011
- Nilotinib
  - Garg, 2009
  - Giles, 2010
  - Nicolini, 2009
- Ponatinib
  - Cortes, 2012
  - Cortes, 2012 non-T315I subgroup
  - PACE
  - PACE non-T315I subgroup

Proportion achieving response
Figure 3.

- **Bosutinib**
  - *Khoury, 2012*

- **Dasatinib or nilotinib**
  - *Ibrahim, 2010*

- **Nilotinib**
  - *Giles, 2010*
  - *Nicolini, 2009*

- **Ponatinib**
  - *Cortes, 2012*
  - *Cortes, 2012 non-T315I subgroup*
  - *PACE*
  - *PACE non-T315I subgroup*

Graph shows the proportion achieving response against different treatments and study identifiers.