NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [ID671]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Incyte Corporation
   - Chronic Myeloid Leukaemia Support Group
   - Leukaemia CARE
   - National Cancer Research Institute, Association of Cancer Physicians and Royal College of Physicians – joint response
   - Royal College of Pathologists
   - Pfizer

   'No comment' response received from Department of Health

3. **Comments on the Appraisal Consultation Document from experts:**
   - Sara Mulvanny – patient expert, nominated by Chronic Myeloid Leukaemia Support Group
   - Jane Apperley – clinical expert nominated by Incyte Corporation

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Evidence Review Group critique of companies ACD response**

   - Ponatinib for treating chronic myeloid leukaemia
     - Evidence Review Group erratum
   - Ponatinib for treating acute lymphoblastic leukaemia

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Incyte	**Executive summary** Incyte welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) as we believe there are areas of the ACD where: • Not all the relevant evidence has been taken into account: o Expert advice to the ERG has not been incorporated in the chronic phase chronic myeloid leukaemia (CML) modelling o Summary of Product Characteristics (SmPC) recommended dose reduction improves the cost effectiveness o Bosutinib is not the most appropriate comparator for all chronic phase CML patients • There are a number of factual errors within the recommendations. The interpretation of aspects of the clinical and cost-effectiveness evidence is not therefore reasonable or plausible, and if a Final Appraisal Determination were to be published from the ACD it would not provide a sound basis for guidance to the NHS. Incyte has commented that the external expert advice to the ERG for the modelling of chronic phase CML patients who do not respond to tyrosine kinase inhibitor (TKI) therapy has not been adequately incorporated into the analysis. This results in an economic model that relies on a clinically implausible result where chronic phase CML patients who are classified as having “No Response” (NR) to treatment are modelled to have better outcomes than patients who achieve a complete haematologic response (CHR). Relying on a clinically implausible result is unreasonable and we ask that the Appraisal Committee (“The Committee”) considers the more clinically plausible options proposed by Incyte.	Comments noted.

	We would wish to remind the Committee that, as previously documented, the SmPC for ponatinib was updated 1st February 2017 with the recommendation that patients who achieve a major cytogenetic response (MCyR) should be considered for a dose reduction to 15 mg. The clinical experts present at the Committee meeting on 16th January agreed that this would be routine clinical practice in England, and this will result in a substantially greater proportion of patients on a reduced, lower-cost dose of ponatinib than submitted in the original economic model, thereby improving the cost effectiveness of ponatinib. In line with NICE's obligation to appraise the product in accordance with the SmPC, we request that dose reduction is taken into account. Incyte is pleased that the Committee recognises the value of ponatinib to patients diagnosed with the T315I mutation in chronic phase CML. However, not only are there a number of other specific mutations that confer resistance to bosutinib, dasatinib, and nilotinib, but it is recognised that patients may become resistant through other mechanisms. For these patients who have no other treatment options, best supportive care (BSC) is a more appropriate comparator for modelling purposes rather than bosutinib. In order further to reduce the uncertainty, the Committee will be aware that Incyte has submitted a revised patient access scheme (PAS). We trust that this, along with the revised data, will allow the Committee to make a recommendation in the best interests of this small group of chronic phase CML patients.	
Incyte	***Incyte proposes a new PAS discount*** Incyte acknowledges that the Committee evaluated the cost effectiveness of ponatinib whilst taking into account the confidential PAS discount for bosutinib. We consider it likely that inclusion of the PAS discount for bosutinib contributed to the Committee's conclusion that ICERs for ponatinib compared with bosutinib in chronic phase CML exceeded the threshold that is usually considered cost effective. To reduce the impact of uncertainty in the cost effectiveness of ponatinib, Incyte offers to increase the simple PAS discount to [redacted]. This discount would lower the financial burden of the disease further and, we hope, enable the NHS to provide access to ponatinib to the full indicated population. The impact of this revised PAS along with the other points raised in this response is demonstrated in Table 1 on page 8. **[Table 1 was presented but is not replicated here, for further details see committee papers]**	The committee considered the responses to the appraisal consultation document together with new evidence and a revised patient access scheme submitted by the company. The committee considered the impact of the new PAS discount on the ICERs for ponatinib in its discussions. See FAD section 4.24
Incyte	**Incyte comments** Incyte would like to provide the following comments on the recommendations in the ACD for ponatinib: a)	Thank you for your comment. The committee revised the recommendations to make ponatinib available to the full population in the ponatinib marketing

	1 Recommendations 1.1 Ponatinib is recommended as an option for treating chronic myeloid leukaemia (CML) in adults with: • chronic phase CML • only when the T315I gene mutation is present With regards to this recommendation for chronic phase CML, we request that the Committee considers our comments on the interpretation of evidence and recommendation for guidance, presented in the pages below. 1.1 Ponatinib is recommended as an option for treating chronic myeloid leukaemia (CML) in adults with: • accelerated phase or blast phase CML within its marketing authorisation 1.2 Ponatinib is recommended, within its marketing authorisation, as an option for treating Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) in adults We agree that, with regards to accelerated phase and blast phase CML and Ph+ ALL, the relevant evidence has been taken into account and the summaries are reasonable interpretations of the evidence. We agree with the recommendations for ponatinib to be used within its marketing authorisation for accelerated phase and blast phase CML and Ph+ ALL.	authorisation (see FAD section 1.1).
Incyte	***Has all of the relevant evidence been taken into account?*** Incyte does not agree that the relevant evidence has been taken into account in the appraisal of ponatinib for chronic phase CML. Incyte believes that the expert clinical advice on the modelling of the non-responders in chronic phase CML has not been taken into account fully. Section 5.2.6.1.4.1 'Exiting the NR state due to progressed disease' (page 136) of the ERG report states: "Clinical advice received by the ERG suggested that the proportion of patients in PFS would lie between the exponential and the log-normal lines" The ACD, however, relies solely on the log-normal fit for the non-responding patients which results in the clinically implausible impact of non-responding patients achieving better outcomes than patients who	The committee noted the company's concerns. It saw analyses from the ERG that fitted a range of curves to PFS and noted their effects on the cost-effectiveness analyses. See FAD section 4.21.

	responded to treatment. As this is unreasonable, Incyte requests that the Committee considers alternatives to ensure a better fit and a clinically plausible model. As previously documented, the SmPC for ponatinib was updated during the course of this appraisal. Incyte notified NICE on 12th January 2017 that the CHMP endorsed changes to the SmPC recommending patients who achieve MCyR on ponatinib be considered for dose reduction to 15 mg. A dose reduction to 15 mg, would apply to the 55% of patients who achieved MCyR in the PACE trial (median time to MCyR: 2.8 months), and therefore reduces the acquisition cost and improves the cost effectiveness of ponatinib.	FAD section 4.3 has been updated to include further details on dose reduction from the SPC.
Incyte	***Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?*** **The exponential fit is a more clinically plausible distribution than the Committee's selection of the log-normal fit to estimate the probability of progression-free survival (PFS) in no response** *ACD Section 4.19, pages 12-13* Incyte disagrees with the Committee's decision to select the best fit (log-normal) distribution to estimate PFS in patients not responding to treatment, because this yields a clinically implausible relationship between PFS and response to TKI therapy. To estimate PFS among patients not responding to treatment, Incyte selected the exponential fit. This was not the best fit, but it was chosen because it was the only fitting function that did not result in the clinically implausible situation of "PFS in no response" being better than "PFS in CHR". It is a well-established principle in CML therapy that responders have better outcomes than non-responders; indeed, the European LeukemiaNet recommendations for the management of CML state, "The response to TKI is the most important prognostic factor."[1] Data from the PACE study shown in Figure 1A and B confirm that PFS in non-responders is worse than PFS among patients who achieved CHR on ponatinib. **[Figures 1A and 1B were presented but are not replicated here, for further details see the committee papers]** Adopting the clinically implausible assumption that PFS is longer for non-responders (ie, selecting the log-normal distribution) is a critically important error, because this biases the cost-effectiveness analysis to favour bosutinib, since bosutinib is less effective than ponatinib and is associated with a higher proportion of patients who do not respond to treatment. Furthermore, the Committee's acceptance of the log-normal distribution based on goodness of fit, despite the clinically unrealistic consequences, is inconsistent with the Committee's criticism that Incyte "chose its parametric distributions based on the Akaike information criterion (AIC) and Bayesian information criterion (BIC), but did not take into account clinical expert advice on the plausibility of the curves that were selected for its base case." To clarify, during development of the economic model, Incyte sought the expert opinion of	The committee noted the company's concerns. It saw analyses from the ERG that fitted a range of curves to PFS and noted their effects on the ICER. It considered that no curve was a good fit, and a sensible way to capture this and other uncertainties was to consider a range of possible ICERs. See FAD section 4.21.

	Dr Richard Clark of the Haematology Department at the Royal Liverpool University Hospital, to verify the plausibility of those curves selected for the base case, whenever the choice of curve was not straightforward. Indeed, as noted above and in the ERG report, the external expert to the ERG commented that "the proportion of patients in PFS would lie between the exponential and the log-normal lines." Although testing a range of parametric functions would yield results between those obtained from using either the log-normal or exponential function, our position is that the exponential function is the only one that guarantees that PFS in no response is never better than PFS in CHR at any point in the simulation. This is our reason for having used the exponential function. Incyte had previously described the issue with the best fit distribution for PFS in no response when we provided comments on the ERG report *(Issue 3 Exiting the non-response (NR) state due to progressed disease)*. In order to demonstrate this issue more clearly Incyte has combined Figure 11 and Figure 13 of the ERG CML report to show the impact of the log-normal ERG preferred function (Figure 2, below). As can be seen in the chart, using the log-normal function in the model means that non-responding patients have a better PFS than patients in response. Incyte asserts that this is clinically implausible. **[Figure 2 was presented but is not replicated here, for further details see committee papers]** The ERG acknowledged our comments and subsequently performed a scenario analysis in which the exponential fit was used instead of the log-normal distribution. As stated in the ERG report Errata (Section 1.2 page 18, paragraph 5): "*If only an exponential function was considered plausible for PFS in non-responders then the ICER compared with bosutinib ranges from £22,995 to £30,741 per QALY gained."* Using the most realistic distribution for estimating PFS in patients not responding to treatment, the ICERs compared to bosutinib are largely below £30,000, and therefore we believe that the most clinically plausible conclusion should be that ponatinib is acceptably cost effective for all indicated patients in chronic phase CML.	
Incyte	**Incyte proposes new Patient Access Scheme (PAS) discount** *ACD Section 4.23, pages 14-15* Incyte acknowledges that the Committee evaluated the cost effectiveness of ponatinib while taking into account the confidential PAS discounts for bosutinib, dasatinib, and nilotinib. We consider it likely that inclusion of the PAS discount for bosutinib contributed to the Committee's conclusion that ICERs for ponatinib compared with bosutinib in chronic phase CML exceeded the threshold that is usually considered cost effective. To reduce the impact of uncertainty in the cost effectiveness of ponatinib, Incyte offers to increase the simple PAS discount to [redacted]. This discount would lower the financial burden of the disease further and, we hope, will enable the NHS to provide access to ponatinib to the full indicated population.	The committee considered the responses to the appraisal consultation document together with new evidence and a revised patient access scheme submitted by the company. The committee considered the impact of the new PAS discount on the ICERs for ponatinib in its discussions.

	We are submitting an amended version of our reconstructed ERG model (v0.1 071216) for chronic phase CML for the Committee's consideration. As the PAS discount for bosutinib is confidential, Incyte does not know the price for this treatment in England. As a conservative assumption, we assumed that bosutinib is offered at the same price as the Glivec® list price. In this amended model, we have reconstructed the ERG's base-case analysis, with three modifications: 1) We used a proxy for the price of bosutinib with the PAS to be the list price of Glivec® in England[3] 2) We used the exponential fit for PFS in no response as this is the distribution that provides a clinically plausible estimation of PFS in patients who do not respond to treatment, as explained above 3) We applied a [redacted]% discount to the cost of ponatinib As shown in Table 1 (analysis reference number 13), the cost effectiveness of ponatinib compared with bosutinib in this new analysis was below the £30,000/QALY threshold that is typically considered cost effective, where there is identifiable unmet need. **[Table 1 was presented but is note replicated here, for further details see the committee papers]**	
Incyte	**ACD should mention potential for lower ponatinib dosing with maintained response per new ponatinib SmPC dosing guidance** *ACD Section 4.2, page 6* Incyte would like to call attention to the new ponatinib SmPC published 1 February 2017. The dosing guidance in the ponatinib SmPC has been updated to reflect long-term data from the PACE study that show maintenance of response among patients with chronic phase CML who have a dose reduction for any reason.[4] The recommended starting dose of ponatinib is 45 mg. Per SmPC guidance, dose reductions to 15 mg among patients with chronic phase CML who have achieved a MCyR should be considered.[4] Extrapolating from the PACE study this means 55% of patients could reduce the dose of ponatinib to 15 mg within a median of 2.8 months.[4] This dose reduction, in accordance with the new SmPC guidance, will contribute significantly to a lower overall cost of treatment with ponatinib. Currently, Section 4.2 of the ACD refers to dose reduction to manage side effects, and Incyte believes that for completeness this section should also mention the new dosing guidance among patient with chronic phase CML who have achieved a MCyR.[4]	Comment noted. This section has been updated (see FAD section 4.3)
Incyte	**BSC should be considered the appropriate comparator in other patient populations in addition to the T315I-positive subgroup** *ACD Section 4.23, pages 14-15 and Section 4.30, pages 18-19* Incyte welcomes the Committee's positive appraisal of the cost effectiveness of ponatinib among patients who have the T315I mutation, which is resistant to all other TKIs currently available. The Committee considered BSC to be the most relevant comparator in these patients. Incyte would like to note that BSC is also the only appropriate comparator to ponatinib in other chronic phase CML patient populations. There are seven other *BCR/ABL* mutations (ie, not only T315I) that have been demonstrated to confer moderate to high resistance	Thank you for your comment. The committee revised the recommendations to make ponatinib available to the full population in the ponatinib marketing

	to bosutinib.[5] Most of these mutations also mean that patients will be resistant to dasatinib and nilotinib and so no alternative treatment is available. Since the Committee recognised the cost effectiveness of ponatinib compared with BSC, it follows that ponatinib should be considered a cost-effective treatment in other patient populations such as those in whom ponatinib is indicated and who have either experienced prior resistance or intolerance to bosutinib or in whom bosutinib is not otherwise clinically appropriate. It is unfair to deny access to ponatinib to these T315I-negative patients for whom bosutinib is clearly not a relevant comparator, while recommending ponatinib for the T315I-positive subgroup. In the company submission, Incyte provided a scenario analysis to evaluate the cost effectiveness of ponatinib in the population of chronic phase CML patients who received at least three prior TKIs (fourth-line setting). In this scenario, bosutinib was not considered as a comparator due to a lack of published data. In the ACD, the Committee did not take into account the results of this scenario, which showed that the cost effectiveness of ponatinib compared with BSC in the fourth-line setting was below £30,000 (with PAS).	authorisation (see FAD section 1.1).
Incyte	**Misunderstandings and factual inaccuracies** Incyte noted the following factual inaccuracies in the ACD which potentially render the conclusions not to recommend ponatinib for the full licensed indication unsound: 1. *Section 4.21, pages 13–14* • The ACD states: "It heard from the ERG that assuming drug wastage, that is, no vial sharing between patients in this model, resulted in an increase in the ICER." Incyte would like to clarify that the dosage form of ponatinib is a tablet, so the legitimate concerns about wastage of drugs supplied in vials do not apply to ponatinib. As for any drug, patients may not adhere fully to their prescribed ponatinib regimen, but any missed doses would be taken at a later time, so should not be characterised as "drug wastage". We recommend that this section be revised to refer to adherence rather than drug wastage. In any such revision, we request retention of the following important points noted by the clinical experts, which increase the potential for good adherence to ponatinib: these patients are generally well-informed about their disease and aware of the seriousness of the effect of missing doses on maintaining their response to treatment; and patients are monitored to ensure a response was being maintained. Since the ACD states that the Committee considered drug wastage with ponatinib and an associated increase in the ICER, Incyte is concerned that this may have influenced the Committee's conclusions on the cost effectiveness of ponatinib. Accordingly, we request clarification on how recognition that drug wastage does not apply to ponatinib would alter the Committee's conclusions. 2. *Section 4.18, Table 1, page 12* • The ICER for chronic phase CML vs bosutinib presented in this table does not reflect the complete ERG base-case scenario. In their CML report, the ERG clearly state, "In CP-CML the ICER for ponatinib is uncertain, ranging from £22,995 to £42,637 per QALY gained in comparison with bosutinib" (Section 1.7, page 18). Therefore, Incyte believes the ACD should report the ERG base-case scenario as £22,995 to £42,637, and not £19,986–£52,121.	FAD section 4.23 has been updated.

	• Incyte believes the upper range ICER vs bosutinib in the blast phase CML base case should be £22,545 as reported in the ERG report Errata, page 22 (ie, not £22,512). 3. *Section 4.8, page 8* • The ACD states that "The Committee heard from experts that clinical practice in England is changing because of new treatments like ponatinib and that treatment for CML would be tailored to the needs of the patients. It heard that the recent availability of generic imatinib was likely to lead to pressure for use of this drug as initial treatment because of its lower cost. It also heard, that people who were intolerant to or whose disease was unresponsive to imatinib, would wish to stop therapy as early as possible, resulting in a push for immediate use of a new-generation TKI, such as ponatinib. The Committee concluded that bosutinib was the most appropriate comparator." The underlined sentence does not align with the wording of the ponatinib SmPC, as this drug is indicated after failure of dasatinib or nilotinib, and not in second-line therapy following initial treatment with imatinib. Incyte requests that the Committee considers the need to amend the sentence to more closely reflect the patient population for which ponatinib is indicated.	This section has been updated (see FAD section 4.24) The FAD has been updated.
Incyte	**Effect of alternative distributions on the ICERs** *ACD Section 4.19, page 12* The ACD states that "The Committee discussed the ERG's exploratory analyses on the company's deterministic ICERs. It heard from the ERG that the parametric distributions fitted where individual patient data were unavailable were inappropriate, and that the company had not explored the effect of alternative distributions on the ICER." Incyte would like to clarify that the underlined statement failed to take account of the analysis carried out by the company in response to the ERG clarification letter. We explored the effect of alternative distributions on the ICERs using the Guyot methodology suggested by the ERG when this was possible, as described in our responses to the ERG clarification letter. The results of our analysis showed that ICERs were more favourable to ponatinib when the Guyot method was used. The ERG exploratory analysis 2a confirms that the use of the alternative Guyot method leads to more favourable results for ponatinib (Table 1**Error! Reference source not found.**). We suggest that the Committee consider adding a sentence to clarify that the use of the Guyot method would have improved the cost-effectiveness results for ponatinib. **[Table 1 was presented but is note replicated here, for further details see the committee papers]**	The committee considered this comment and concluded that this section accurately captured the concerns of the ERG.
Incyte	***Are the recommendations sound and a suitable basis for guidance to the NHS?*** The current recommendations do not take account of all available evidence and are therefore not sound or a suitable basis for NHS guidance at the present time. All patients eligible for ponatinib according to the full marketing authorisation should have access to treatment in England. Incyte considers that clinically plausible	Comment noted

	model parameterisation yields ICERs for ponatinib vs bosutinib that are below the threshold for acceptable cost effectiveness in chronic phase CML. In addition, Incyte has proposed a new PAS to improve still further the cost effectiveness of ponatinib compared with bosutinib in chronic phase CML. The rationale for the new PAS is to enable the NHS to provide ponatinib to the indicated population and lower the financial barriers that prevent patients who have few, if any, alternative options from achieving a significant clinical benefit with ponatinib.	
Incyte	***Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?*** No aspects of the recommendation need special consideration to avoid unlawful discrimination. **References** 1. Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122(6):872-84. 2. ARIAD Pharma Ltd. A Pivotal Phase 2 Trial of Ponatinib (AP24534) in Patients with Refractory Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia: Clinical Study Report Update. Report Date: 21 January 2016 (Database extraction: 03 August 2015). Cambridge, MA. 2016. p. 1-6462. 3. Imatinib: British National Formulary - NHS Evidence. Available from: https://www.evidence.nhs.uk/formulary/bnf/current/8-malignant-disease-and-immunosuppression/81-cytotoxic-drugs/815-other-antineoplastic-drugs/protein-kinase-inhibitors/imatinib. 4. Iclusig® (ponatinib) 15-mg, 30-mg, and 45-mg film-coated tablets: Summary of Product Characteristics. Surrey, UK: ARIAD Pharma Ltd.; 2017 [updated 1 February 2017; cited 2017 13 February]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002695/WC500145646.pdf. 5. Redaelli S, Piazza R, Rostagno R, Magistroni V, Perini P, Marega M, et al. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol. 2009;27(3):469-71. **[Appendices 29 to 32 were presented but are not replicated here, for further details see the committee papers]**	Thank you for your comment. The committee revised the recommendations to make ponatinib available to the full population in the ponatinib marketing authorisation (see FAD section 1.1).
Royal College of Pathologists	The outcome of this STA is very disappointing for the CML community and has been extensively discussed at the NCRI CML Working Party and with patients and carers. We are obviously pleased that ponatinib has been approved for patients with CML in chronic phase who have the T315I mutation, and for a wider range	Thank you for your comment. The committee considered the responses

	of indications in accelerated phase and blast crisis, but find the lack of access in chronic phase highly illogical. To prolong the life of a patient with CML, we have learnt over the past 50 years, initially with allogeneic stem cell transplantation (allo-SCT) and now with tyrosine kinase inhibitors (TKI), that our efforts should be focussed in the chronic phase. Patients with progression, either to acceleration or blast crisis, will die of their disease. We have no effective treatments for these conditions. Even allo-SCT, which allows us to deliver the highest possible doses of chemotherapy, is ineffective in advanced phase disease. So the results of this appraisal, in which we can use ponatinib in acceleration and blast crisis, where any responses are destined to be short-lived, makes little sense. If we want to give patients with resistant chronic phase disease a chance of a prolonged survival we should treat them as early as possible. If this recommendation is accepted then these patients have to be allowed to progress to access a drug that would have an increased chance of efficacy if we had used it a few months earlier. The reason to use ponatinib in advanced phase disease is to achieve a short-lived second chronic phase that provides a window of response to permit consideration of allo-SCT The number of patients in the UK who might benefit from ponatinib is relatively small. We are talking of patients who are truly resistant to at least one second generation TKI or who have demonstrated intolerance to at least two second generation TKI. Our initial measurement of response uses a sensitive molecular assay, RQ-PCR 3 months after the start of treatment. Patients who achieve a result <10% are destined to have an outstanding long-term survival, predicted to be a normal life expectancy. When newly diagnosed patients are treated with imatinib, about 75% will achieve this milestone, but this figure rises to 90% when treated first-line with a second generation TKI. The failure to achieve a RQ-PCR <10% at 3 months is not necessarily due to resistance, it is sometimes related to an inability to take the drugs consistently because of adverse events. Of those treated with imatinib, at least 50% will achieve a result <10%, 3 months after receiving a second generation TKI. Of the 50% who do not, some is genuine resistance and some is due to intolerance. The latter may respond if treatment is changed to an alternative second generation TKI. . Similarly some of the 10% of patients who do not reach a result <10% after frontline treatment with a second generation TKI due to intolerance or a genuine resistance, can benefit from an alternative second generation TKI. The reason for discussing the proportion of responses to first, second and third line therapy is to emphasise how few patients will actually be eligble for ponatinib. In addition ponatinib is a drug with potentially serious side effects. The phase III randomised study of ponatinib vs imatinib in newly diagnosed patients (EPIC) was discontinued prematurely because of the occurrence of arterial thrombotic events on imatinib. Given that the median age of onset of CML is 60-65 years, a time at which patients are already susceptible to cardio-, cerebro- and peripheral vascular disease, it is highly unlikely that ponatinib will be used inappropriately. Furthermore it will be discontinued if there is no evidence of response, to prevent	to the appraisal consultation document together with new evidence and a revised patient access scheme submitted by the company. The committee considered the impact of the new PAS discount on the ICERs for ponatinib in its discussions and revised the recommendations to make ponatinib available to the full population in the ponatinib marketing authorisation (see FAD section 1.1).

	unnecessary risk to patients. Since the response rate to ponatinib used third or fourth line is about 50%, this means that half the patients will discontinue after a few months. Our major concern is that ponatinib was compared with bosutinib, which is completely inappropriate for patients with resistance to dasatinib or nilotinib. Bosutinib is certainly no more potent that either of these agents and the results of the phase III randomised study of imatinib vs bosutinib in newly diagnosed patients (BELA) might suggest that it is less potent. Unlike dasatinib and nilotinib, bosutinib did not achieve the primary endpoint of a better complete cytogenetic remission rate than imatinib at one year, and as a consequence is not licensed for first-line treatment. We feel that the choice of bosutinib as an alternative to the most potent TKI, is not rational and has come about because of the sequential appraisals of the various drugs and not a logical consideration of the best way to manage real patients. Why do the panel consider bosutinib a suitable comparator in patients who are already known to be resistant to equivalent or more potent drugs? Receiving ponatinib at this point is the individual patient's last chance to receive a potentially effective agent before either considering allo-SCT or resigning themselves to inevitable progression and death. Prescribing bosutinib is a futile exercise. We completely accept, and trust that the panel do also, that we should not be treating patients with ineffective agents. But if this is accepted then how can the use of bosutinb as a comparator be justified? We urge the panel to consider resistance and intolerance as different indications for ponatinib and make recommendations accordingly. **Resistance:** at the time of resistance to a second generation drug, current practice is to perform a kinase domain mutation analysis. If the T315I is present (approx. 5% of patients in chronic phase) the patient can receive ponatinib. If there is another mutation present that is known to confer resistance to the current second generation drug, it makes sense to offer an alternative with efficacy. But the majority of patients do not have a mutation and should be offered ponatinib so as to reduce the risk of progression **Intolerance:** for patients who are intolerant of a second generation drug, where intolerance by definition indicates responsiveness but an inability to take the drug because of adverse events, ponatinib should not be the first choice. If the patient has demonstrated previous intolerance or resistance to imatinib, then it would be entirely reasonable to offer one or both of the alternative second generation drugs. If the patient has never received imatinib and responded deeply and rapidly to the initial second generation TKI, then imatinib would be an appropriate treatment. In these situations ponatinb would not be indicated until the patient had been intolerant of at least two second generation TKI.	
Luekaemia CARE	We are writing on behalf of leukaemia patients in response to the recently published ACD for the appraisal of ponatinib – ID 671. We are pleased to see that the committee intends to recommend the use of ponatinib for acute lymphoblastic leukaemia patients (ALL) and chronic myeloid leukaemia (CML) patients with accelerated or	The committee considered the responses to the appraisal consultation document together with new

	blast phase CML, or chronic phase CML with the T315i mutation. However, we are disappointed by the decision not to recommend ponatinib for chronic phase CML patients without the T315i mutation. This decision exacerbates a perverse situation created by the Cancer Drugs Fund, where patients with a 'hard to treat' mutation can access this treatment, whilst those without it cannot. Patients without the T315i mutation who have exhausted their alternative treatment options (e.g. post bosutinib) or where other TKIs are clinically not appropriate (due to comorbidities), are in the same situation as those with the T315i mutation (i.e. without access to an effective treatment for their condition). If this recommendation is upheld in the final guidance, it would leave these patients in the chronic phase without access to treatment, waiting for disease progression. Once their disease has progressed to accelerated or blast phase, they would be able to routinely access ponatinib. This cannot be ethical, logical or a cost-effective use of NHS resources. Ponatinib has been licenced for use within this indication since July 2013, but is only now undergoing appraisal by NICE, following the original scoping in 2013. Ponatinib has been approved for use within this indication by the Scottish Medicines Consortium, since April 2015. As such, not recommending ponatinib within this indication leaves patients in England unable to access a treatment that is routinely available to similar patients in Scotland. We would also like to highlight the impact of this decision on existing guidance from the All Wales Medicines Strategy Group, recommending the use of ponatinib in this setting. This decision could remove access for patients in Wales to a treatment that has been recommended since January 2015. We think that every leukaemia patient has a right to fair and equal access to treatment, regardless of where in the UK they live. Patients in this setting have been waiting long enough for NICE to recommend ponatinib. We urge you not to issue a recommendation that leaves these patients waiting for disease progression before they can access treatment. As such, we ask you to approve ponatinib for CML patients in the chronic phase, with and without the T315i mutation and make it consistently available throughout the UK to all those who could benefit from it.	evidence and a revised patient access scheme submitted by the company. The committee considered the impact of the new PAS discount on the ICERs for ponatinib in its discussions and revised the recommendations for ponatinib to make the drug available to the full population as specified in the company's ponatinib marketing authorisation (see FAD section 1.1).
Chronic Myeloid Leukaemia Support Group	1.1 Since our sole focus is with CML, the CMLSg will not comment on the sections in the ACD dedicated to ALL. 1.2 We welcome the Committee's provisional recommendations that patients in accelerated (AP) and blast (BP) phases of CML should have access to ponatinib treatment as we do their decision that patients, in any of the three phases of CML, exhibiting the T315i mutation should continue to be able to access ponatinib treatment.	Comments noted. Section 4.3 of the FAD refers to the updated SPC.

	1.3 We welcome the very prompt response from NHS England (NHSE) to the Committee's decision that will enable clinicians treating these three patient sub populations to apply to the (new) Cancer Drugs Fund for reimbursement for their ponatinib treatment. 1.4 We also welcome the EMA's recent publication of amendments to the Summary of Product Characteristics (SmPC) for Iclusig (ponatinib) following consideration of ongoing data from the pivotal clinical trial (PACE). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/002695/WC500148271.pdf 1.4.1 The key amendment being for clinicians to consider dose reduction to 15mg/day for chronic phase (CP) patients achieving a major cytogenetic response subject, on a case by case basis, to certain conditions being met. 1.4.2 This amendment aligns with current clinical practice in the UK where the overwhelming majority of CP patients are administering doses of ponatinib below 45 mg/day with the dose for some patients, like the patient expert attending the first committee meeting, being as low as 15mg every other day.	
Chronic Myeloid Leukaemia Support Group	2. However, we regret that the Committee did not recommend that eligible patients in CP, the phase over 90% of the CML patient population are diagnosed in, be treated with ponatinib. 2.1 The decisive factor in the Committee's decision not to recommend ponatinib for CP treatment seemed to rest on their acceptance of the Evidence Review Group's (ERG) criticism that a lack of comprehensiveness in the company's cost effectiveness evaluation rendered the ICER range advanced questionable and their further judgement that the range of CP ICER values subsequently generated by the ERG in mitigation were found to be more plausible (ACD: section 4.19) than those offered by the company. 2.2 Since the upper end of the ERG's range exceeded that of the 'willingness to pay' threshold, adopted by the Institute and applicable to this (CP) sub population, the Committee concluded that their recommendation should be negative. 2.3 The breach of the threshold was also said to be the driver for a 'within the CDF' (provisional positive) recommendation being unavailable due to a failure to meet the 'plausible potential' criteria that would permit consideration for this recommendation. 2.4 Although we accept that decision making by Committees should not be considered a precedent setting and/or rote like activity; we note that value is placed on achieving consistency in the application of judgement across appraisals ('Guide to the methods of technology appraisal' 2013: section 6.2.15) 2.4.1 In that context, we would respectfully draw the Committee's attention to the first award of a provisional recommendation permitting access to the CDF post FAD where an an ICER range of £41,705 to £89,296 was accepted (for 'osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer': TA 416 section 4.19 where EoL entry criteria were satisfied).	The committee considered the responses to the appraisal consultation document together with new evidence and a revised patient access scheme submitted by the company. The committee considered the impact of the new PAS discount on the ICERs for ponatinib in its discussions and revised the recommendations for ponatinib to make the drug available to the full population as specified in the company's ponatinib marketing authorisation (see FAD section 1.1).

Chronic Myeloid Leukaemia Support Group	3. However our principal concern is that the negative recommendation for the CP patient sub population for whom ponatinib might be considered an appropriate treatment option introduces a further element of risk into a clinical environment which is at an already elevated level of risk given multiple TKI treatment failure would invariably have occurred. 3.1 Should the Committee's recommendation become final and adopted into routine use in the NHS, this sub population would be subjected to a delay in treatment onset until their condition had significantly deteriorated to a point where they had entered a more advanced stage of disease. 3.1.1 Although the routine expectation would be that this next stage would be AP, it is not unknown for a patient to progress directly from CP to BP.	Comment noted. The committee revised the recommendations for ponatinib to make the drug available to the full population as specified in the company's ponatinib marketing authorisation (see FAD section 1.1)
Chronic Myeloid Leukaemia Support Group	4. An initial global level observation would be that the Committee's decision generates a clinical environment that does not align with existing cancer policy making. 4.1 This is set out in the 2015 "Achieving World Class Cancer Outcomes: A Strategy for England 2015-2020" where early definitive diagnosis closely followed by rapid movement to the treatment clinical opinion decides is the most effective remains the best guarantor for overall survival. 4.1.2 Taking the cancer waiting time (CWT) standards as an example of policy implementation, the critical importance of 'time' in the treatment of malignancies is clearly evident.	The committee revised the recommendations for ponatinib to make the drug available to the full population as specified in the company's ponatinib marketing authorisation (see FAD section 1.1).
Chronic Myeloid Leukaemia Support Group	5. Translated into the current clinical consensus for the treatment of CML (represented by the 2013 ELN Recommendations for the management of CML) this amounts to a rapid movement through the TKI treatment options in the search for a TKI considered effective enough to deliver an optimal response whilst also being well tolerated to ensure continuity of treatment and an acceptable QoL. 5.1 The ELN recommendations do not however amount to a prescription for robotic clinical behaviour that moves mechanistically, trialling one TKI after another until all are exhausted. Rather, its character is process like, involving a specialist unit MDT exercising deliberation and judgment with their final recommendation requiring a patient's consent and co-operation. It therefore does not necessarily involve all available options becoming real time lines of treatment for a patient although this is not to deny its occurrence in some instances.	Comment noted
Chronic Myeloid Leukaemia Support Group	6. The ACD referred to the expert clinicians critique of the Care Pathway for patients in either AP or BP (Committee Papers: Pre Meeting Briefing slide 6 of the set) noting. *The committee heard from experts that blast phase CML was the most acute phase of CML and that, depending on response to treatment, life expectancy would be less than 6 months. In blast phase CML, clinicians would want them to have the most clinically appropriate TKI available as soon as possible, and it would be unlikely that they would have the time to offer an alternative TKI therapy if the initial TKI used was not effective.* (ACD: section 4.7)	Comment noted. The committee revised the recommendations for ponatinib to make the drug available to the full i population as specified in the ponatinib company's marketing authorisation (see FAD section 1.1).

	6.1 We would argue that ponatinib represents *'the most clinically appropriate TKI'* for CP patients following multiple TKI failure unless ponatinib treatment is contraindicated by, for example, a patient with a history of arterial thrombosis. 6.2 Ponatinib amounts to the most clinically appropriate TKI because, as the committee noted,: *'…although ponatinib is the only drug that is specifically licensed for the T315I gene mutation, it is generally also more effective than other treatments in those people who do not have the T315I gene mutation'* (ACD: section 4.12) 6.3 We remain puzzled why the Committee, given the parts of the ACD quoted in 6 & 6.2 above, was not prompted to go on to explore the place and performance of ponatinib, the sole 3rd Generation TKI, in the CP treatment pathway relative to other treatment options and in particular other second generation (2G) TKIs. Had they done so they might have considered some of the observations made by one of the clinical experts in their written submission (The joint submission by the National Cancer Research Institute, Royal College of Physicians, Royal College of Radiologists, and Association of Cancer Physicians). A summary of the joint submission would be that the clinical evidence points to ponatinib outperforming all other TKIs in all lines of treatment other than first using the achievement of CCyR as a baseline. "All other TKIs" above refers to 1st or 2nd generation TKIs where the latter would include, bosutinib, selected as the most appropriate comparator (ACD: section 4.6). The joint submission goes on to note the effectiveness of ponatinib against many mutations against which 2nd generation TKIs, including bosutinib, have been shown to be less effective. 6.4 We are not of course advocating the blanket use of ponatinib as a second line treatment or indeed in any line of treatment, nor are we proposing that all CP patients will obtain an optimal response following ponatinib treatment. What we are requesting is that recognition be accorded to the strategic importance of being able to deploy the most potent TKI if specialist clinical opinion favours it for a clinically challenged patient in CP. 6.5 Put briefly, we can find no clinical rationale for waiting until clinical circumstances become significantly worse before being able to use the agent most likely to prevent that occurring. 6.6 We therefore respectfully ask the Committee to reverse its initial decision to a positive recommendation for the use of ponatinib for the eligible CP patient population.	

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Clinical expert	Thank you for offering me the opportunity to comment on the consultation. My comments relate to my particular area of expertise, chronic myeloid leukaemia (CML) I welcome the approval to use ponatinib in CML in accelerated phase and blast crisis under the following circumstances • when the disease is resistant to dasatinib or nilotinib or • when they cannot have dasatinib or nilotinib and for whom imatinib is not clinically appropriate or • when the T315I gene mutation is present However I am disappointed that the approval for use in chronic phase was restricted to patients with a T315I mutation and not extended to those who are resistant and/or intolerant to other tyrosine kinase inhibitors. The proposed recommendations will mean that some patients who have a very high chance of responding to ponatinib will instead be offered a costly and risky allogeneic stem cell transplant, and if ineligible for transplant, will progress to a fatal blast crisis. I would like to suggest that ponatinb is made available for patients in chronic phase who have demonstrated resistance to a second generation TKI, and for patients in chronic phase who have demonstrated intolerance to at least two second generation TKI. In making my comments I am struck by the restraints that are placed on such consultations by having to consider each tyrosine kinase inhibitor (TKI) individually rather than addressing the management of chronic myeloid leukaemia as a pathway. The majority of patients respond well and durably to the first generation TKI, imatinib, with a smaller proportion requiring one of the second generation TKI, dasatinib, nilotinib and bosutinib. Approximately half of these patients will be resistant to these drugs, and more than 90% of these will not have a T315I mutation. The need for a third generation inhibitor, namely ponatinib, is restricted to a very small number of patients (probably 50-60 per annum in the UK) for whom the only possible alternative is allogeneic stem cell transplantation (allo-SCT). This procedure is restricted to younger individuals with well-matched donors and carries a high risk of mortality or long-term morbidity. The remaining patients face	The committee considered the responses to the appraisal consultation document together with new evidence and a revised patient access scheme submitted by the company. The committee considered the impact of the new PAS discount on the ICERs for ponatinib in its discussions and revised the recommendations for ponatinib to make the drug available to the full population as specified in the company's ponatinib marketing authorisation (see FAD section 1.1).

Nominating organisation	Comment [sic]	Response
	inevitable progression to blast transformation and death. Ponatinib has very limited efficacy in this situation with low response rates that lack durability. This introduces an element of discrimination towards older patients. The conclusion of the panel seems illogical to this physician. We will be allowed to use ponatinib when these patients inevitably progress. We will incur the expense in the same number of patients but with no expectation of durable response, whereas earlier treatment would have given about half of these individuals the prospect of a normal life expectancy. Despite the clear patient pathway, this appraisal chose to use bosutinib, another second generation TKI, as the comparator for ponatinib. The point was made at the meeting that this was an inappropriate comparator, especially for patients with resistance to second generation drugs, and its use as such cannot be justified by the panel. • The terms first, second and third generation TKI, are used for good reason. Each successive generation of drug had increased potency and activity against an increasing number of BCR-ABL1 kinase domain mutations, but in addition better outcome in patients in whom mutations could not be demonstrated but who had demonstrated resistance to prior therapy. • The second generation TKI have activity against many of the >50 mutations that rendered patients resistant to imatinib, but are equally effective in patients who exhibited imatinib resistance but did not have BCR-ABL1 kinase domain mutations. In the Phase II studies of dasatinib, nilotinib and bosutinib in these circumstances the incidence of complete cytogenetic remission (CCyR) was approximately 40-50% for each of the three drugs, irrespective of the presence of a mutation. The value of identifying a mutation in an individual patient is not because it indicates an increased probability of response compared to a patient without a mutation, but because it helps to direct the choice of the second generation drug, which have some differences in activity against the individual mutations	

Nominating organisation	Comment [sic]	Response
	• Bosutinib was developed 2-3 years later than dasatinib and nilotinib, and was initially tested in a Phase II study of patients who had failed imatinib (second line) or imatinib and dasatinib and/or nilotinib (third and fourth line) for reasons of intolerance or resistance. CCyR rates were approximately 40% in second line for imatinib resistance, equivalent to the efficacy of dasatinib or nilotinib in this setting. However in third line the CCyR rate was only 22% in patients in whom prior resistance had been demonstrated. • The third generation drug, ponatinib, is so-called because it has activity against the T315I mutation. When ponatinib was tested in the large Phase II study, PACE, this activity was confirmed but the study also demonstrated a higher rate of CCyR in patients without a T315I mutation in the third line setting. CCyR rates were 48%, more than double that of bosutinib. • Further evidence of the increased potency of ponatinib over second generation drugs can be inferred from the results in the first-line setting when each of bosutinib, dasatinib, nilotinib and ponatinib were compared to imatinib. Dasatinib and nilotinib demonstrated increased potency over imatinib with CCyR rates at 12 months being 77% vs 66% (dasatinib vs imatinib) and 80% vs 65% (nilotiinib vs imatinib) but bosutinib did not with a CCyR rate of 70% compared to imatinib at 68%. Deeper responses, namely major molecular responses (MMR) at one year were 46% for dasatinib, 51% for nilotinib and 41% for bosutinib compared to a consistent 27% for imatinib across each of the studies. However in the Phase III EPIC study of ponatinib vs imatinib, which was stopped prematurely because of concern about the occurrence of arterial thrombotic events on ponatinib, the MMR rate at only 6 months was 62% for ponatinib and 22% for imatinib. At 12 months limited numbers of patients were available for evaluation but the MMR rate for ponatinib had reached 80%, again almost double that of the second generation agents. Concerns regarding the safety of ponatinib in patients who might well respond well to imatinib are well	Comment noted. However, this evidence was not presented. The committee revised the recommendations for ponatinib to make the drug available to the full population as specified in the company's ponatinib marketing authorisation (see FAD section 1.1).

Nominating organisation	Comment [sic]	Response
	known but these concerns should not detract from the very clear demonstration of the increased potency of ponatinib over the second generation drugs In summary, for patients who demonstrate **resistance** to dasatinib or nilotinib it makes little sense to offer them bosutinib, a drug of equivalent efficacy to the drug they have just failed. The situation with respect to patients who have demonstrated **intolerance** to dasatinib or nilotinib is less clear cut. Intolerance implies that the patient is sensitive in terms of efficacy to whichever drug they are taking, but are having problems with side effects. Most physicians will accept an algorithm that offers patients an alternative second generation drug before suggesting ponatinib, but for those who demonstrate intolerance to at least two second generation TKI, ponatinib is a reasonable strategy and would avoid allogeneic stem cell transplantation in patients who are sensitive to TKI.	
Clinical expert	Further points worthy of consideration include 1. Normal clinical care: haematologists are well aware of the adverse effects of ponatinib and the association with potentially life threatening thrombotic events. They are unlikely to continue to prescribe a drug with an adverse risk profile if it is ineffective. Balancing risk-benefit is part of daily practice. The recommendation for ponatinib could include three monthly assessment of the benefit with instructions to discontinue treatment of there is no clear evidence of response 2. Point 4.4 is incorrect and suggests a misunderstanding. A reduction in tumour load at 3 months is measured by a specific assay for molecular response, RQ-PCR, and the international recommendations are that an optimal responder would have a value <10% at 3 months. Some 70-75% of patients achieve this on first-line imatinib and this figures rises to 90% for patients treated first-line with dasatinib or nilotinib. The 30% figure quoted in 4.4 is the proportion of patients who **fail** to reach this milestone on imatinib. Similarly the suggestion that the 50% of patients who then fail to	Comment noted This section has been updated to incorporate the information provided.

Nominating organisation	Comment [sic]	Response
	respond to another drug (not-specified) would be offered bosutinib fails to acknowledge that this is only because of current NICE guidance and not because it is a logical way to manage patients resistant to imatinib, nilotinib and dasatinib. In fact bosutinib can now be offered to some patients who have only failed imatiinib, if there are particular circumstances that would preclude the use of dasatinib or nilotinib.	
	3. Point 4.7 is also inaccurate. The three month response is measured by the RQ-PCR referred to above and is a molecular response not a cytogenetic response.	This section has been updated to incorporate the information provided
	4. Point 4.8 also suggests a misunderstanding. In the absence of the T315I mutation, patients who fail imatinib for either of resistance or intolerance, would not be offered ponatinb directly, but would first be offered at least one second generation TKI. This point ends in a statement that bosutinib is therefore a suitable comparator for ponatinib but without justification.	This section has been updated to incorporate the information provided
	5. Point 4.11 discusses the appropriateness of an analysis involving a comparison between the PACE study of ponatinib and the study published by Khoury relating to the use of bosutinib as third line therapy. However no thought is given to try to compare the potency of ponatinib and bosutinib in the management of CML. The data I presented earlier suggests that the use of all these drugs in the frontline setting provides additional evidence of the increased potency of ponatinib over bosutinib.	The committee noted the absence of comparative evidence and concluded that despite concerns the MAIC conducted by the company could be used for decision-making (see FAD section 4.10).
	6. Point 4.11 refers to the use of the ERG, which was discussed at the panel meeting. There was a lack of agreement about the outcome of patients who were non-responders to ponatinib in the PACE study. Because the PACE study was only permitted to follow-up patients who were on study or who had recently (30 days) discontinued ponatinib, there are no good outcome data on the survival of these patients. Figures 11 and 13 in the ERG presented a range of curves based on different mathematical models. Figure 13 suggests that several of these models concluded that there would be a plateau in survival such that 30% of non-responders to ponatinib would have a prolonged progression free survival,	The ERG explored a number of curves of best fit for PFS, and incorporated these into its base case figures, which the committee considered in its discussions

Nominating organisation	Comment [sic]	Response
	whereas the log normal curve suggests that these patients would continue to progress and die. It is unclear to me which curve was used and whether an inappropriate choice would affect the ICER. The disease course for untreated patients is inevitable progression and death. Furthermore the lack of response to 3 or 4 second and third generation TKI indicate a group of patients with a very high risk of progression, such that the log normal curve is a more realistic prediction. This may need to be revisited if the ICER will change with an alternative model. 7. The conclusion of point 4.23, namely that the range of ICERs for ponatinib compared with bosutinib presented by the ERG continued to exceed the range that is usually considered to be cost effective, relies on the bosutinib PAS. Disappointingly the decision regarding the availability of ponatinib therefore relies on cost rather than the potential for efficacy. Bosutinib is not a suitable comparator to ponatinib for patients with resistance to resistance to dasatinib or nilotinib, so the economic argument is irrelevant. 8. Point 4.29 suggests that the life expectancy of patients with chronic phase CML exceeds 4 years regardless of treatment. Whereas this statement is true for the majority of patients at the time of diagnosis it is not true for patients with resistance to second line TKI who do not receive effective treatment. These individuals have a very poor prognosis compared to a newly diagnosed patient because they have just proved themselves resistant to TKI treatment. They return to the prognosis of a patient in the pre-TKI era, when the median survival was 6 years from diagnosis. The median value was accompanied by a very wide range, from a few months to >20 years. This heterogeneity has never been adequately explained but it is highly likely that patients who have failed otherwise highly effective treatment in the form of TKI will progress earlier than the median. Progression to blast crisis is highly likely within a short period of time and will not be of the order of 4 years.	The committee revised the recommendations for ponatinib to make the drug available to the full population as specified in the company's ponatinib marketing authorisation (see FAD section 1.1). This section has been updated to make it clear that this is an average figure
Clinical expert	In summary I ask the panel to reconsider their decision and allow us to use ponatinib in	Thank you for your comment. The committee considered the responses to the appraisal consultation document together with new evidence

Nominating organisation	Comment [sic]	Response
	• patients with CML in chronic phase who have a T315I mutation • patients with CML in chronic phase who have demonstrated resistance to one second generation TKI (will include patients who have or have not received prior imatinib)and do not have a kinase domain mutation that might confer sensitivity to an alternative second generation TKI • patients with CML in chronic phase who have demonstrated intolerance to at least two second generation TKI	and a revised patient access scheme submitted by the company. The committee considered the impact of the new PAS discount on the ICERs for ponatinib in its discussions and revised the recommendations for ponatinib to make the drug available to the full population as specified in the company's ponatinib marketing authorisation (see FAD section 1.1).
Patient expert	I'm glad that the Committee has recommended Ponatinib for patients with later stages of CML or if a patient has the T315i mutation, however, I'm very disappointed that patients in Chronic phase CML (like myself) without mutations won't be able to use Ponatinib. I find it hard to comprehend this decision because the patients who have been omitted from this approval are the ones who must have failed one or more of the other TKI's (otherwise they wouldn't be considering Ponatinib as a treatment option), therefore their need for an effective treatment is it just as great as patients with the T315i mutation, or in other stages of CML. My situation was slightly different because I obtained Ponatinib on the PACE trial after Dasatinib proved unsuccessful. However, If I had been diagnosed with CML today and failed Dasatinib, I wouldn't be offered Ponatinib, and since Ponatinib has treated my CML so successfully, this is a quite an unsettling thought. As I said in my submission to the Committee, when your CML proves to be resistant and your current TKI treatment is unsuccessful, it's a very stressful and daunting time for a patient. The fear that your CML will progress to the next accelerated or blast phase is a terrifying thought, especially since that means it's much harder to treat. Waiting until the CML is more advanced before being able to use the most potent TKI is nonsensical: it makes more sense to treat a CML which has shown resistance earlier rather than later, thus avoiding wasting money on failing treatment options that aren't potent enough to impede a resistant CML. If a patient failed all the other TKIs but didn't have the T315i mutation and weren't in an accelerated phase, then the only option would be a bone	Thank you for your comment. The committee considered the responses to the appraisal consultation document together with new evidence and a revised patient access scheme submitted by the company. The committee considered the impact of the new PAS discount on the ICERs for ponatinib in its discussions and revised the recommendations for ponatinib to make the drug available to the full population as specified in the company's marketing authorisation (see FAD section 1.1).

Nominating organisation	Comment [sic]	Response
	marrow transplant. If that had happened to myself than I would have had to take a year off work to recover. This would have had a profound impact on my career and earnings since I'm self-employed. In addition, I wouldn't have been able to have children in the future because the transplant would have pushed me into an early menopause, and since I'm a woman in my late 20's, I'm very grateful that Ponatinib has allowed me to retain the option of having a family in the future. The transplant itself is a risky procedure, with some implications that cannot be foreseen or prevented, therefore it makes sense to try a much less dangerous treatment option such a Ponatinib before going down that route. In addition, the transplant isn't a viable option for some patients who have other medical conditions or who are unable to find a suitable donor. I'm very grateful that Ponatinib has had a transformative effect for myself and I now lead a very active, social and enjoyable life which is unencumbered by CML. I'm aware that Ponatinib doesn't necessarily have the same result for all patients and each patient has a different response to each of the TKIs: I myself know someone who was successfully treated with Dasatinib. However, it's important to have as many TKI's available as possible, and all CML patients should have the opportunity to try Ponatinib if they need that option. I strongly believe that this option should be available earlier rather than later, when it's most likely to be successful rather than when a patient is deemed to satisfy all the predetermined requirements. In summary, I urge the Committee to reconsider their recommendation about chronic phase CML.	
Royal College of Physicians	The NCRI-ACP-RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments. Ponatinib is recommended as an option for treating chronic myeloid leukaemia (CML) in adults with: • chronic phase CML - only when the T315I gene mutation is present • accelerated phase or blast phase CML - when the disease is resistant to dasatinib or nilotinib or	Thank you for your comment. The committee considered the responses to the appraisal consultation document together with new evidence and a revised patient access scheme submitted by the company. The committee considered the impact of the new PAS discount on the ICERs for ponatinib in its discussions and revised the recommendations for ponatinib to make the drug available to the full population as specified in the company's marketing authorisation (see FAD section 1.1).

Nominating organisation	Comment [sic]	Response
	- when they cannot have dasatinib or nilotinib and for whom imatinib is not clinically appropriate or - when the T315I gene mutation is present and the company provides ponatinib with the discount agreed in the patient access scheme. Our experts are extremely disappointed that for chronic phase CML we can still only access ponatinib when the T315I mutation is present, and this is not within the standard that CML-CP should be managed today. The indication for CP- CML should be as for AP-CML. It has been set out in the original application that: • The majority of patients are resistant without a detectable mutation • The T315I mutation is very rare (5% of identifiable mutations) • CML is much more difficult to treat when the disease progresses to AP-CML, and BP-CML outcomes have yet to improve significantly despite the advent of tyrosine kinase inhibitors (TKIs) • The most successful way of treating advanced phase CML (AP and BP) is to prevent it from happening Ponatinib is the most potent BCR-ABL inhibitor, and to limit it to advanced phase CML means that we patients will have to be allowed to progress before we can treat them appropriately. This will reduce patient chances of survival. Ponatinib improves the rates of complete cytogenetic response (which is a surrogate marker of survival), for resistant CML-CP patients in second AND third line settings, in comparison with any of the other second generation TKIs (dasatinib, nilotinib and bosutinib). **Ref: 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, J. H.; Bryden, P.; Sidhu, M. K.; Huang, H.; McGarry, L. J.; Lustgarten, S.; Mealing, S.; Woods, B.; Whelan, J.; Hawkins, N. Leukemia research, Vol. 39, No. 1, 01.2015, p. 58-64.	

Nominating organisation	Comment [sic]	Response
Royal College of Physicians	Bosutinib, which was recently approved, is not considered in this Appraisal consultation document. Our experts are concerned at the prospect of exposing patients to other second generation TKIs that will not be effective. Bosutinib and dasatinib are both dual brc-abl src kinase inhibitors. Are unlikely to salvage a patient with bosutinib after dasatinib failure, and this is clearly evident from the bosutinib studies- lack of durability of response. Bosutinib has to be placed in the same sentences as dasatinib and nilotinib .e.g • when the disease is resistant to dasatinib, nilotinib or bosutinib • when they cannot have dasatinib, nilotinib or bosutinib and for whom imatinib is not clinically appropriate Otherwise physicians will have to give their patients a futile second generation TKI for a period of time, just to satisfy the NICE criteria for ponatinib access. This forces physicians to give inappropriate care. The inclusion of bosutinib will not provide a cost-pressure, and of course will be cost-effective.	The wording of the recommendation is consistent with the marketing authorisation for ponatinib. NICE technology appraisal guidance is only issued in accordance with the marketing authorisation.
Royal College of Physicians	**The committee concluded that the evidence on the clinical-effectiveness of ponatinib in people with the T315I gene mutation was sufficient for decision-making.** It is clear from all studies that T315I does not predict for response to ponatinib. Patients who respond do so according to the line of therapy. Most patients with the T315I were treated with ponatinib second line. This seems to have been omitted from the decision making process and needs to be re-addressed.	The committee noted the results of the PACE trial which showed that although clinical outcomes were worse in patients with the T315I gene mutation, they were broadly similar, and therefore ponatinib was effective in these patients. It therefore judged that the clinical evidence available in these patients was sufficient for decision making.
Royal College of Physicians	**The committee considered the place of ponatinib in the current pathway was as a treatment option when imatinib, nilotinib and dasatinib are not clinically appropriate, and therefore bosutinib was the most appropriate comparator.** There are no randomised studies that directly compare any of the second generation drugs (2G-TKI). All studies compare a 2G-TKI with imatinib. From the data is it clear that all 2G-TKI are equally effective, but have considerably different side-effect profiles. There is no reason to compare ponatinib with bosutinib, over any other 2G-TKI.	The committee considered bostuinib an appropriate comparator, t because it considered bosutinib to be the drug patients would most likely receive if ponatinib were not available, and is considered in established practice in the NHS in England. The committee revised the recommendations for ponatinib to make the drug available to the full population as specified in the company's ponatinib marketing authorisation (see FAD section 1.1).

Nominating organisation	Comment [sic]	Response
	As outlined in physicians' statements for ponatinib, if a CML-CP patient fails imatinib (as per ELN criteria), their chance of achieving a CCyR is 50% on any of the 2G-TKI and this includes bosutinib of course. If they fail this second line of therapy, their chance of achieving a CCyR with the next 2G-TKI (any of the others that have not been tried, including bosutinib), the chance of achieving a CCyR is 10%-30%. Without ponatinib, this patient would be transplanted (assuming a donor is available). The correct comparator to ponatinib is allogeneic transplant therefore. With ponatinib, third line, the rates of CCyR increase to 50%, and a transplant with its resultant morbidity and mortality can be avoided. If this restrictive approach to ponatinib in CML-CP is allowed, we will once more have limited access in England, whereas Wales and Scotland will be able to treat their patients appropriately, and within the ponatinib licence. In summary, we strongly feel that the indication for CML-CP should be as for advanced phase CML, supported by overwhelming clinical data, in order to stop sub-standard treatment of CML patients in CP. We hope the panel will reconsider the evidence.	

Comments received from commentators

Commentator	Comment [sic]	Response
Pfizer	Pfizer would like to thank NICE for the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal. We wish to comment on a number of issues regarding the evidence discussed in the ACD. Firstly, we are concerned about the appropriateness of comparison between the PACE study [1] and Khoury et al [2]. PACE patients were heavily pre-treated with multiple tyrosine kinase inhibitors (TKIs), whereas only 288 patients from Study 200 (Khoury et al) were previously treated with imatinib. The MAIC could therefore be considered to have significant bias based on the undefined baseline characteristics of the patient; the basic phenotype of a heavily pre-treated patient may not have been captured by individual patient level data to which they had access for their MAIC. In addition, the MAIC approach was only used for patients with chronic phase CML because only in these patients was the data comprehensive, to allow the matching technique to be used. It is therefore unclear as to how the manufacturer was able to derive an ICER vs bosutinib in patients with blast phase chronic myeloid leukaemia. Pfizer asks the committee to consider these issues above and view the results from the MAIC with extreme caution prior to the finalisation of their recommendation. **References** [1] Cortes et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med. 2013 Nov 7;369(19):1783-96. [2] Khoury et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood. 2012 Apr 12;119 (15):3403-12.	The committee concluded that the MAIC conducted by the company could be used for decision-making Nonetheless it did make clear its concerns, which are reflected in the committee considerations in the FAD.
Department of Health	No comment	Thank you for your response

Comments received from members of the public

Role*	Section	Comment [sic]	Response
Director of Pharmacy	1	Regarding the ponatinib for Ph +ve ALL in ACD, it states that it can be used when- • the disease is resistant to dasatinib or • they cannot have dasatinib and for whom imatinib is not clinically appropriate or • the T315I gene mutation is present and however dasatinib is currently not commissioned in England for Ph +ve ALL. There is therefore currently no access to an alternative TKI to imatinib for Ph +ve ALL. Applying for dasatinib via IFR previously is not possible as this is a cohort. On the NICE website it states that dasatinib for Ph+ve ALL was removed from the appraisals programme in Dec 2008 and its currently not available via CDF. The NICE TA therefore implies we should access dasatinib before ponatinib (unless T315I mutation) but we cant	Thank you for your comment. We acknowledge that dasatnib for people with Ph+ ALL was delisted from the CDF in November 2015 and there is no NICE guidance for people with Ph+ ALL. NICE technology appraisal guidance is only issued in accordance with the marketing authorisation, so the FAD recommendation is in line with the marketing authorisation for ponatinib.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Single Technology Appraisal (STA)

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [ID671]

Incyte comments on the Appraisal Consultation Document

Executive summary

Incyte welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) as we believe there are areas of the ACD where:

- Not all the relevant evidence has been taken into account:
  - Expert advice to the ERG has not been incorporated in the chronic phase chronic myeloid leukaemia (CML) modelling
  - Summary of Product Characteristics (SmPC) recommended dose reduction improves the cost effectiveness
  - Bosutinib is not the most appropriate comparator for all chronic phase CML patients
- There are a number of factual errors within the recommendations.

The interpretation of aspects of the clinical and cost-effectiveness evidence is not therefore reasonable or plausible, and if a Final Appraisal Determination were to be published from the ACD it would not provide a sound basis for guidance to the NHS.

Incyte has commented that the external expert advice to the ERG for the modelling of chronic phase CML patients who do not respond to tyrosine kinase inhibitor (TKI) therapy has not been adequately incorporated into the analysis. This results in an economic model that relies on a clinically implausible result where chronic phase CML patients who are classified as having "No Response" (NR) to treatment are modelled to have better outcomes than patients who achieve a complete haematologic response (CHR). Relying on a clinically implausible result is unreasonable and we ask that the Appraisal Committee ("The Committee") considers the more clinically plausible options proposed by Incyte.

We would wish to remind the Committee that, as previously documented, the SmPC for ponatinib was updated 1st February 2017 with the recommendation that patients who achieve a major cytogenetic response (MCyR) should be considered for a dose reduction to 15 mg. The clinical experts present at the Committee meeting on 16th January agreed that this would be routine clinical practice in England, and this will result in a substantially greater proportion of patients on a reduced, lower-cost dose of ponatinib than submitted in the original economic model, thereby improving the cost effectiveness of ponatinib. In line with NICE's obligation to appraise the product in accordance with the SmPC, we request that dose reduction is taken into account.

Incyte is pleased that the Committee recognises the value of ponatinib to patients diagnosed with the T315I mutation in chronic phase CML. However, not only are there

a number of other specific mutations that confer resistance to bosutinib, dasatinib, and nilotinib, but it is recognised that patients may become resistant through other mechanisms. For these patients who have no other treatment options, best supportive care (BSC) is a more appropriate comparator for modelling purposes rather than bosutinib.

In order further to reduce the uncertainty, the Committee will be aware that Incyte has submitted a revised patient access scheme (PAS). We trust that this, along with the revised data, will allow the Committee to make a recommendation in the best interests of this small group of chronic phase CML patients.

Incyte proposes a new PAS discount

Incyte acknowledges that the Committee evaluated the cost effectiveness of ponatinib whilst taking into account the confidential PAS discount for bosutinib. We consider it likely that inclusion of the PAS discount for bosutinib contributed to the Committee's conclusion that ICERs for ponatinib compared with bosutinib in chronic phase CML exceeded the threshold that is usually considered cost effective.

To reduce the impact of uncertainty in the cost effectiveness of ponatinib, Incyte offers to increase the simple PAS discount to [redacted]. This discount would lower the financial burden of the disease further and, we hope, enable the NHS to provide access to ponatinib to the full indicated population. The impact of this revised PAS along with the other points raised in this response is demonstrated in Table 1 on page 8.

Incyte comments

Incyte would like to provide the following comments on the recommendations in the ACD for ponatinib:

1 Recommendations

1.1 Ponatinib is recommended as an option for treating chronic myeloid leukaemia (CML) in adults with:
- chronic phase CML
  - only when the T315I gene mutation is present

With regards to this recommendation for chronic phase CML, we request that the Committee considers our comments on the interpretation of evidence and recommendation for guidance, presented in the pages below.

1.1 Ponatinib is recommended as an option for treating chronic myeloid leukaemia (CML) in adults with:
- accelerated phase or blast phase CML within its marketing authorisation

1.2 Ponatinib is recommended, within its marketing authorisation, as an option for treating Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) in adults

We agree that, with regards to accelerated phase and blast phase CML and Ph+ ALL, the relevant evidence has been taken into account and the summaries are reasonable interpretations of the evidence. We agree with the recommendations for ponatinib to be used within its marketing authorisation for accelerated phase and blast phase CML and Ph+ ALL.

Has all of the relevant evidence been taken into account?

Incyte does not agree that the relevant evidence has been taken into account in the appraisal of ponatinib for chronic phase CML.

Incyte believes that the expert clinical advice on the modelling of the non-responders in chronic phase CML has not been taken into account fully. Section 5.2.6.1.4.1 'Exiting the NR state due to progressed disease' (page 136) of the ERG report states:

> "Clinical advice received by the ERG suggested that the proportion of patients in PFS would lie between the exponential and the log-normal lines"

The ACD, however, relies solely on the log-normal fit for the non-responding patients which results in the clinically implausible impact of non-responding patients achieving better outcomes than patients who responded to treatment. As this is unreasonable, Incyte requests that the Committee considers alternatives to ensure a better fit and a clinically plausible model.

As previously documented, the SmPC for ponatinib was updated during the course of this appraisal. Incyte notified NICE on 12th January 2017 that the CHMP endorsed changes to the SmPC recommending patients who achieve MCyR on ponatinib be considered for dose reduction to 15 mg. A dose reduction to 15 mg, would apply to the 55% of patients who achieved MCyR in the PACE trial (median time to MCyR: 2.8 months), and therefore reduces the acquisition cost and improves the cost effectiveness of ponatinib.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

1 The exponential fit is a more clinically plausible distribution than the Committee's selection of the log-normal fit to estimate the probability of progression-free survival (PFS) in no response

ACD Section 4.19, pages 12-13

Incyte disagrees with the Committee's decision to select the best fit (log-normal) distribution to estimate PFS in patients not responding to treatment, because this yields a clinically implausible relationship between PFS and response to TKI therapy.

To estimate PFS among patients not responding to treatment, Incyte selected the exponential fit. This was not the best fit, but it was chosen because it was the only fitting function that did not result in the clinically implausible situation of "PFS in no response" being better than "PFS in CHR". It is a well-established principle in CML therapy that responders have better outcomes than non-responders; indeed, the European LeukemiaNet recommendations for the management of CML state, "The

response to TKI is the most important prognostic factor."[1] Data from the PACE study shown in Figure 1 A and B confirm that PFS in non-responders is worse than PFS among patients who achieved CHR on ponatinib.

Figure 1. Probability of PFS in patients with chronic phase CML treated with two (A) or three (B) prior TKIs

A)

B)

In the PACE study, patients who received two **(A)** or three **(B)** prior TKIs and achieved CHR with ponatinib (green line) had a higher probability of PFS than patients who did not respond to treatment (purple line).
CHR, complete haematologic response; CML, chronic myeloid leukaemia; NR, no response; PFS, progression-free survival; TKIs, tyrosine kinase inhibitors
Source: [redacted]

Adopting the clinically implausible assumption that PFS is longer for non-responders (ie, selecting the log-normal distribution) is a critically important error, because this biases the cost-effectiveness analysis to favour bosutinib, since bosutinib is less effective than ponatinib and is associated with a higher proportion of patients who do not respond to treatment.

Furthermore, the Committee's acceptance of the log-normal distribution based on goodness of fit, despite the clinically unrealistic consequences, is inconsistent with the Committee's criticism that Incyte "chose its parametric distributions based on the Akaike information criterion (AIC) and Bayesian information criterion (BIC), but did not take into account clinical expert advice on the plausibility of the curves that were selected for its base case." To clarify, during development of the economic model, Incyte sought the expert opinion of Dr Richard Clark of the Haematology Department at the Royal Liverpool University Hospital, to verify the plausibility of those curves selected for the base case, whenever the choice of curve was not straightforward.

Indeed, as noted above and in the ERG report, the external expert to the ERG commented that "the proportion of patients in PFS would lie between the exponential and the log-normal lines." Although testing a range of parametric functions would yield results between those obtained from using either the log-normal or exponential function, our position is that the exponential function is the only one that guarantees that PFS in no response is never better than PFS in CHR at any point in the simulation. This is our reason for having used the exponential function.

Incyte had previously described the issue with the best fit distribution for PFS in no response when we provided comments on the ERG report *(Issue 3 Exiting the non-response (NR) state due to progressed disease)*. In order to demonstrate this issue more clearly Incyte has combined Figure 11 and Figure 13 of the ERG CML report to show the impact of the log-normal ERG preferred function (Figure 2, below). As can be seen in the chart, using the log-normal function in the model means that non-responding patients have a better PFS than patients in response. Incyte asserts that this is clinically implausible.

Figure 2. Adopting a log-normal function to estimate PFS creates a clinically implausible situation in which patients who did not respond to TKI therapy have a better PFS compared to patients who achieved a complete haematologic response

CHR, complete haematologic response; NR, no response; PFS, progression-free survival
This figure represents a combination of Figure 11—Extrapolation of the candidate curves presented by the company relating to progression-free survival for patients with CHR (log-logistic amended by ERG [AIC data] and Figure 13—Extrapolation of the candidate curves presented by the company relating to progression-free survival for patients with NR (log-logistic amended by ERG [AIC data]) from the ERG CML report.
Adapted from: Figures 11 and 13 of ID671 Ponatinib CML final ERG report v0.2 110117 TL NICE2 [ACIC].docx

The ERG acknowledged our comments and subsequently performed a scenario analysis in which the exponential fit was used instead of the log-normal distribution. As stated in the ERG report Errata (Section 1.2 page 18, paragraph 5): "*If only an exponential function was considered plausible for PFS in non-responders then the ICER compared with bosutinib ranges from £22,995 to £30,741 per QALY gained.*" Using the most realistic distribution for estimating PFS in patients not responding to treatment, the ICERs compared to bosutinib are largely below £30,000, and therefore we believe that the most clinically plausible conclusion should be that ponatinib is acceptably cost effective for all indicated patients in chronic phase CML.

2 Incyte proposes new Patient Access Scheme (PAS) discount

ACD Section 4.23, pages 14-15

Incyte acknowledges that the Committee evaluated the cost effectiveness of ponatinib while taking into account the confidential PAS discounts for bosutinib, dasatinib, and nilotinib. We consider it likely that inclusion of the PAS discount for bosutinib contributed to the Committee's conclusion that ICERs for ponatinib compared with bosutinib in chronic phase CML exceeded the threshold that is usually considered cost effective.

To reduce the impact of uncertainty in the cost effectiveness of ponatinib, Incyte offers to increase the simple PAS discount to [redacted]. This discount would lower the financial burden of the disease further and, we hope, will enable the NHS to provide access to ponatinib to the full indicated population.

We are submitting an amended version of our reconstructed ERG model (v0.1 071216) for chronic phase CML for the Committee's consideration. As the PAS discount for bosutinib is confidential, Incyte does not know the price for this treatment in England. As a conservative assumption, we assumed that bosutinib is offered at the same price as the Glivec® list price. In this amended model, we have reconstructed the ERG's base-case analysis, with three modifications:

1) We used a proxy for the price of bosutinib with the PAS to be the list price of Glivec® in England[3]
2) We used the exponential fit for PFS in no response as this is the distribution that provides a clinically plausible estimation of PFS in patients who do not respond to treatment, as explained above
3) We applied a [redacted]% discount to the cost of ponatinib

As shown in Table 1 (analysis reference number 13), the cost effectiveness of ponatinib compared with bosutinib in this new analysis was below the £30,000/QALY threshold that is typically considered cost effective, where there is identifiable unmet need.

Table 1. Amended ERG model (chronic phase CML): The impact of the deterministic exploratory analyses on the cost effectiveness of ponatinib compared with bosutinib

Ref No.	Analysis	Cost per QALY gained (£) Ponatinib vs bosutinib
ERG exploratory analyses		
0	N/A (company's base case)	18,213
2a	Recalculation of the survivor functions (excluding PFS exponentials)	16,297
4	Incorporating a three-month stopping rule for bosutinib	21,313
5	No half-cycle correction of intervention costs	17,785
7a	Reducing the costs assumed post-progression in CP-CML or post–allo-SCT for CP-CML patients to that of BSC	21,717
8	Assuming life table data are probabilities not rates	18,226
9a	Assuming ratios of HRQoL between CP-CML and other CML states are maintained	18,017
10	2a, 4,5, 7a, 8 and 9a, using the curves believed most credible by the company	23,059
ERG-selected base-case analyses		
11	As 10, but choosing alternative distributions in addition to those selected by the company (range) – (11a) As 11a, but assuming the same distribution for DoR for ponatinib and bosutinib (range)	19,986 – 52,121 22,995 – 42,637
Incyte's proposed analyses		
12	Max value in 11, but assuming bosutinib price = Glivec® list price and exponential fit for PFS in no response	33,860
13	**As 12 but with new PAS**	**29,848**

Allo-SCT, allogeneic stem cell transplantation; BSC, best supportive care; CML, chronic myeloid leukaemia; CP, chronic phase; DoR, duration of response; HRQoL, health-related quality of life; PAS, patient access scheme; PFS, progression-free survival; QALY, quality-adjusted life year

3 ACD should mention potential for lower ponatinib dosing with maintained response per new ponatinib SmPC dosing guidance

ACD Section 4.2, page 6

Incyte would like to call attention to the new ponatinib SmPC published 1 February 2017. The dosing guidance in the ponatinib SmPC has been updated to reflect long-term data from the PACE study that show maintenance of response among patients with chronic phase CML who have a dose reduction for any reason.[4] The recommended starting dose of ponatinib is 45 mg. Per SmPC guidance, dose reductions to 15 mg among patients with chronic phase CML who have achieved a MCyR should be considered.[4] Extrapolating from the PACE study this means 55% of patients could reduce the dose of ponatinib to 15 mg within a median of 2.8 months.[4]

This dose reduction, in accordance with the new SmPC guidance, will contribute significantly to a lower overall cost of treatment with ponatinib. Currently, Section 4.2 of the ACD refers to dose reduction to manage side effects, and Incyte believes that for completeness this section should also mention the new dosing guidance among patient with chronic phase CML who have achieved a MCyR.[4]

4 BSC should be considered the appropriate comparator in other patient populations in addition to the T315I-positive subgroup

ACD Section 4.23, pages 14-15 and Section 4.30, pages 18-19

Incyte welcomes the Committee's positive appraisal of the cost effectiveness of ponatinib among patients who have the T315I mutation, which is resistant to all other TKIs currently available. The Committee considered BSC to be the most relevant comparator in these patients. Incyte would like to note that BSC is also the only appropriate comparator to ponatinib in other chronic phase CML patient populations. There are seven other *BCR/ABL* mutations (ie, not only T315I) that have been demonstrated to confer moderate to high resistance to bosutinib.[5] Most of these mutations also mean that patients will be resistant to dasatinib and nilotinib and so no alternative treatment is available. Since the Committee recognised the cost effectiveness of ponatinib compared with BSC, it follows that ponatinib should be considered a cost-effective treatment in other patient populations such as those in whom ponatinib is indicated and who have either experienced prior resistance or intolerance to bosutinib or in whom bosutinib is not otherwise clinically appropriate. It is unfair to deny access to ponatinib to these T315I-negative patients for whom bosutinib is clearly not a relevant comparator, while recommending ponatinib for the T315I-positive subgroup.

In the company submission, Incyte provided a scenario analysis to evaluate the cost effectiveness of ponatinib in the population of chronic phase CML patients who received at least three prior TKIs (fourth-line setting). In this scenario, bosutinib was not considered as a comparator due to a lack of published data. In the ACD, the Committee did not take into account the results of this scenario, which showed that the cost effectiveness of ponatinib compared with BSC in the fourth-line setting was below £30,000 (with PAS).

5 Misunderstandings and factual inaccuracies

Incyte noted the following factual inaccuracies in the ACD which potentially render the conclusions not to recommend ponatinib for the full licensed indication unsound:

1. *Section 4.21, pages 13–14*
   - The ACD states: "It heard from the ERG that assuming drug wastage, that is, no vial sharing between patients in this model, resulted in an increase in the ICER." Incyte would like to clarify that the dosage form of ponatinib is a tablet, so the legitimate concerns about wastage of drugs supplied in vials do not apply to ponatinib. As for any drug, patients may not adhere fully to their prescribed ponatinib regimen, but any missed doses would be taken at a later time, so should not be characterised as "drug wastage". We recommend that this section be revised to refer to adherence rather than drug wastage. In any such revision, we request retention of the following important points noted by the clinical experts, which increase the potential for good adherence to ponatinib: these patients are generally well-informed about their disease and aware of the seriousness of the effect of missing doses on maintaining their response to treatment; and patients are monitored to ensure a response was being maintained. Since the ACD states that the Committee considered drug wastage with ponatinib and an associated increase in the ICER, Incyte is concerned that this may have influenced the Committee's conclusions on the cost effectiveness of ponatinib. Accordingly, we request clarification on how recognition that drug wastage does not apply to ponatinib would alter the Committee's conclusions.
2. *Section 4.18, Table 1, page 12*
   - The ICER for chronic phase CML vs bosutinib presented in this table does not reflect the complete ERG base-case scenario. In their CML report, the ERG clearly state, "In CP-CML the ICER for ponatinib is uncertain, ranging from £22,995 to £42,637 per QALY gained in comparison with bosutinib" (Section 1.7, page 18). Therefore, Incyte believes the ACD should report the ERG base-case scenario as £22,995 to £42,637, and not £19,986–£52,121.
   - Incyte believes the upper range ICER vs bosutinib in the blast phase CML base case should be £22,545 as reported in the ERG report Errata, page 22 (ie, not £22,512).

3. *Section 4.8, page 8*
    - The ACD states that "The Committee heard from experts that clinical practice in England is changing because of new treatments like ponatinib and that treatment for CML would be tailored to the needs of the patients. It heard that the recent availability of generic imatinib was likely to lead to pressure for use of this drug as initial treatment because of its lower cost. It also heard, that people who were intolerant to or whose disease was unresponsive to imatinib, would wish to stop therapy as early as possible, resulting in a push for immediate use of a new-generation TKI, such as ponatinib. The Committee concluded that bosutinib was the most appropriate comparator."

      The underlined sentence does not align with the wording of the ponatinib SmPC, as this drug is indicated after failure of dasatinib or nilotinib, and not in second-line therapy following initial treatment with imatinib. Incyte requests that the Committee considers the need to amend the sentence to more closely reflect the patient population for which ponatinib is indicated.

6 Effect of alternative distributions on the ICERs

ACD Section 4.19, page 12

The ACD states that "The Committee discussed the ERG's exploratory analyses on the company's deterministic ICERs. It heard from the ERG that the parametric distributions fitted where individual patient data were unavailable were inappropriate, and that the company had not explored the effect of alternative distributions on the ICER."

Incyte would like to clarify that the underlined statement failed to take account of the analysis carried out by the company in response to the ERG clarification letter. We explored the effect of alternative distributions on the ICERs using the Guyot methodology suggested by the ERG when this was possible, as described in our responses to the ERG clarification letter. The results of our analysis showed that ICERs were more favourable to ponatinib when the Guyot method was used. The ERG exploratory analysis 2a confirms that the use of the alternative Guyot method leads to more favourable results for ponatinib (Table 1). We suggest that the Committee consider adding a sentence to clarify that the use of the Guyot method would have improved the cost-effectiveness results for ponatinib.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The current recommendations do not take account of all available evidence and are therefore not sound or a suitable basis for NHS guidance at the present time. All patients eligible for ponatinib according to the full marketing authorisation should have access to treatment in England. Incyte considers that clinically plausible model parameterisation yields ICERs for ponatinib vs bosutinib that are below the threshold for acceptable cost effectiveness in chronic phase CML. In addition, Incyte has

proposed a new PAS to improve still further the cost effectiveness of ponatinib compared with bosutinib in chronic phase CML. The rationale for the new PAS is to enable the NHS to provide ponatinib to the indicated population and lower the financial barriers that prevent patients who have few, if any, alternative options from achieving a significant clinical benefit with ponatinib.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No aspects of the recommendation need special consideration to avoid unlawful discrimination.

References

1. Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013;122(6):872-84.

2. ARIAD Pharma Ltd. A Pivotal Phase 2 Trial of Ponatinib (AP24534) in Patients with Refractory Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia: Clinical Study Report Update. Report Date: 21 January 2016 (Database extraction: 03 August 2015). Cambridge, MA. 2016. p. 1-6462.

3. Imatinib: British National Formulary - NHS Evidence. Available from: https://www.evidence.nhs.uk/formulary/bnf/current/8-malignant-disease-and-immunosuppression/81-cytotoxic-drugs/815-other-antineoplastic-drugs/protein-kinase-inhibitors/imatinib.

4. Iclusig® (ponatinib) 15-mg, 30-mg, and 45-mg film-coated tablets: Summary of Product Characteristics. Surrey, UK: ARIAD Pharma Ltd.; 2017 [updated 1 February 2017; cited 2017 13 February]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002695/WC500145646.pdf.

5. Redaelli S, Piazza R, Rostagno R, Magistroni V, Perini P, Marega M, et al. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol. 2009;27(3):469-71.

Appendices

Appendix 29: Probability of PFS in patients with chronic phase CML treated with two or three prior TKIs

Appendix 30: Log-normal vs exponential distribution to estimate PFS in patients treated with TKI therapy

Appendix 31: Ponatinib Summary of Product Characteristics (1February2017)

Appendix 32: Ponatinib CP ERG amended model v0.1 071216 (ACIC) _newPAS

Single Technology Appraisal (STA) : Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [ID671]

Comment by the Chronic Myeloid Leukaemia Support Group (CMLSg) on the Appraisal consultation document (ACD).

1.1 Since our sole focus is with CML, the CMLSg will not comment on the sections in the ACD dedicated to ALL.

1.2 We welcome the Committee's provisional recommendations that patients in accelerated (AP) and blast (BP) phases of CML should have access to ponatinib treatment as we do their decision that patients, in any of the three phases of CML, exhibiting the T315i mutation should continue to be able to access ponatinib treatment.

1.3 We welcome the very prompt response from NHS England (NHSE) to the Committee's decision that will enable clinicians treating these three patient sub populations to apply to the (new) Cancer Drugs Fund for reimbursement for their ponatinib treatment.

1.4 We also welcome the EMA's recent publication of amendments to the Summary of Product Characteristics (SmPC) for Iclusig (ponatinib) following consideration of ongoing data from the pivotal clinical trial (PACE).
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/002695/WC500148271.pdf

1.4.1 The key amendment being for clinicians to consider dose reduction to 15mg/day for chronic phase (CP) patients achieving a major cytogenetic response subject, on a case by case basis, to certain conditions being met.

1.4.2 This amendment aligns with current clinical practice in the UK where the overwhelming majority of CP patients are administering doses of ponatinib below 45 mg/day with the dose for some patients, like the patient expert attending the first committee meeting, being as low as 15mg every other day.

2. However, we regret that the Committee did not recommend that eligible patients in CP, the phase over 90% of the CML patient population are diagnosed in, be treated with ponatinib.

2.1 The decisive factor in the Committee's decision not to recommend ponatinib for CP treatment seemed to rest on their acceptance of the Evidence Review Group's (ERG) criticism that a lack of comprehensiveness in the company's cost effectiveness evaluation rendered the ICER range advanced questionable and their further judgement that the range of CP ICER values subsequently generated by the ERG in mitigation were found to be more plausible (ACD: section 4.19) than those offered by the company.

2.2 Since the upper end of the ERG's range exceeded that of the 'willingness to pay' threshold, adopted by the Institute and applicable to this (CP) sub population, the Committee concluded that their recommendation should be negative.

2.3 The breach of the threshold was also said to be the driver for a 'within the CDF' (provisional positive) recommendation being unavailable due to a failure to meet the 'plausible potential' criteria that would permit consideration for this recommendation.

2.4 Although we accept that decision making by Committees should not be considered a precedent setting and/or rote like activity; we note that value is placed on achieving consistency in the application of judgement across appraisals ('Guide to the methods of technology appraisal' 2013: section 6.2.15)

2.4.1 In that context, we would respectfully draw the Committee's attention to the first award of a provisional recommendation permitting access to the CDF post FAD where an an ICER range of £41,705 to £89,296 was accepted (for 'osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer': TA 416 section 4.19 where EoL entry criteria were satisfied).

3. However our principal concern is that the negative recommendation for the CP patient sub population for whom ponatinib might be considered an appropriate treatment option introduces a further element of risk into a clinical environment which is at an already elevated level of risk given multiple TKI treatment failure would invariably have occurred.

3.1 Should the Committee's recommendation become final and adopted into routine use in the NHS, this sub population would be subjected to a delay in treatment onset until their condition had significantly deteriorated to a point where they had entered a more advanced stage of disease.

3.1.1 Although the routine expectation would be that this next stage would be AP, it is not unknown for a patient to progress directly from CP to BP.

4. An initial global level observation would be that the Committee's decision generates a clinical environment that does not align with existing cancer policy making.

4.1 This is set out in the 2015 "Achieving World Class Cancer Outcomes: A Strategy for England 2015-2020" where early definitive diagnosis closely followed by rapid movement to the treatment clinical opinion decides is the most effective remains the best guarantor for overall survival.

4.1.2 Taking the cancer waiting time (CWT) standards as an example of policy implementation, the critical importance of 'time' in the treatment of malignancies is clearly evident.

5. Translated into the current clinical consensus for the treatment of CML (represented by the 2013 ELN Recommendations for the management of CML) this amounts to a rapid movement through the TKI treatment options in the search for a TKI considered effective enough to deliver an optimal response whilst also being well tolerated to ensure continuity of treatment and an acceptable QoL.

5.1 The ELN recommendations do not however amount to a prescription for robotic clinical behaviour that moves mechanistically, trialling one TKI after another until all are exhausted. Rather, its character is process like, involving a specialist unit MDT exercising deliberation and judgment with their final recommendation requiring a patient's consent and co-operation. It therefore does not necessarily involve all available options becoming real time lines of treatment for a patient although this is not to deny its occurrence in some instances.

6. The ACD referred to the expert clinicians critique of the Care Pathway for patients in either AP or BP (Committee Papers: Pre Meeting Briefing slide 6 of the set) noting.

The committee heard from experts that blast phase CML was the most acute phase of CML and that, depending on response to treatment, life expectancy would be less than 6 months. In blast phase CML, clinicians would want them to have the most clinically appropriate TKI available as soon as possible, and it would be unlikely that they would have the time to offer an alternative TKI therapy if the initial TKI used was not effective. (ACD: section 4.7)

6.1 We would argue that ponatinib represents *'the most clinically appropriate TKI'* for CP patients following multiple TKI failure unless ponatinib treatment is contraindicated by, for example, a patient with a history of arterial thrombosis.

6.2 Ponatinib amounts to the most clinically appropriate TKI because, as the committee noted,:

'*…although ponatinib is the only drug that is specifically licensed for the T315I gene mutation, it is generally also more effective than other treatments in those people who do not have the T315I gene mutation'* (ACD: section 4.12)

6.3 We remain puzzled why the Committee, given the parts of the ACD quoted in 6 & 6.2 above, was not prompted to go on to explore the place and performance of ponatinib, the sole 3rd Generation TKI, in the CP treatment pathway relative to other treatment options and in particular other second generation (2G) TKIs.

Had they done so they might have considered some of the observations made by one of the clinical experts in their written submission (The joint submission by the National Cancer Research Institute, Royal College of Physicians, Royal College of Radiologists, and Association of Cancer Physicians).

A summary of the joint submission would be that the clinical evidence points to ponatinib outperforming all other TKIs in all lines of treatment other than first using the achievement of CCyR as a baseline.

"All other TKIs" above refers to 1st or 2nd generation TKIs where the latter would include, bosutinib, selected as the most appropriate comparator (ACD: section 4.6).

The joint submission goes on to note the effectiveness of ponatinib against many mutations against which 2nd generation TKIs, including bosutinib, have been shown to be less effective.

6.4 We are not of course advocating the blanket use of ponatinib as a second line treatment or indeed in any line of treatment, nor are we proposing that all CP patients will obtain an optimal response following ponatinib treatment.

What we are requesting is that recognition be accorded to the strategic importance of being able to deploy the most potent TKI if specialist clinical opinion favours it for a clinically challenged patient in CP.

6.5 Put briefly, we can find no clinical rationale for waiting until clinical circumstances become significantly worse before being able to use the agent most likely to prevent that occurring.

6.6 We therefore respectfully ask the Committee to reverse its initial decision to a positive recommendation for the use of ponatinib for the eligible CP patient population.

One Birch Court
Blackpole East
Worcester
WR3 8SG
[redacted]

Monday, 06 March 2017

Dear NICE Technology Appraisal Committee C,

Re: Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia

We are writing on behalf of leukaemia patients in response to the recently published ACD for the appraisal of ponatinib – ID 671.

We are pleased to see that the committee intends to recommend the use of ponatinib for acute lymphoblastic leukaemia patients (ALL) and chronic myeloid leukaemia (CML) patients with accelerated or blast phase CML, or chronic phase CML with the T315i mutation. However, we are disappointed by the decision not to recommend ponatinib for chronic phase CML patients without the T315i mutation.

This decision exacerbates a perverse situation created by the Cancer Drugs Fund, where patients with a 'hard to treat' mutation can access this treatment, whilst those without it cannot. Patients without the T315i mutation who have exhausted their alternative treatment options (e.g. post bosutinib) or where other TKIs are clinically not appropriate (due to comorbidities), are in the same situation as those with the T315i mutation (i.e. without access to an effective treatment for their condition).

If this recommendation is upheld in the final guidance, it would leave these patients in the chronic phase without access to treatment, waiting for disease progression. Once their disease has progressed to accelerated or blast phase, they would be able to routinely access ponatinib. This cannot be ethical, logical or a cost-effective use of NHS resources.

Ponatinib has been licenced for use within this indication since July 2013, but is only now undergoing appraisal by NICE, following the original scoping in 2013. Ponatinib has been approved for use within this indication by the Scottish Medicines Consortium, since April 2015. As such, not recommending ponatinib within this indication leaves patients in England unable to access a treatment that is routinely available to similar patients in Scotland. We would also like to highlight the impact of this decision on existing guidance from the All Wales Medicines Strategy Group, recommending the use of ponatinib in this setting. This decision could remove access for patients in Wales to a treatment that has been

recommended since January 2015. We think that every leukaemia patient has a right to fair and equal access to treatment, regardless of where in the UK they live.

Patients in this setting have been waiting long enough for NICE to recommend ponatinib. We urge you not to issue a recommendation that leaves these patients waiting for disease progression before they can access treatment. As such, we ask you to approve ponatinib for CML patients in the chronic phase, with and without the T315i mutation and make it consistently available throughout the UK to all those who could benefit from it.

Yours Sincerely,

[redacted]

[redacted]

Leukaemia CARE

Royal College of Physicians
11 St Andrews Place
Regent's Park
London NW1 4LE
Tel: +44 (0)20 3075 1560

www.rcplondon.ac.uk

From The Registrar
[redacted]

National Institute for Health and Care Excellence
10 Spring Gardens
London
SW1A 2BU
tacommc@nice.org.uk

13 March 2017

Dear Stephanie

Re: Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [ID671]

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 33,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The NCRI-ACP-RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments.

Ponatinib is recommended as an option for treating chronic myeloid leukaemia (CML) in adults with:
- **chronic phase CML**

- only when the T315I gene mutation is present
- **accelerated phase or blast phase CML**

- when the disease is resistant to dasatinib or nilotinib or
- when they cannot have dasatinib or nilotinib and for whom imatinib is not clinically appropriate or
- when the T315I gene mutation is present and
- **the company provides ponatinib with the discount agreed in the patient access scheme.**

Our experts are extremely disappointed that for chronic phase CML we can still only access ponatinib when the T315I mutation is present, and this is not within the standard that CML-CP should be managed today. The indication for CP- CML should be as for AP-CML.

It has been set out in the original application that:
- The majority of patients are resistant without a detectable mutation
- The T315I mutation is very rare (5% of identifiable mutations)
- CML is much more difficult to treat when the disease progresses to AP-CML, and BP-CML outcomes have yet to improve significantly despite the advent of tyrosine kinase inhibitors (TKIs)
- The most successful way of treating advanced phase CML (AP and BP) is to prevent it from happening

Ponatinib is the most potent BCR-ABL inhibitor, and to limit it to advanced phase CML means that we patients will have to be allowed to progress before we can treat them appropriately. This will reduce patient chances of survival.

Ponatinib improves the rates of complete cytogenetic response (which is a surrogate marker of survival), for resistant CML-CP patients in second AND third line settings, in comparison with any of the other second generation TKIs (dasatinib, nilotinib and bosutinib).

Ref: 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, J. H.; Bryden, P.; Sidhu, M. K.; Huang, H.; McGarry, L. J.; Lustgarten, S.; Mealing, S.; Woods, B.; Whelan, J.; Hawkins, N. Leukemia research, Vol. 39, No. 1, 01.2015, p. 58-64.

Bosutinib, which was recently approved, is not considered in this Appraisal consultation document. Our experts are concerned at the prospect of exposing patients to other second generation TKIs that will not be effective. Bosutinib and dasatinib are both dual brc-abl src kinase inhibitors. Are unlikely to salvage a patient with bosutinib after dasatinib failure, and this is clearly evident from the bosutinib studies- lack of durability of response.

Bosutinib has to be placed in the same sentences as dasatinib and nilotinib .e.g

- **when the disease is resistant to dasatinib, nilotinib or bosutinib**
- **when they cannot have dasatinib, nilotinib or bosutinib and for whom imatinib is not clinically appropriate**

Otherwise physicians will have to give their patients a futile second generation TKI for a period of time, just to satisfy the NICE criteria for ponatinib access. This forces physicians to give inappropriate care.

The inclusion of bosutinib will not provide a cost-pressure, and of course will be cost-effective.

The committee concluded that the evidence on the clinical-effectiveness of ponatinib in people with the T315I gene mutation was sufficient for decision-making.

It is clear from all studies that T315I does not predict for response to ponatinib. Patients who respond do so according to the line of therapy. Most patients with the T315I were treated with ponatinib second line. This seems to have been omitted from the decision making process and needs to be re-addressed.

The committee considered the place of ponatinib in the current pathway was as a treatment option when imatinib, nilotinib and dasatinib are not clinically appropriate, and therefore bosutinib was the most appropriate comparator.

There are no randomised studies that directly compare any of the second generation drugs (2G-TKI). All studies compare a 2G-TKI with imatinib. From the data is it clear that all 2G-TKI are equally effective, but have considerably different side-effect profiles. There is no reason to compare ponatinib with bosutinib, over any other 2G-TKI.

As outlined in physicians' statements for ponatinib, if a CML-CP patient fails imatinib (as per ELN criteria), their chance of achieving a CCyR is 50% on any of the 2G-TKI and this includes bosutinib of course. If they fail this second line of therapy, their chance of achieving a CCyR with the next 2G-TKI (any of the others that have not been tried, including bosutinib), the chance of achieving a CCyR is 10%-30%. Without ponatinib, this patient would be transplanted (assuming a donor is available). The correct comparator to ponatinib is allogeneic transplant therefore.

With ponatinib, third line, the rates of CCyR increase to 50%, and a transplant with its resultant morbidity and mortality can be avoided.

If this restrictive approach to ponatinib in CML-CP is allowed, we will once more have limited access in England, whereas Wales and Scotland will be able to treat their patients appropriately, and within the ponatinib licence.

In summary, we strongly feel that the indication for CML-CP should be as for advanced phase CML, supported by overwhelming clinical data, in order to stop sub-standard treatment of CML patients in CP. We hope the panel will reconsider the evidence.

Yours sincerely

[redacted]
Registrar

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [ID671]

Response to Consultation

[redacted]

On behalf of the Royal College of Pathologists
March 2017

I confirm that:

- I am involved in the treatment of people with chronic myeloid leukaemia and have specialist expertise in this area
- I work principally for the NHS
- I have published papers on topics in chronic myeloid leukaemia
- I hold no official office with the company of the technology nor with any company of a directly competing technology (official office is taken to mean paid employment, unpaid directorship or membership of a standing advisory committee)
- I have no other conflict of interest that might preclude my involvement with this appraisal

Signed:

Date: 6th March 2017

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The outcome of this STA is very disappointing for the CML community and has been extensively discussed at the NCRI CML Working Party and with patients and carers. We are obviously pleased that ponatinib has been approved for patients with CML in chronic phase who have the T315I mutation, and for a wider range of indications in accelerated phase and blast crisis, but find the lack of access in chronic phase highly illogical.

To prolong the life of a patient with CML, we have learnt over the past 50 years, initially with allogeneic stem cell transplantation (allo-SCT) and now with tyrosine kinase inhibitors (TKI), that our efforts should be focussed in the chronic phase. Patients with progression, either to acceleration or blast crisis, will die of their disease. We have no effective treatments for these conditions. Even allo-SCT, which allows us to deliver the highest possible doses of chemotherapy, is ineffective in advanced phase disease. So the results of this appraisal, in which we can use ponatinib in acceleration and blast crisis, where any responses are destined to be short-lived, makes little sense. If we want to give patients with resistant chronic phase disease a chance of a prolonged survival we should treat them as early as possible. If this recommendation is accepted then these patients have to be allowed to progress to access a drug that would have an increased chance of efficacy if we had used it a few months earlier. The reason to use ponatinib in advanced phase disease is to achieve a short-lived second chronic phase that provides a window of response to permit consideration of allo-SCT

The number of patients in the UK who might benefit from ponatinib is relatively small. We are talking of patients who are truly resistant to at least one second generation TKI or who have demonstrated intolerance to at least two second generation TKI.

Our initial measurement of response uses a sensitive molecular assay, RQ-PCR 3 months after the start of treatment. Patients who achieve a result <10% are destined to have an outstanding long-term survival, predicted to be a normal life expectancy. When newly diagnosed patients are treated with imatinib, about 75% will achieve this milestone, but this figure rises to 90% when treated first-line with a second generation TKI. The failure to achieve a RQ-PCR <10% at 3 months is not necessarily due to resistance, it is sometimes related to an inability to take the drugs consistently because of adverse events.

Of those treated with imatinib, at least 50% will achieve a result <10%, 3 months after receiving a second generation TKI. Of the 50% who do not, some is genuine resistance and some is due to intolerance. The latter may respond if treatment is changed to an alternative second generation TKI. . Similarly some of the 10% of patients who do not reach a result <10% after frontline treatment with a second generation TKI due to intolerance or a genuine resistance, can benefit from an alternative second generation TKI.

The reason for discussing the proportion of responses to first, second and third line therapy is to emphasise how few patients will actually be eligble for

ponatinib. In addition ponatinib is a drug with potentially serious side effects. The phase III randomised study of ponatinib vs imatinib in newly diagnosed patients (EPIC) was discontinued prematurely because of the occurrence of arterial thrombotic events on imatinib. Given that the median age of onset of CML is 60-65 years, a time at which patients are already susceptible to cardio-, cerebro- and peripheral vascular disease, it is highly unlikely that ponatinib will be used inappropriately. Furthermore it will be discontinued if there is no evidence of response, to prevent unnecessary risk to patients. Since the response rate to ponatinib used third or fourth line is about 50%, this means that half the patients will discontinue after a few months.

Our major concern is that ponatinib was compared with bosutinib, which is completely inappropriate for patients with resistance to dasatinib or nilotinib. Bosutinib is certainly no more potent that either of these agents and the results of the phase III randomised study of imatinib vs bosutinib in newly diagnosed patients (BELA) might suggest that it is less potent. Unlike dasatinib and nilotinib, bosutinib did not achieve the primary endpoint of a better complete cytogenetic remission rate than imatinib at one year, and as a consequence is not licensed for first-line treatment. We feel that the choice of bosutinib as an alternative to the most potent TKI, is not rational and has come about because of the sequential appraisals of the various drugs and not a logical consideration of the best way to manage real patients.

Why do the panel consider bosutinib a suitable comparator in patients who are already known to be resistant to equivalent or more potent drugs? Receiving ponatinib at this point is the individual patient's last chance to receive a potentially effective agent before either considering allo-SCT or resigning themselves to inevitable progression and death. Prescribing bosutinib is a futile exercise. We completely accept, and trust that the panel do also, that we should not be treating patients with ineffective agents. But if this is accepted then how can the use of bosutinb as a comparator be justified?

We urge the panel to consider resistance and intolerance as different indications for ponatinib and make recommendations accordingly.

Resistance: at the time of resistance to a second generation drug, current practice is to perform a kinase domain mutation analysis. If the T315I is present (approx. 5% of patients in chronic phase) the patient can receive ponatinib. If there is another mutation present that is known to confer resistance to the current second generation drug, it makes sense to offer an alternative with efficacy. But the majority of patients do not have a mutation and should be offered ponatinib so as to reduce the risk of progression

Intolerance: for patients who are intolerant of a second generation drug, where intolerance by definition indicates responsiveness but an inability to take the drug because of adverse events, ponatinib should not be the first choice. If the patient has demonstrated previous intolerance or resistance to imatinib, then it would be entirely reasonable to offer one or both of the

alternative second generation drugs. If the patient has never received imatinib and responded deeply and rapidly to the initial second generation TKI, then imatinib would be an appropriate treatment. In these situations ponatinb would not be indicated until the patient had been intolerant of at least two second generation TKI.

Pfizer Response to the Appraisal Consultation Document for:

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia [ID671]

Pfizer would like to thank NICE for the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal. We wish to comment on a number of issues regarding the evidence discussed in the ACD.

Firstly, we are concerned about the appropriateness of comparison between the PACE study [1] and Khoury et al [2]. PACE patients were heavily pre-treated with multiple tyrosine kinase inhibitors (TKIs), whereas only 288 patients from Study 200 (Khoury et al) were previously treated with imatinib. The MAIC could therefore be considered to have significant bias based on the undefined baseline characteristics of the patient; the basic phenotype of a heavily pre-treated patient may not have been captured by individual patient level data to which they had access for their MAIC.

In addition, the MAIC approach was only used for patients with chronic phase CML because only in these patients was the data comprehensive, to allow the matching technique to be used. It is therefore unclear as to how the manufacturer was able to derive an ICER vs bosutinib in patients with blast phase chronic myeloid leukaemia.

Pfizer asks the committee to consider these issues above and view the results from the MAIC with extreme caution prior to the finalisation of their recommendation.

References

[1] Cortes et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med. 2013 Nov 7;369(19):1783-96.

[2] Khoury et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood. 2012 Apr 12;119 (15):3403-12.

Comment on the ACD from Sara Mulvanny (CML patient being treated with ponatinib)

I'm glad that the Committee has recommended Ponatinib for patients with later stages of CML or if a patient has the T315i mutation, however, I'm very disappointed that patients in Chronic phase CML (like myself) without mutations won't be able to use Ponatinib.

I find it hard to comprehend this decision because the patients who have been omitted from this approval are the ones who must have failed one or more of the other TKI's (otherwise they wouldn't be considering Ponatinib as a treatment option), therefore their need for an effective treatment is it just as great as patients with the T315i mutation, or in other stages of CML.

My situation was slightly different because I obtained Ponatinib on the PACE trial after Dasatinib proved unsuccessful. However, If I had been diagnosed with CML today and failed Dasatinib, I wouldn't be offered Ponatinib, and since Ponatinib has treated my CML so successfully, this is a quite an unsettling thought.

As I said in my submission to the Committee, when your CML proves to be resistant and your current TKI treatment is unsuccessful, it's a very stressful and daunting time for a patient. The fear that your CML will progress to the next accelerated or blast phase is a terrifying thought, especially since that means it's much harder to treat. Waiting until the CML is more advanced before being able to use the most potent TKI is nonsensical: it makes more sense to treat a CML which has shown resistance earlier rather than later, thus avoiding wasting money on failing treatment options that aren't potent enough to impede a resistant CML.

If a patient failed all the other TKIs but didn't have the T315i mutation and weren't in an accelerated phase, then the only option would be a bone marrow transplant. If that had happened to myself than I would have had to take a year off work to recover. This would have had a profound impact on my career and earnings since I'm self-employed. In addition, I wouldn't have been able to have children in the future because the transplant would have pushed me into an early menopause, and since I'm a woman in my late 20's, I'm very grateful that Ponatinib has allowed me to retain the option of having a family in the future.

The transplant itself is a risky procedure, with some implications that cannot be foreseen or prevented, therefore it makes sense to try a much less dangerous treatment option such a Ponatinib before going down that route. In addition, the transplant isn't a viable option for some patients who have other medical conditions or who are unable to find a suitable donor.

I'm very grateful that Ponatinib has had a transformative effect for myself and I now lead a very active, social and enjoyable life which is unencumbered by CML. I'm aware that Ponatinib doesn't necessarily have the same result for all patients and each patient has a different response to each of the TKIs: I myself know someone who was successfully treated with Dasatinib. However, it's important to have as many TKI's available as possible, and all CML patients should have the opportunity to try Ponatinib if they need that option. I strongly believe that this option should be available earlier rather than later, when it's most likely to be successful rather than when a patient is deemed to satisfy all the predetermined requirements.

In summary, I urge the Committee to reconsider their recommendation about chronic phase CML.

Response to NICE consultation

Single Technology Appraisal [ID671]

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia

Jane Apperley MBChB, FRCP, FRCPath

Imperial College, London

Thank you for offering me the opportunity to comment on the consultation. My comments relate to my particular area of expertise, chronic myeloid leukaemia (CML)

I welcome the approval to use ponatinib in CML in accelerated phase and blast crisis under the following circumstances

- when the disease is resistant to dasatinib or nilotinib or
- when they cannot have dasatinib or nilotinib and for whom imatinib is not clinically appropriate or
- when the T315I gene mutation is present

However I am disappointed that the approval for use in chronic phase was restricted to patients with a T315I mutation and not extended to those who are resistant and/or intolerant to other tyrosine kinase inhibitors. The proposed recommendations will mean that some patients who have a very high chance of responding to ponatinib will instead be offered a costly and risky allogeneic stem cell transplant, and if ineligible for transplant, will progress to a fatal blast crisis. I would like to suggest that ponatinb is made available for patients in chronic phase who have demonstrated resistance to a second generation TKI, and for patients in chronic phase who have demonstrated intolerance to at least two second generation TKI.

In making my comments I am struck by the restraints that are placed on such consultations by having to consider each tyrosine kinase inhibitor (TKI) individually rather than addressing the management of chronic myeloid leukaemia as a pathway. The majority of patients respond well and durably to the first generation TKI, imatinib, with a smaller proportion requiring one of the second generation TKI, dasatinib, nilotinib and bosutinib. Approximately half of these patients will be resistant to these drugs, and more than 90% of these will not have a T315I mutation. The need for a third generation inhibitor, namely ponatinib, is restricted to a very small number of patients (probably 50-60 per annum in the UK) for whom the only possible alternative is allogeneic stem cell transplantation (allo-SCT). This procedure is restricted to younger individuals with well-matched donors and carries a high risk of mortality or long-term morbidity. The remaining patients face inevitable progression to blast transformation and death. Ponatinib has very limited efficacy in this situation with low response rates that lack durability. This introduces an element of discrimination towards older patients.

The conclusion of the panel seems illogical to this physician. We will be allowed to use ponatinib when these patients inevitably progress. We will incur the expense in the same number of patients but with no expectation of durable response, whereas earlier treatment would have given about half of these individuals the prospect of a normal life expectancy.

Despite the clear patient pathway, this appraisal chose to use bosutinib, another second generation TKI, as the comparator for ponatinib. The point was made at the meeting that this was an inappropriate comparator, especially for patients with resistance to second generation drugs, and its use as such cannot be justified by the panel.

- The terms first, second and third generation TKI, are used for good reason. Each successive generation of drug had increased potency and activity against an increasing number of BCR-ABL1 kinase domain mutations, but in addition better outcome in patients in whom mutations could not be demonstrated but who had demonstrated resistance to prior therapy.

- The second generation TKI have activity against many of the >50 mutations that rendered patients resistant to imatinib, but are equally effective in patients who exhibited imatinib resistance but did not have BCR-ABL1 kinase domain mutations. In the Phase II studies of dasatinib, nilotinib and bosutinib in these circumstances the incidence of complete cytogenetic remission (CCyR) was approximately 40-50% for each of the three drugs, irrespective of the presence of a mutation. The value of identifying a mutation in an individual patient is not because it indicates an increased probability of response compared to a patient without a mutation, but because it helps to direct the choice of the second generation drug, which have some differences in activity against the individual mutations

- Bosutinib was developed 2-3 years later than dasatinib and nilotinib, and was initially tested in a Phase II study of patients who had failed imatinib (second line) or imatinib and dasatinib and/or nilotinib (third and fourth line) for reasons of intolerance or resistance. CCyR rates were approximately 40% in second line for imatinib resistance, equivalent to the efficacy of dasatinib or nilotinib in this setting. However in third line the CCyR rate was only 22% in patients in whom prior resistance had been demonstrated.

- The third generation drug, ponatinib, is so-called because it has activity against the T315I mutation. When ponatinib was tested in the large Phase II study, PACE, this activity was confirmed but the study also demonstrated a higher rate of CCyR in patients without a T315I mutation in the third line setting. CCyR rates were 48%, more than double that of bosutinib.

- Further evidence of the increased potency of ponatinib over second generation drugs can be inferred from the results in the first-line setting when each of bosutinib, dasatinib, nilotinib and ponatinib were compared to imatinib. Dasatinib and nilotinib demonstrated increased potency over imatinib with CCyR rates at 12 months being 77% vs 66% (dasatinib vs imatinib) and 80% vs 65% (nilotiinib vs imatinib) but bosutinib did not with a CCyR rate of 70% compared to imatinib at 68%. Deeper responses, namely major molecular responses (MMR) at one year were 46% for dasatinib, 51% for nilotinib and 41% for bosutinib compared to a consistent 27% for imatinib across each of the studies. However in the Phase III EPIC study of ponatinib vs imatinib, which was stopped prematurely because of concern about the occurrence of arterial thrombotic events on ponatinib, the MMR rate at only 6 months was 62% for ponatinib and 22% for imatinib. At 12 months limited numbers of patients were available for evaluation but the MMR rate for ponatinib had reached 80%, again almost double that of the second generation agents. Concerns regarding the safety of ponatinib in patients who might well respond well to imatinib are well known but these

concerns should not detract from the very clear demonstration of the increased potency of ponatinib over the second generation drugs

In summary, for patients who demonstrate **resistance** to dasatinib or nilotinib it makes little sense to offer them bosutinib, a drug of equivalent efficacy to the drug they have just failed.

The situation with respect to patients who have demonstrated **intolerance** to dasatinib or nilotinib is less clear cut. Intolerance implies that the patient is sensitive in terms of efficacy to whichever drug they are taking, but are having problems with side effects. Most physicians will accept an algorithm that offers patients an alternative second generation drug before suggesting ponatinib, but for those who demonstrate intolerance to at least two second generation TKI, ponatinib is a reasonable strategy and would avoid allogeneic stem cell transplantation in patients who are sensitive to TKI.

Further points worthy of consideration include

1. Normal clinical care: haematologists are well aware of the adverse effects of ponatinib and the association with potentially life threatening thrombotic events. They are unlikely to continue to prescribe a drug with an adverse risk profile if it is ineffective. Balancing risk-benefit is part of daily practice. The recommendation for ponatinib could include three monthly assessment of the benefit with instructions to discontinue treatment of there is no clear evidence of response
2. Point 4.4 is incorrect and suggests a misunderstanding. A reduction in tumour load at 3 months is measured by a specific assay for molecular response, RQ-PCR, and the international recommendations are that an optimal responder would have a value <10% at 3 months. Some 70-75% of patients achieve this on first-line imatinib and this figures rises to 90% for patients treated first-line with dasatinib or nilotinib. The 30% figure quoted in 4.4 is the proportion of patients who **fail** to reach this milestone on imatinib. Similarly the suggestion that the 50% of patients who then fail to respond to another drug (not-specified) would be offered bosutinib fails to acknowledge that this is only because of current NICE guidance and not because it is a logical way to manage patients resistant to imatinib, nilotinib and dasatinib. In fact bosutinib can now be offered to some patients who have only failed imatiinib, if there are particular circumstances that would preclude the use of dasatinib or nilotinib.
3. Point 4.7 is also inaccurate. The three month response is measured by the RQ-PCR referred to above and is a molecular response not a cytogenetic response.
4. Point 4.8 also suggests a misunderstanding. In the absence of the T315I mutation, patients who fail imatinib for either of resistance or intolerance, would not be offered ponatinb directly, but would first be offered at least one second generation TKI. This point ends in a statement that bosutinib is therefore a suitable comparator for ponatinib but without justification.
5. Point 4.11 discusses the appropriateness of an analysis involving a comparison between the PACE study of ponatinib and the study published by Khoury relating to the use of bosutinib as third line therapy. However no thought is given to try to compare the potency of ponatinib and bosutinib in the management of CML. The data I presented earlier suggests that the use of all these drugs in the frontline setting provides additional evidence of the increased potency of ponatinib over bosutinib.
6. Point 4.11 refers to the use of the ERG, which was discussed at the panel meeting. There was a lack of agreement about the outcome of patients who were non-responders to ponatinib

in the PACE study. Because the PACE study was only permitted to follow-up patients who were on study or who had recently (30 days) discontinued ponatinib, there are no good outcome data on the survival of these patients. Figures 11 and 13 in the ERG presented a range of curves based on different mathematical models. Figure 13 suggests that several of these models concluded that there would be a plateau in survival such that 30% of non-responders to ponatinib would have a prolonged progression free survival, whereas the log normal curve suggests that these patients would continue to progress and die. It is unclear to me which curve was used and whether an inappropriate choice would affect the ICER. The disease course for untreated patients is inevitable progression and death. Furthermore the lack of response to 3 or 4 second and third generation TKI indicate a group of patients with a very high risk of progression, such that the log normal curve is a more realistic prediction. This may need to be revisited if the ICER will change with an alternative model.

7. The conclusion of point 4.23, namely that the range of ICERs for ponatinib compared with bosutinib presented by the ERG continued to exceed the range that is usually considered to be cost effective, relies on the bosutinib PAS. Disappointingly the decision regarding the availability of ponatinib therefore relies on cost rather than the potential for efficacy. Bosutinib is not a suitable comparator to ponatinib for patients with resistance to resistance to dasatinib or nilotinib, so the economic argument is irrelevant.
8. Point 4.29 suggests that the life expectancy of patients with chronic phase CML exceeds 4 years regardless of treatment. Whereas this statement is true for the majority of patients at the time of diagnosis it is not true for patients with resistance to second line TKI who do not receive effective treatment. These individuals have a very poor prognosis compared to a newly diagnosed patient because they have just proved themselves resistant to TKI treatment. They return to the prognosis of a patient in the pre-TKI era, when the median survival was 6 years from diagnosis. The median value was accompanied by a very wide range, from a few months to >20 years. This heterogeneity has never been adequately explained but it is highly likely that patients who have failed otherwise highly effective treatment in the form of TKI will progress earlier than the median. Progression to blast crisis is highly likely within a short period of time and will not be of the order of 4 years.

In summary I ask the panel to reconsider their decision and allow us to use ponatinib in

- patients with CML in chronic phase who have a T315I mutation
- patients with CML in chronic phase who have demonstrated resistance to one second generation TKI (will include patients who have or have not received prior imatinib)and do not have a kinase domain mutation that might confer sensitivity to an alternative second generation TKI
- patients with CML in chronic phase who have demonstrated intolerance to at least two second generation TKI

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	[redacted]
Organisation	University Hospitals Bristol NHS Foundation Trust
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Regarding the ponatinib for Ph +ve ALL in ACD, it states that it can be used when- • the disease is resistant to dasatinib or • they cannot have dasatinib and for whom imatinib is not clinically appropriate or • the T315I gene mutation is present and however dasatinib is currently not commissioned in England for Ph +ve ALL. There is therefore currently no access to an alternative TKI to imatinib for Ph +ve ALL. Applying for dasatinib via IFR previously is not possible as this is a cohort. On the NICE website it states that dasatinib for Ph+ve ALL was removed from the appraisals programme in Dec 2008 and its currently not available via CDF. The NICE TA therefore implies we should access dasatinib before ponatinib (unless T315I mutation) but we cant.
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Ponatinib for treating chronic myeloid leukaemia: A Single Technology Appraisal

Additional Work Post ACD Comments

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK Andrew Rawdin, Research Assistant, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
Date completed	09/03/2017

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6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The company have changed the level of the discount in the PAS to [redacted]. The impact of the exploratory analyses undertaken by the ERG when using the new PAS are reported in this section. Note, references to supportive tables, figures and sections refer to those in the original ERG report.

All analyses have been undertaken using the list price of drugs relevant to the decision problem with the exception of ponatinib: the results including the PAS discounts for comparator drugs are provided in a separate confidential appendix. The results presented have been generated amending the version of the AP-CML / BP-CML model provided by the company on the 14th December 2016 which provided separate resource usages for AP-CML and BP-CML: these results were similar to those generated by the model version submitted on the 11th December 2016 which used identical resource usage for AP-CML and BP-CML.

The analyses are undertaken in comparison to the previous intervention on the efficiency frontier and against other interventions that could, based on the chosen assumptions, become the previous intervention on the efficiency frontier.

The results presented are subject to further levels of uncertainty, such as the lack of a robust PSA, the lack of continuity corrections for low observed counts, and the inherent uncertainty associated with data produced via an MAIC for the CP-CML analyses.

6.1 Results for CP-CML

The results are presented in Table 1. The ERG's base case does not include drug wastage and thus the ICER is likely to be lower than the ICER if the true level of wastage was incorporated. Treatment-related deaths have not been incorporated in the base case; this is favourable to ponatinib compared with BSC and allo-SCT.

The ranges in the ICER relating to plausible fits to the survivor function are large, thereby indicating considerable uncertainty in the ICER.

6.1.1 Results for ponatinib compared with bosutinib for CP-CML patients

For the comparison of ponatinib with bosutinib, the largest drivers of the ICER include: drug wastage; the estimation of costs post-progression and post-allo-SCT relapse; the inclusion of a stopping rule for bosutinib; the use of the log-normal distribution rather than the Gompertz distribution for DoR for both

ponatinib and bosutinib; and use of the log-normal distribution rather than the exponential distribution for characterising PFS for those patients who achieve NR from treatment. The fit of the exponential and the log-normal distributions to PFS for those with NR performed by the company can be seen in **Error! Reference source not found.**. The company's fit of the Gompertz and log-normal distributions to DoR are shown in **Error! Reference source not found.** and **Error! Reference source not found.** for ponatinib and **Error! Reference source not found.** for bosutinib.

The ERG believes that the ICER is likely to lie in the range £19,680 - £37,381 although any drug wastage would increase these values. The upper bound can be reduced to £31,313 (data not presented in table) if it is believed that the data for PFS in NR can be best represented by an exponential curve, although the ERG notes that both the exponential curves fitted by the company and the ERG provide a poor fit to the observed data. If exponential distributions are fitted to all PFS curves the range becomes £18,987 - £31,377.

6.1.2 Results for ponatinib compared with BSC for CP-CML patients

For the comparison of ponatinib with BSC, the largest drivers of the ICER include: drug wastage; and the estimation of costs post-progression. For the comparison of ponatinib with BSC, the ERG believes that the ICER is likely to lie in the range £15,820 - £24,581 although any drug wastage or ponatinib-related deaths would increase these values: assuming an exponential curve for PFS in NR would decrease the upper value of the ICER range to £23,597 (data not presented in table). If exponential distributions are fitted to all PFS curves the range becomes £17,297 - £23,945.

6.1.3. Results for ponatinib compared with allo-SCT for CP-CML patients

For the comparison of ponatinib with allo-SCT, the largest drivers of the ICER include: drug wastage; the estimation of costs post-progression and post-allo-SCT relapse; and the assumed distribution for characterising OS following allo-SCT (either Gompertz or exponential) for patients in CP-CML. The company's fits of the Gompertz and exponential distributions to OS data post allo-SCT are provided in **Error! Reference source not found.**. The ERG believes that the ICER for the comparison of ponatinib versus allo-SCT is highly uncertain. However, it is likely that the ICER is greater than £15,000 and it possible that ponatinib could be dominated by SCT. Assuming an exponential distribution for PFS in NR increased the lower estimate of the ICER range to £19,030 (data not presented in table). When the Gompertz distribution was selected for OS after allo-SCT the ICER was generally greater than £50,000; contrastingly when the exponential distributions were used the ICER was typically lower than £25,000. Clinical advice received by the ERG suggested that the Gompertz distribution was likely to be the more plausible of the two distributions. If exponential distributions are fitted to all PFS curves the range becomes £20,634 - dominated.

6.1.4 Results for ponatinib compared with interferon alfa for AP-CML patients

The ERG believes that probability that interferon alfa would be on the efficiency frontier is low, regardless of the assumptions made. As such, no further analyses were conducted by the ERG.

Table 1: Impact of the ERG's deterministic exploratory analyses in CP-CML

		Cost per QALY gained (£)		
Ref No	**Exploratory Analyses**	**Pon vs Bos**	**Pon vs BSC**	**Pon vs allo-SCT**
0	N/A (company's base case)	14,922	12,887	806
1a	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	10,387 – 37,401	9582 – 19,512	Dominant – 8416
1b	As 1a, but using the same distribution for DoR for ponatinib and bosutinib (range)	11,792 – 33,336	N/A	N/A
1c	As 1a, but solely using the company's exponential distribution for PFS in NR (range)	10,387 – 23,426	9582 – 18,463	Dominant – 8416
1d	Combining 1b and 1c	14,804 – 33,336	12,771 – 19,582	Dominant – 3624
2a	Recalculation of the survivor functions (excluding PFS exponentials)	13,010	11,320	Dominant
2b	As 2a, but use of the ERG's estimated exponential distribution for PFS in NR	13,603	12,384	Dominant
2c	As 2a, but use of the ERG's estimated exponential distributions for PFS for all response groups	14,566	12,906	Dominant
3	Assuming drug wastage	26,273	21,095	12,081
4	Incorporating a three-month stopping rule for bosutinib	18,058	N/A	N/A
5	No half-cycle correction of intervention costs	14,397	13,327	2140
6	Including treatment-related deaths	14,584	14,331	2659
7a	Reducing the costs assumed post-progression in CP-CML or post allo-SCT for CP-CML patients to that of BSC.	18,426	16,375	18,476
7b	Reducing costs post-progression in CP-CML or post allo-SCT for CP-CML patients to that estimated for generic imatinib.	18,293	16,242	17,803
8	Assuming life table data are probabilities not rates	14,932	12,896	803
9a	Assuming ratios of HRQoL between CP-CML and other CML states are maintained	14,761	12,747	817
9b	Assuming decrements of HRQoL between CP-CML and other CML states are maintained	14,682	12,678	823
10	2a, 4, 5, 7a, 8 and 9a, using the curves believed most credible by the company	19,743	15,923	23,690
11. ERG base case ICERs	As 10, but choosing alternative distributions in addition to those selected by the company (range) – (11a)	16,959 – 45,896	15,820 – 24,581	15,156 – Dominated
	As 11a, but assuming the same distribution for DoR for ponatinib and bosutinib (range)	19,680 – 37,381	N/A	N/A
	As 11a, but assuming an exponential distributions for PFS (range)	18,987 – 31,377	17,297 – 23,945	20,634 – Dominated

The ERG base case ICERs are likely to be favourable to ponatinib as neither drug wastage nor treatment-related deaths are assumed

All analyses are changes from the company's base case unless stated. ↑ cost per QALY yielded

6.2 Results for AP-CML

The results are presented in Table 2.

The ERG's base case includes drug wastage, assuming that prescriptions occur at three-monthly intervals: the ICER would be lower if shorter prescription periods were incorporated, although this was not possible due to the length of time cycles employed in the company's model. Treatment-related deaths have not been incorporated in the base case, which is likely to have been favourable to ponatinib compared with BSC and allo-SCT.

The ranges in the ICER relating to plausible fits to the survivor function are large in the comparison of ponatinib with allo-SCT indicating considerable uncertainty in the ICER.

6.1.1 Results for ponatinib compared with bosutinib for AP-CML patients

For the comparison of ponatinib with bosutinib, ponatinib typically dominated bosutinib. As such, no further analyses were conducted by the ERG.

6.1.2 Results for ponatinib compared with BSC for AP-CML patients

For the comparison of ponatinib with BSC the ERG believes it unlikely that the ICER is greater than £18,000 per QALY gained.

6.1.3 Results for ponatinib compared with allo-SCT for AP-CML patients

For the comparison of ponatinib with allo-SCT the largest drivers of the ICER is the distribution assumed for OS post allo-SCT. The fits of the Gompertz and exponential distributions to OS data post allo-SCT produced by the company are provided in **Error! Reference source not found.**: the distributions estimated by the ERG are shown in Appendix 1 (**Error! Reference source not found.**).

The ICER for the comparison of ponatinib with allo-SCT is believed to be uncertain by the ERG: ponatinib could dominate allo-SCT, that is being less expensive and providing more health to the patient, or the ICER could be greater than £61,000 per QALY gained.

Table 2: Impact of the ERG's deterministic exploratory analyses in AP-CML

		Cost per QALY gained (£) – Ponatinib vs	
Ref No	**Exploratory Analyses**	**BSC**	**Allo-SCT**
0	N/A (company's base case)	14,590	12,996
1	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	7350 – 15,703	Dominant – 94,062
2	Recalculation of the survivor functions	10,215	11,985
3	Assuming drug wastage	15,061	13,832
4	No half-cycle correction of intervention costs	16,251	15,880
5	Including treatment-related deaths	14,584	12,377
6	Assuming life table data are probabilities not rates	14,594	13,003
7	2,3, 4, and 6 using the curves believed most credible by the company	12,590	15,787
8 ERG base case ICER	As 7, but choosing alternative distributions in addition to those selected by the company (range)	7123 – 17,625	Dominant – 61,896

Note: the ERG base case ICERs are likely to be unfavourable to ponatinib as drug wastage is included with an assumption of prescriptions at three-monthly intervals.

Ponatinib typically dominates bosutinib

Note: All analyses are changes from the company's base case unless stated.

6.3 Results for BP-CML

The results are presented in

Table 3.

The ERG's base case includes drug wastage, assuming that prescriptions occur at three-monthly intervals: the ICER would be lower if shorter prescription periods were incorporated, although this was not possible due to the length of time cycles employed in the model. Treatment-related deaths have not been incorporated in the base case which is likely to have been favourable to ponatinib compared with BSC and allo-SCT.

The ranges in the ICER relating to plausible fits to the survivor function are large in the comparison of ponatinib with allo-SCT indicating considerable uncertainty in the ICER.

6.3.1 Results for ponatinib compared with bosutinib for BP-CML patients

For the comparison of ponatinib with BSC the ERG believes it unlikely that the ICER is greater than £22,000 per QALY gained.

6.3.2 Results for ponatinib compared with BSC for BP-CML patients

For the comparison of ponatinib with BSC, ponatinib typically dominated BSC due to the high costs of monitoring and follow-up of BP-CML patients, which are assumed to be greater than £20,000 per three-month period; these are largely driven by hospitalisation costs. As such, no further analyses were conducted.

6.3.3 Results for ponatinib compared with allo-SCT for BP-CML patients

For the comparison of ponatinib with allo-SCT, the largest drivers of the ICER is the distribution assumed for OS post allo-SCT for those with remission and those without remission (either Gompertz or exponential). The fits of the Gompertz and exponential distributions to OS data post allo-SCT produced by the company are provided in **Error! Reference source not found.**: the distributions estimated by the ERG are shown in Appendix 1 (**Error! Reference source not found.**).

The ERG considers the ICER for ponatinib versus allo-SCT to be uncertain: allo-SCT could be dominated by ponatinib, that is being more expensive and providing less health to the patient, or the ICER could be lower than £6000 per QALY gained.

Table 3: Impact of the ERG's deterministic exploratory analyses in BP-CML

		Cost per QALY gained (£)	
Ref No	**Exploratory Analyses**	**Ponatinib vs bosutinib**	**Allo-SCT vs Ponatinib**
0	N/A (company's base case)	17,130	Dominated
1	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	10,873 – 18,330	8604 - Dominated
2	Recalculation of the survivor functions	15,401	159,990
3	Assuming drug wastage	17,476	Dominated
4	Incorporating a three-month stopping rule for bosutinib	21,440	N/A
5	No half-cycle correction of intervention costs	17,263	Dominated
6	Including treatment-related deaths	16,174	Dominated
7	Assuming life table data are probabilities not rates	17,131	Dominated
8	2,3, 4,5, and 7 using the curves believed most credible by the company	20,107	110,415
9 ERG base case ICER	As 8, but choosing alternative distributions in addition to those selected by the company (range)	16,209 – 21,404	5053 - Dominated

Note: the ERG base case ICERs are likely to be unfavourable to ponatinib as drug wastage is included with an assumption of prescriptions at three-monthly intervals.

Note: the comparison of ponatinib with allo-SCT is the cost per QALY gained of allo-SCT compared with ponatinib (South-West quadrant).

Ponatinib typically dominates BSC

Note: All analyses are changes from the company's base case unless stated.

6.4 Exploratory analyses for patients known to be with, and without, the T315I mutation

The company did not present results for patients with, and without the T315I mutation.

The ERG believes that for patients known to have the T315I mutation the most appropriate comparison would exclude bosutinib. This results in an estimated ICER in CP-CML in the range £15,820 - £24,581 per QALY gained compared with BSC, and remaining uncertain compared with allo-SCT. In AP-CML, the ICER is estimated to be in the range £7123 - £17,625 per QALY gained compared with BSC, and remaining uncertain compared with allo-SCT. In BP-CML, ponatinib is estimated to dominate BSC, and the ICER is uncertain compared with allo-SCT.

For patients known to not have the T315I mutation it is anticipated that the lower and upper values in the range in the cost per QALY gained compared with bosutinib would increase, that is, become less favourable to ponatinib. However, the precise increase in these values is unknown.

6.5 Exploratory analyses assessing the ICER if induction chemotherapy was considered as a comparator in BP-CML

Clinical advisors to the ERG suggested that induction chemotherapy should have been considered as a comparator in BP-CML. To explore the impacts of allowing this comparator it was assumed that the results for induction chemotherapy in Ph+ ALL were generalisable to patients in BP-CML. The ICER for ponatinib compared with induction chemotherapy has been estimated to be below £5000 per QALY gained.

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Additional Work Post ACD Comments – ERG response to company comments (received 15 March 2017)

In Section 6.1.1 (Results for ponatinib compared with bosutinib for CP-CML patients) with the new increased PAS the ERG concludes:

The ERG believes that the ICER is likely to lie in the range £19,680 - £37,381 although any drug wastage would increase these values. The upper bound can be reduced to £31,313 (data not presented in table) if it is believed that the data for PFS in NR can be best represented by an exponential curve, although the ERG notes that both the exponential curves fitted by the company and the ERG provide a poor fit to the observed data. If exponential distributions are fitted to all PFS curves the range becomes £18,987 - £31,377.

However, some of these results are not consistent with results in the previous ERG report with a lower PAS:

1. It was previously stated in the ERG report Errata (Section 1.2 page 18, paragraph 5): "If only an exponential function was considered plausible for PFS in non-responders then the ICER compared with bosutinib ranges from £22,995 to £30,741 per QALY gained." This is not consistent with the upper bound of £31,313 in the current document, particularly as the PAS has been increased.

   ERG response: The numbers reported by the company relate to a different scenario than that reported by the ERG. For clarity, we have reported the ICERs for all combinations at the end of this document.

2. Table 1 in the current document does not seem to be compatible with the same analysis done by the ERG in the original report with the previous lower PAS. When comparing Table 1: Impact of the ERG's deterministic exploratory analyses in CP-CML at row "1d Combining 1b and 1c" with the same case in Table 66 in the original ERG report we note that for the comparison ponatinib vs bosutinib the range is now £14,804-33,336 while it was previously £15,319-25,181. It is not clear how incorporating an increased PAS produces a higher bound of ICER.

   ERG response: This is a typo. The correct range is £11,792 – £21,238

3. Using the ERG amended CP-CML model we have been able to exactly replicate the upper bound of the ERG base case (£37,381/QALY). However, by our calculations the following step of simply changing the functions for PFS produces different results: changing only PFS in NR to exponential brings the upper bound to £26,714; changing all the PFS curves to the exponential brings the upper bound to £27,580. Can the ERG clarify what other change was introduced into the model?

   ERG response: The numbers reported by the company relate to a different scenario than that reported by the ERG. For clarity, we have reported the ICERs for all combinations at the end of this document.

ERG base case ICER ranges for ponatinib vs bosutinib in CP-CML

Refer to Table 66 in the main report for scenario numbers

Scenario	ICER Range (£)
As 10, but choosing alternative distributions in addition to those selected by the company (range) – (11a)	16,959 - 45,896
As 11a, but assuming the same distribution for DoR for ponatinib and bosutinib (range)	19,680 – 37,381
As 11a, but assuming an exponential distribution for PFS for NR (range)	16,959 – 31,313
As 11a, but assuming the same distribution for DoR for ponatinib and bosutinib and an exponential distribution for PFS (range)	19,680 – 26,714
As 11a, but assuming exponential distributions for PFS in all response categories (range)	18,987 – 31,377
As 11a, but assuming the same distribution for DoR for ponatinib and bosutinib and exponential distributions for PFS in all response categories (range)	21,414 – 27,580

The version of this table containing the confidential bosutinib PAS has been provided to the Appraisal Committee in a separate document.

Ponatinib for treating acute lymphoblastic leukaemia: A Single Technology Appraisal Additional Work Post ACD Comments

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK Andrew Rawdin, Research Assistant, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
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6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The company have changed the level of the discount in the PAS to [redacted]. The impact of the exploratory analyses undertaken by the ERG when using the new PAS are reported in this section. Note, references to supportive tables, figures and sections refer to those in the original ERG report.

The ERG's base case includes drug wastage, with the assumption, due to the construct of the model that prescriptions are at three-monthly intervals. As such, the ICER is likely to be higher than if the true frequency of prescriptions is included.

The results presented are subject to further levels of uncertainty, such as the lack of a robust PSA and the lack of continuity corrections for low observed counts.

6.1 Results for people who are suitable for allo-SCT

The results are presented in Table 1.

The ranges in the ICER relating to plausible fits to the survivor function are large indicating considerable uncertainty in the ICER. The fit of the extrapolated curves to the data are shown in **Error! Reference source not found.** and **Error! Reference source not found.** for OS on ponatinib; **Error! Reference source not found.** and **Error! Reference source not found.** for time on treatment with ponatinib; and **Error! Reference source not found.** (Appendix 1) for OS after allo-SCT.

6.1.1 Results for ponatinib compared with induction chemotherapy

For the comparison of ponatinib with induction chemotherapy, key drivers of the ICER are: the choices of the distribution of the survivor function; the method used to fit the survivor function for survival post allo-SCT; the removal of the half-cycle correction of the intervention costs; and the appropriateness of having differential OS for those who experience NR based on initial treatment. The ERG believes that the ICER for ponatinib compared with induction chemotherapy is likely to be below £5,000 per QALY gained, although notes the uncertainty caused by the naïve indirect comparison.

6.1.2 Results for ponatinib compared with BSC

For the comparison of ponatinib with BSC, the largest drivers of the ICER are the choices of the survivor functions, and the method used to fit the survivor function for survival post allo-SCT. For the comparison of ponatinib with BSC, the ERG believes that the ICER is likely to lie in the range £7,000 to £30,000 per QALY gained.

Table 1: The impact of the ERG's deterministic exploratory analyses in patients suitable for allo-SCT

		Cost per QALY (£)	
Ref No	**Exploratory Analyses**	**Ponatinib vs induction chemotherapy**	**Ponatinib vs BSC**
0	N/A (Company Base Case)	29,812	26,319
1	Recalculation of the OS post allo-SCT curve	54,615	52.949
2	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	22,840 – 51,337	19,694 – 31,577
3	Assuming drug wastage	31,062	26,610
4	No half-cycle correction of intervention costs	41,293	28,992
5	Including treatment related deaths	26,739	25,524
6	Removal of immortality for a small subset of patients	30,523	26,653
7a	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the ponatinib value	Dominant	12,661
7b	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the BSC value	Dominant	18,690
8	1, 3,4 and 6 using the curves believed most credible by the company	84,570	61,273
9	1, 3,4, 6 and 7a using the curves believed most credible by the company	4138	29,995
10. ERG base case ICERs	As 9, but choosing alternative distributions in addition to those selected by the company (range)	Dominant - 4138	7156 – 29,995

Allo-SCT, allogeneic stem cell transplant; BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; N/A, not applicable; NR, non-responders; OS, overall survival; QALY, quality-adjusted life year
Note: the ICERs may be unfavourable to ponatinib as it is assumed that prescriptions are at three-monthly intervals when assessing drug wastage.

6.1.3 Results for patients known to be with, and without, the T315I mutation

Based on clinical advice provided to the ERG it is believed that for patients known to have the T315I mutation the most appropriate comparison would exclude induction chemotherapy and would result in an ICER likely to lie in the range £7,000 to £30,000 per QALY gained. Based on this clinical advice, for patients known to not have the T315I mutation it is anticipated that the lower and upper values in the range in the cost per QALY gained compared with induction chemotherapy would increase, that is, become less favourable to ponatinib. However, the precise increase in these values is unknown.

6.2 Results for people who are not suitable for allo-SCT

The results are presented in Table 2.

The ranges in the ICER relating to plausible fits to the survivor function are large indicating considerable uncertainty in the ICER. The fit of the extrapolated curves to the data are shown in **Error! Reference source not found.** and **Error! Reference source not found.** for OS on ponatinib; **Error! Reference source not found.** and **Error! Reference source not found.** for time on treatment with ponatinib; and **Error! Reference source not found.** for OS after allo-SCT.

6.2.1 Results for ponatinib compared with BSC

For the comparison of ponatinib with BSC whether half-cycle correction of intervention costs should be applied, and whether the OS for NR on ponatinib and BSC are equal are key drivers of the ICER. The ERG believes that ponatinib is likely to dominate BSC, although this is dependent on the assumption that OS after NR is independent of whether the patient received ponatinib or BSC.

Table 2: The impact of the ERG's deterministic exploratory analyses in patients unsuitable for allo-SCT

		Cost per QALY (£)
Ref No	**Exploratory Analyses**	**Ponatinib vs BSC**
0	N/A (Company Base Case)	31,210
1	Choosing alternative distributions in addition to those selected by the company, using the company's fits (range)	24,790 – 33,105
2	Assuming drug wastage	33,826
3	No half-cycle correction of intervention costs	44,031
4	Including treatment related deaths	27,489
5a	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the ponatinib value	Dominant
5b	Setting OS the same for NR regardless of whether the patient had ponatinib or BSC – set at the BSC value	Dominant
8	2 and 3 using the curves believed most credible by the company	47,884
9	2, 3,4 and 5a using the curves believed most credible by the company	Dominant
10. ERG base case ICERs	As 9, but choosing alternative distributions in addition to those selected by the company (range)	Dominant to Dominant

BSC, best supportive care; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; N/A, not applicable; NR, non-responders QALY, quality-adjusted life year

Note: the ICERs may be unfavourable to ponatinib as it is assumed that prescriptions are at three-monthly intervals when assessing drug wastage.