NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Dasatinib, nilotinib and standard-dose imatinib for the first line treatment of chronic myeloid leukaemia (incl part-review of TA 70)

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. **Response to comments on the ACD received by Manufacturers**, prepared by Peninsula Technology Assessment Group (PenTAG)
   - Addendum #2 and #3 to the Assessment Report
   - Erratum to the Assessment Report

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - BMS
   - Novartis Pharmaceuticals
   - The Chronic Myeloid Leukaemia Support Group
   - The Royal College of Nursing
   - The Royal College of Pathologists and British Society for Haematology
   - NHS North Yorkshire and York

   DH responded with 'no comment'

4. **Comments on the Appraisal Consultation Document from experts –** *None received*

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

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 CLINICAL EXCELLENCE

Health Technology Appraisal

Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia (part review of technology appraisal guidance 70)

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 manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

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 may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
BMS	1. **The AC has not adequately considered the comments made by Bristol-Myers Squibb on the PenTAG Assessment Report**. The ACD is clear that the Committee carefully considered comments received by Bristol-Myers Squibb (4.3.14) and, furthermore, were satisfied that the Assessment Group had adequately addressed the issues raised by presenting a range of scenarios rather than a single base-case cost-effectiveness analysis. We assert that Scenarios 1 and 2 are basically flawed, and so we question how the Committee can be satisfied that these scenarios are an adequate basis for making its recommendations. Furthermore, as noted in the ACD, our comments on the Assessment Report highlighted fundamental issues with the PenTAG model – such as its inability to reflect the underlying nature of the disease, and its estimation of unreliable treatment durations (See Appendices **[not reproduced here]**). **Scenarios 1, 2, 3 and 4 cannot be considered appropriate as the basis for the Committee's recommendations as they are all reliant on the cumulative survival approach.** Furthermore, our response to the AR highlighted issues with the AG model in estimating survival via the surrogate approach: *"Consequently, even when adjusting for background non-CML mortality, the predicted mean survival (especially for those who do not respond) is far too high (CCR; 24.4 years, Non-CCyR: 14.3 years, MMR: 24.2 years, No MMR: 21.3 years). The figures for MMR are striking, suggesting that achieving the highest possible level of response to treatment only offers an additional 3 years of life – and that if this level is not achieved, a patient will still live for over 20 years!*	The Committee agreed that only short-term data were available for survival on first-line dasatinib and nilotinib and that the Assessment Group had adequately acknowledged and addressed the advantages and disadvantages of different survival modelling approaches by presenting a range of scenarios rather than a single base-case cost-effectiveness analysis. It noted that, by using a cumulative survival approach in its base-case scenario analyses, the Assessment Group had used a similar approach to modelling survival as Novartis in its economic model and that the surrogate survival approach used in its sensitivity analyses was similar to the approach used by Bristol-Myers Squibb in its model. The Committee also noted that many of the weaknesses associated with these alternative approaches to modelling survival that were highlighted by Bristol-Myers Squibb were clearly acknowledged by the Assessment Group and were also reflected in both manufacturers' models. It agreed with the Assessment Group that, although probabilistic sensitivity analysis has an important role in exploring parameter uncertainty in NICE appraisals, its usefulness is limited in situations in which there is substantial structural uncertainty: in this case there is extensive uncertainty around the possible treatment sequences following first-line tyrosine kinase inhibitor treatment failure and modelling of short-term survival data. The Committee therefore concluded that the Assessment Group had adequately addressed this structural uncertainty by presenting a range of deterministic scenario analyses. The Committee also considered the comments received from Novartis about the Assessment Group's economic model. The Committee noted that the Assessment Group had accepted Novartis' comments in relation to the costs of medical management in the chronic phase and had subsequently reduced the cost in its model.

Consultee	Comment	Response
	These small differences in a patient's prognosis, with and without response, clearly diminish the importance of the proportion of patients who respond overall. A recent indirect comparison meta-analysis of first line treatments concluded that treatment with dasatinib was significantly associated with achieving MMR (Odds ratio 2.23 dasatinib compared to imatinib: Table 12 BMS submission document). *Despite the superior performance on this key clinical endpoint the predicted difference for dasatinib compared to imatinib is a mere 0.6 years. The approach used in the AG model, therefore, is not in line with the clinical evidence and strongly biases all results against dasatinib."* As the Assessment Group did not respond to this point in their commentary, we would invite the Committee to re-evaluate whether the analyses using the surrogate approach (as implemented by the AG) should be considered reliable or adequate given the issues we have (once again) highlighted. In addition, in Appendix C **[not reproduced here]**, we raise further concerns regarding the validity of the AG approach to estimating survival via surrogate markers. **If the Committee had adequately considered our comments and the evidence available, it would recognise that such concerns cannot simply be addressed by the range of scenarios presented. We feel the cumulative survival approach lacks clinical validity, while the surrogate survival approach (as implemented by the AG) lacks face validity.**	The Committee noted that when these changes were made, the revised base-case ICERs for the scenarios that compared nilotinib with imatinib followed by no second-line nilotinib were £25,000 (scenario 1) and £20,000 per QALY gained (scenario 2). The Committee also noted that, in response to additional comments received from Novartis, the Assessment Group had also explored the effect of adjustments to the mean dose intensity of imatinib (increased from 100% to 106%) and mean survival after stem cell transplantation (reduced from 17 years to 7.5 years). The Committee agreed that the adjustment to mean survival after stem cell transplantation, which resulted in ICERs of £17,000 and £18,000 per QALY gained in scenarios 1 and 2, was plausible, but that an increased dose of imatinib taken from a single time point in one trial could not be assumed to reflect the evidence as a whole or clinical practice. For all scenarios, dasatinib continued to be dominated by nilotinib or to generate ICERs of over £200,000 per QALY gained compared with imatinib. The Committee was satisfied that the Assessment Group had appropriately addressed comments received from the manufacturers on its economic model and that the ICERs generated from the Assessment Group's revised analysis provided a suitable basis for recommendation. The Committee considered which of the scenarios modelled by the Assessment Group gave the most realistic estimates of cost effectiveness for dasatinib, nilotinib and standard-dose imatinib. At the time of the first appraisal committee meeting, the Committee was aware that there was considerable uncertainty about which treatments would be given to people with chronic phase CML following first-line treatment – this was driven by uncertainty about the final guidance that would be issued by NICE on the second-line treatment of chronic and accelerated phase CML; that is, in adults whose CML is resistant to standard-dose imatinib or who are intolerant of imatinib (published as NICE technology appraisal guidance 241 by the time of the second appraisal committee meeting). Page 3 of 39

Consultee	Comment	Response
		The Committee was also aware at the first appraisal committee meeting that a scenario of second-line imatinib following first-line treatment with nilotinib or dasatinib had not been modelled by the Assessment Group despite clinical specialist opinion that this would be a plausible treatment pathway for people with CML that is intolerant to a first-line second-generation tyrosine kinase inhibitor. The Committee also considered the comments received from consultees following consultation on the ACD that scenarios 1 and 2 of the Assessment Group's model did not reflect clinical practice and should not be used to inform the recommendations. The Committee accepted that hydroxyurea and stem cell transplantation would not be routinely used in the second-line setting in place of a tyrosine kinase inhibitor. The Committee therefore considered that scenarios 3 and 4 were initially incomplete (at the time of the first appraisal committee meeting) but that scenarios 1 and 2 of the Assessment Group's model provided only relatively approximate estimates of the cost effectiveness of first-line treatment with tyrosine kinase inhibitors. The Committee therefore considered the further additional analyses carried out by the Assessment Group after consultation on the ACD. It noted that the Assessment Group had modelled two additional scenarios – one comprising first-line treatment with nilotinib followed by second-line standard-dose imatinib, and the other comprising first-line treatment with dasatinib followed by second-line standard-dose imatinib. In both scenarios, hydroxyurea and stem cell transplantation were only considered as third-line treatments. The Committee agreed that these analyses were an important addition to the Assessment Group's model because they enabled a comparison in scenarios 3 and 4 of all the relevant first- and second-line treatment sequences. See FAD sections 4.3.14-4.3.17

Consultee	Comment	Response
	Despite the superior performance on this key clinical endpoint the predicted difference for dasatinib compared to imatinib is a mere 0.6 years. The approach used in the AG model, therefore, is not in line with the clinical evidence and strongly biases all results against dasatinib." As the Assessment Group did not respond to this point in their commentary, we would invite the Committee to re-evaluate whether the analyses using the surrogate approach (as implemented by the AG) should be considered reliable or adequate given the issues we have (once again) highlighted. In addition, in Appendix C **[not reproduced here]**, we raise further concerns regarding the validity of the AG approach to estimating survival via surrogate markers. **If the Committee had adequately considered our comments and the evidence available, it would recognise that such concerns cannot simply be addressed by the range of scenarios presented. We feel the cumulative survival approach lacks clinical validity, while the surrogate survival approach (as implemented by the AG) lacks face validity.**	The Committee considered the Assessment Group's analysis of short-term surrogate response markers as predictors of longer-term patient-relevant outcomes. The Committee noted that the clinical evidence was taken from a mixture of longer-term randomised and observational studies of imatinib only. However, the Committee accepted that the results of the analysis, which showed that people with either a complete cytogenetic response or major molecular response after 12 months experienced better long-term survival, could be potentially applied to people receiving dasatinib or nilotinib. See FAD section 4.3.8 The Committee noted the key criticisms from Bristol-Myers Squibb about the different modelling approaches used to estimate survival on first- and second-line treatment, which Bristol-Myers Squibb argued were inconsistent with the underlying disease and resulted in incorrect or unreliable treatment durations being modelled. However, the Committee agreed that only short-term data were available for survival on first-line dasatinib and nilotinib and that the Assessment Group had adequately acknowledged and addressed the advantages and disadvantages of different survival modelling approaches by presenting a range of scenarios rather than a single base-case cost-effectiveness analysis. It noted that, by using a cumulative survival approach in its base-case scenario analyses, the Assessment Group had used a similar approach to modelling survival as Novartis in its economic model and that the surrogate survival approach used in its sensitivity analyses was similar to the approach used by Bristol-Myers Squibb in its model. The Committee also noted that many of the weaknesses associated with these alternative approaches to modelling survival that were highlighted by Bristol-Myers Squibb were clearly acknowledged by the Assessment Group and were also reflected in both manufacturers' models. See FAD Section 4.3.14

Consultee	Comment	Response
BMS	2. **The Appraisal has not given fair consideration to the evidence for dasatinib**. The Committee justifies its exclusion of dasatinib in the 2nd line setting with reference to its FAD in the ongoing appraisal for chronic and accelerated phase CML in adults whose CML is resistant to or intolerant to standard-dose imatinib. However, as the Committee will be aware, this FAD is subject to appeal and so is not final. As noted in our response to the Assessment Report, it is inappropriate to exclude consideration of dasatinib (as well as imatinib) in the 2nd line setting from this appraisal because correct consideration of the evidence in the 1st line setting requires accurate consideration of the evidence in 2nd line. Notwithstanding our comments about the validity of Scenarios 1 and 2, the exclusion of data for dasatinib in the 2nd line setting has unnecessarily reduced the accuracy of this appraisal. **To avoid the perception that the Committee's unratified recommendation in the 2nd line setting may be driving its approach to the 1st line setting and to ensure the accuracy of the 1st line evaluation, the assessment should have comprehensively included all relevant comparators in both settings.** **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** *We believe the summary of clinical effectiveness is a reasonable interpretation of the evidence; however, the summaries of cost effectiveness are not.*	The Committee agreed that, with the publication of the guidance on dasatinib, high-dose imatinib and nilotinib when imatinib has failed because of resistance or intolerance (NICE technology appraisal guidance 241), it would not be appropriate to include dasatinib as a second or third-line treatment in the modelling for this appraisal. The Committee was aware that NICE technology appraisal guidance 241 considered the use of the tyrosine kinase inhibitors in cases of imatinib resistance or intolerance only but had not considered their use following first-line treatment with nilotinib or dasatinib. The Committee considered that this was because standard-dose imatinib was the only recommended first-line tyrosine kinase inhibitor for the treatment of chronic phase CML at the time of appraisal, and it agreed that the same rationale that underpinned the recommendations in TA 241 should also apply to the use of dasatinib after first-line treatment with an alternative first-line tyrosine kinase inhibitor. See FAD section 4.3.25

Consultee	Comment	Response
BMS	3. **The Appraisal Committee does not adequately justify its recommendation in favour of standard-dose imatinib**. In Section 4.3.17, the AC concludes nilotinib represents a cost effective use of NHS resources and should be recommended as a 1st-line treatment option for people with chronic-phase CML. This is a conclusion based on comparison with standard-dose imatinib. In Section 4.3.19, the Committee go on to recommend standard-dose imatinib in this setting based on the long-term data from the IRIS trial and the importance of having an alternative TKI for people for whom nilotinib is inappropriate. This recommendation is made despite recognition of the borderline cost-effectiveness results, and without the presentation of any incremental costs and benefits. In short, the Committee consider standard-dose imatinib to be a cost effective use of NHS resources despite not presenting any comparative data for costs and benefits. **Even without any other considerations, this explanation for the Committee's recommendation is perverse. However, given the recent price increase for imatinib, and because this appraisal serves (in part) as an update to TA70, the Committee must provide greater justification for its recommendation in favour of standard-dose imatinib.**	With regard to imatinib, the Committee was aware that the ICERs for first-line nilotinib followed by imatinib compared with first-line imatinib followed by nilotinib were sensitive to a number of parameters, including assumptions about the dose intensity of nilotinib and the average time spent on second-line nilotinib or imatinib treatment. The Committee noted that changes to these input parameters, notably adjusting the modelled dose intensity of first-line nilotinib to SPC-recommended levels, reversed the relative cost-effectiveness of nilotinib and imatinib. In addition, the Committee recognised that, although more of the sensitivity analyses produced favourable ICERs for nilotinib when compared with standard-dose imatinib, imatinib has a proven longer-term record of safety and efficacy: there were 7 years of survival data for first-line imatinib from the IRIS trial, with positive results for complete cytogenetic response and disease progression, while there were still only short-term survival data for dasatinib and nilotinib. Finally, the Committee considered that it was important to have an alternative tyrosine kinase inhibitor treatment available if it is no more expensive than alternatives. The Committee therefore concluded that it would be appropriate to recommend both nilotinib and standard-dose imatinib as options for the first-line treatment of people with chronic phase CML. In addition it recognised that, given that imatinib and nilotinib have comparable cost-effectiveness, should one of the drugs become significantly cheaper, it should be preferred (taking into consideration administration costs, required dose and product price per dose). See FAD section 4.3.19

Consultee	Comment	Response
BMS	4 **Given the scenarios the AC uses as the basis of its recommendation, the lack of Probabilistic Sensitivity Analysis (PSA), in particular, is not acceptable**. We previously commented on the importance of a PSA, noting it is a requirement of the NICE reference case for economic analysis. We again highlight this significant omission. • The Committee has chosen to base its draft recommendation on Scenarios 1 and 2, and does so partly to reduce the uncertainty associated with subsequent lines of treatment. Given this approach, the Committee has effectively removed the structural uncertainty referred to by the Assessment Group as a barrier to conducting a PSA. • As noted, the decision to recommend standard-dose imatinib in this setting is not adequately justified. In the context of the aforementioned reliance on Scenarios 1 and 2, it is essential that a PSA is published to support this decision, to ensure that the Committee has reached a robust assessment **If the Committee decide to continue to base their recommendations on these Scenarios, they must present a PSA as support to their decision.** **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** *The provisional recommendations are neither sound, nor a suitable basis for guidance to the NHS, given the comments made above. In addition, we believe the scenarios used by the AC are a not suitable basis for their recommendations.*	The Committee agreed with the Assessment Group that, although probabilistic sensitivity analysis has an important role in exploring parameter uncertainty in NICE appraisals, its usefulness is limited in situations in which there is substantial structural uncertainty: in this case there is extensive uncertainty around the possible treatment sequences following first-line tyrosine kinase inhibitor treatment failure and modelling of short-term survival data. The Committee therefore concluded that the Assessment Group had adequately addressed this structural uncertainty by presenting a range of deterministic scenario analyses. See FAD Section 4.3.14 It should also be noted that, although the NICE Guide to the Methods of Health Technology Appraisal (2008) states that a probabilistic sensitivity analysis is preferred for exploring parameter uncertainty in cost-effectiveness analysis (see section 5.9.8 and 5.9.10), it is not a part of the NICE reference case.

Consultee	Comment	Response
BMS	5. **The scenarios selected by the Appraisal Committee (AC) to form the basis of its recommendations are not adequate for this purpose**. While we respect the logic applied by the Committee to decide which treatment scenarios give the most realistic estimates of cost effectiveness (4.3.16), we request that on review, and during discussions at the second appraisal committee meeting, the Committee reflect on the following issues: • The extensive amount of published data demonstrating the predictive value of surrogate markers means any analyses based on a cumulative survival approach must be considered obsolete. We provide an up to date summary of published data for the predictive value of surrogate markers in Appendix A **[not reproduced here]**. • Analyses which consider the use of hydroxyurea (HU) in place of 2nd-line TKIs are inappropriate as they do not reflect standard clinical practice. • The uncertainty referred to by the Committee (4.3.16) for 2nd-line use of TKIs in the treatment of chronic and accelerated phase CML will be resolved in a matter of weeks (as the Appeal decision is due in early January 2012). **We realise that the Committee has chosen PenTAG Scenarios 1 and 2 because it considers these minimise the uncertainty associated with assessing TKIs in the 1st line setting. However, on reflection, and for the reasons outlined above, we hope the Committee also recognises these scenarios are not an adequate basis for making its recommendations. To be considered valid by the clinical community, the Committee's recommendations must be based on an assessment of overall survival using surrogate markers, and must include 2nd line use of TKI's.**	**Surrogate Survival Approach** The Committee noted that, by using a cumulative survival approach in its base-case scenario analyses, the Assessment Group had used a similar approach to modelling survival as Novartis in its economic model and that the surrogate survival approach used in its sensitivity analyses was similar to the approach used by Bristol-Myers Squibb in its model. The Committee also noted that many of the weaknesses associated with these alternative approaches to modelling survival that were highlighted by Bristol-Myers Squibb were clearly acknowledged by the Assessment Group and were also reflected in both manufacturers' models. See FAD section 4.3.14 In response to this comment, the Assessment Group state that one disadvantage of the surrogate survival approach is that it assumes that overall survival is purely a function of response (CCyR or MMR at 12 months), and not a function of other factors such as depth and duration of response or the nature of the drug. Although several of the studies cited in Appendix A are claimed by BMS to demonstrate the predictive value of CCyR and MMR on long term outcomes, none of these studies specifically demonstrate that overall survival is solely a function of response, independent of the drug. The Assessment Group repeat another criticism of the Surrogate Survival approach: that overall survival is dependent purely on response to first-line treatment, but no further lines of treatment. For example, overall survival for two patients, neither of whom achieved a response to first-line treatment, would be predicted to be equal, even if one patient subsequently achieved a response to second-line TKI treatment, whereas the other did not.

Consultee	Comment	Response
		<u>Second-line Treatments</u> The Committee accepted that hydroxyurea and stem cell transplantation would not be routinely used in the second-line setting in place of a tyrosine kinase inhibitor. The Committee therefore considered the further analyses conducted by the Assessment Group, which modelled two additional scenarios – one comprising of first-line treatment with nilotinib followed by second-line standard-dose imatinib, and the other comprising of first-line treatment with dasatinib followed by second-line standard-dose imatinib. In both scenarios, hydroxyurea and stem cell transplantation were only considered as third-line treatments. See FAD sections 4.3.16-4.3.18.
Novartis	<u>Section 3.10, 4.1.16, 4.3.9</u> – in our response to the Assessment Report, we explained that QT prolongation, which is listed as a side effect for nilotinib, is in fact a class effect. We are therefore pleased to note that in section 4.3.9, the Committee clarify that QT prolongation was listed in the special warnings and precautions for use in the SPC for both dasatinib and nilotinib. We feel the summary in this ACD portrays a fairer representation of the nilotinib safety profile than previous reports.	Comment noted. The Committee noted that QT interval prolongation was listed in the special warnings and precautions for use in the SPC for both dasatinib and nilotinib. However, the Committee was reassured by the views of the clinical specialists that there was no increased cardiovascular risk at the licensed doses. See FAD section 4.3.9
Novartis	<u>Section 4.1.3</u> – the ACD discusses the ENESTnd trial design and states: 'all study participants had a minimum follow-up of 12 months, with a median duration of 14 months of treatment'. We would like to re-iterate that the latest published data (Kantarjian 2011 – Blood, as referenced in previous responses) reports a minimum follow-up of 24 months, which is correctly referred to later in the report. In addition, 36 month follow-up data has just been presented at ASH 2011. The data continues to support nilotinib as a potential standard of care in CML with superior MMR and CMR by 36 months, significantly lower progression to AP/BC and significantly lower deaths following progression in the nilotinib arms vs the imatinib arms.	Comment noted. Section 4.1.3 of the FAD states: ''all study participants had a minimum follow-up of 24 months, with a median duration of 14 months of treatment' in the ENESnd trial.

Consultee	Comment	Response
Novartis	Section 4.3.6 and 4.3.9 – We are pleased to read that the committee has noted the views of the clinical specialists and patients experts that nilotinib and dasatinib are more effective drugs than imatinib, and that the committee has noted from the clinical trials that all three drugs were well tolerated.	Comment noted.
CML Support Group UK	**1. Treatment lines in Scenarios 1 & 2** (i) Second line treatment: current clinical practice and guidelines Both the specialist clinician evidence and the recommendations of two leading organizations of clinicians are clear on recommended practice. "This reviewer cannot see a time in which any UK physician will routinely use hyroxycarbamide for second line therapy in place of a TKI ..." from Section 2 Professor Apperley's comments on the Assessment Report (AR) In the same section Professor Apperley mentions the use of TKIs as the only interventions in 2nd line treatment, following 1st line imatinib, thus excluding SCT as a possible 2nd line option. The Committee do not offer a rebuttal of the clinicians comments that HU would not "routinely be used as a 2nd line treatment" (4.3.3.) The treatment guidelines approved by the European Leukaemia Net and the British Committee for Standards in Haematology guidelines both recommend only TKIs as 2nd line treatments. These recommendations are specifically mentioned in the 'Current Service Provision' section of the AR (2.8. AR). Scenarios 1 & 2 are described by the Committee as their "preferred scenarios" (4.3.18) and do not model any TKI beyond first line. It is clear the Committee have not therefore 'taken all the relevant evidence' into account.	The Committee accepted that hydroxyurea and stem cell transplantation would not be routinely used in the second-line setting in place of a tyrosine kinase inhibitor. The Committee therefore considered the further analyses conducted by the Assessment Group, which modelled two additional scenarios – one comprising of first-line treatment with nilotinib followed by second-line standard-dose imatinib, and the other comprising of first-line treatment with dasatinib followed by second-line standard-dose imatinib. In both scenarios, hydroxyurea and stem cell transplantation were only considered as third-line treatments. The Committee therefore considered the further additional analyses carried out by the Assessment Group after consultation on the ACD. It noted that the Assessment Group had modelled two additional scenarios – one comprising first-line treatment with nilotinib followed by second-line standard-dose imatinib, and the other comprising first-line treatment with dasatinib followed by second-line standard-dose imatinib. In both scenarios, hydroxyurea and stem cell transplantation were only considered as third-line treatments. The Committee agreed that these analyses were an important addition to the Assessment Group's model because they enabled a comparison in scenarios 3 and 4 of all the relevant first- and second-line treatment sequences. The Committee thus considered the ICERs from scenarios 3 and 4 of the Assessment Group's model, including the results from the further additional analyses presented by the Assessment Group following the first appraisal committee meeting. See FAD sections 4.3.16-4.3.18.

Consultee	Comment	Response
CML Support Group UK	(ii) The logic deployed by the Committee in their decision making Scenarios 1 & 2 are limited to a single subsequent line of treatment with the options in 2nd line being limited to hydroxycarbamide (HU) or stem cell transplantation (SCT). The justification given for abandoning scenarios 3 & 4 was because it resulted in a dual, rather than single, treatment strategy where 1st line nilotinib use was not followed by a 2nd line TKI whereas there was a 2nd line TKI (nilotinib) used after 1st line dasatinib and imatinib. Since this situation is absent in Scenarios 1 & 2, the Committee has defaulted to them as their "preferred scenarios" (4.3.18.) to avoid the "uncertainty associated with subsequent lines of treatment" (4.3.16.) Given the Committee's commitment to the principle of modelling treatment lines beyond a 1st line, we would argue that preferring the unreality of Scenarios 1 & 2 over the uncertainty of Scenarios 3 & 4 does not represent a prudent trade off. To favour some set of events that does not occur over a set that does in part, but is complicated, can hardly be said to be a worthy example of evidence based decision making. Their summary of the clinical evidence is therefore flawed in that their interpretation of the evidence is not reasonable. (iii) Second line treatment lines in current practice (a) As the Committee note (4.3.16.) imatinib was not modelled as a 2nd line treatment following 1st line 2nd generation TKI use in cases were patients are intolerant of a 2nd generation TKI used in 1st line. (b) Neither was dasatinib modelled as a 2nd treatment line to 1st line nilotinib by the AG in any of the four scenarios developed. If the AG had done so this would not have conflicted with the recommendations of the FAD for the other ongoing MTA appraisal mentioned in 4.3.16.since this is restricted to standard dose imatinib treatment failure.	(ii) The logic deployed by the Committee in their decision making The Committee accepted that hydroxyurea and stem cell transplantation would not be routinely used in the second-line setting in place of a tyrosine kinase inhibitor. The Committee therefore considered the further analyses conducted by the Assessment Group, which modelled two additional scenarios – one comprising of first-line treatment with nilotinib followed by second-line standard-dose imatinib, and the other comprising of first-line treatment with dasatinib followed by second-line standard-dose imatinib. In both scenarios, hydroxyurea and stem cell transplantation were only considered as third-line treatments. See FAD Sections 4.3.16-4.3.17 (iii) Second line treatment lines in current practice The Committee agreed that, with the publication of TA 241, it would not be appropriate to include dasatinib as a second or third-line treatment in the modelling for this appraisal. The Committee was aware that TA 241 considered the use of tyrosine kinase inhibitors in cases of imatinib resistance or intolerance only and had not considered their use following first-line treatment with nilotinib or dasatinib. The Committee considered that this was because standard-dose imatinib was the only recommended first-line tyrosine kinase inhibitor for the treatment of chronic phase CML at the time of appraisal, and it agreed that the same rationale that underpinned the recommendations in TA 241 should also apply to the use of dasatinib following first-line treatment with an alternative first-line tyrosine kinase inhibitor. See FAD section 4.3.25.

Consultee	Comment	Response
CML Support Group UK	(iv) Treatment lines in current practice in 3rd and subsequent lines (a) Dasatinib was also not modelled as a 3rd line treatment following 2nd line nilotinib failure following 1st line imatinib failure. Again, as noted in (b) above, there would be no conflict with the FAD recommendations of the other ongoing MTA. Professor Apperley (Section 2 of her comment on the AR) notes "one or more" TKIs being optioned following 1st line imatinib failure which permits dasatinib to represent a rational 3rd line choice in such situations. (b) TKIs lacking marketing authorization (bosutinib and ponatinib) available in the UK on clinical trial would, notes Professor Apperley (in Section 2 of her AR comment), be options in situations of what she describes as "upfront" (ie 1st line) dasatinib and nilotinib failure. In the same section she also mentions the availability of imatinib being a further TKI, post 1st line, option. In this scenario there are 5 TKIs currently available together with the option of an SCT. It is therefore unsurprising that the AR refers to there being "extensive structural uncertainty" (8.1. AR) in the modelling due in part to availability of "very heterogenous treatment and care pathways" (1.8.8.2. AR) for CML patients. This is reflected more broadly in the "unusually large amount of structural uncertainty that is inherent in the present decision problem(s)" (1.7.3. AR). The Committee recognize these issues (4.3.12. & 4.3.16.) and also acknowledge their linkage with subsequent AG economic modelling when they refer to the "wide variation in the cost-effectiveness results across the scenarios presented" (4.3.13.) by the AG.	The Committee agreed that, with the publication of TA 241, it would not be appropriate to include dasatinib as a second or third-line treatment in the modelling for this appraisal. The Committee was aware that TA 241 considered the use of tyrosine kinase inhibitors in cases of imatinib resistance or intolerance only and had not considered their use following first-line treatment with nilotinib or dasatinib. The Committee considered that this was because standard-dose imatinib was the only recommended first-line tyrosine kinase inhibitor for the treatment of chronic phase CML at the time of appraisal, and it agreed that the same rationale that underpinned the recommendations in TA 241 should also apply to the use of dasatinib following first-line treatment with an alternative first-line tyrosine kinase inhibitor. See FAD section 4.3.25.

Consultee	Comment	Response
	In short model outputs (ICER and cost per QALY gained) are directly related to the number of treatment lines, the particular interventions allocated to each treatment line and a host of additional factors that generate the significant levels of uncertainty all acknowledged to be present even after further analytic work (sensitivity analyses) was undertaken. The Committee's summaries of the cost effectiveness evidence are therefore constrained by a consideration of a highly restricted base of evidence on which their decisions were then made. As such all the relevant evidence was not taken into account.	

Consultee	Comment	Response
CML Support Group UK	**2. Treatments for the underlying disease.** **(a) HU** (i) The role of HU in the management of CML The Committee seem to haver on whether to accord HU status as a "treatment" for CML or simply as a "measure" or "agent" available to clinicians in much the same way as other agents are available for the control of clinical events that are a consequence of the underlying disease. We find the AG's decision to include HU as a treatment line in their modelling perplexing given that they recognize that: "Hydroxycarbamide can be used to control the white blood count but does not alter the natural history of the disease" ("Natural history and clinical presentation" section of the AR under the sub heading: Chronic Phase) We find their decision even more perplexing given they do not accord HU a place in the relevant AR section describing CML treatments ("Treatment" 2.4. AR). All other interventions allocated to treatment lines in all four Scenarios developed appear in this section of the AR. The Committee note, and do not reject or qualify, the clinicians comments (in 4.3.3.) that HU "...does not affect the progression of the disease" and that its use is for "palliative purposes" or "as a short term measure between lines of treatment" (my emphasis). We find it perverse that the Committee then limit themselves to scenarios that contain HU as an option in the second of only two treatment lines.	The Committee accepted that hydroxyurea and stem cell transplantation would not be routinely used in the second-line setting in place of a tyrosine kinase inhibitor. The Committee therefore considered the further analyses conducted by the Assessment Group, which modelled two additional scenarios – one comprising of first-line treatment with nilotinib followed by second-line standard-dose imatinib, and the other comprising of first-line treatment with dasatinib followed by second-line standard-dose imatinib. In both scenarios, hydroxyurea and stem cell transplantation were only considered as third-line treatments. The Committee therefore considered the further additional analyses carried out by the Assessment Group after consultation on the ACD. It noted that the Assessment Group had modelled two additional scenarios – one comprising first-line treatment with nilotinib followed by second-line standard-dose imatinib, and the other comprising first-line treatment with dasatinib followed by second-line standard-dose imatinib. In both scenarios, hydroxyurea and stem cell transplantation were only considered as third-line treatments. The Committee agreed that these analyses were an important addition to the Assessment Group's model because they enabled a comparison in scenarios 3 and 4 of all the relevant first- and second-line treatment sequences. The Committee thus considered the ICERs from scenarios 3 and 4 of the Assessment Group's model, including the results from the further additional analyses presented by the Assessment Group following the first appraisal committee meeting. See FAD sections 4.3.16-4.3.18.

Consultee	Comment	Response
CML Support Group UK	(ii) HU as a 2nd line treatment in current clinical practice. As Professor Apperley notes (Section 2 in her comments on the AR): "This reviewer cannot see a time in which any UK physician will routinely use hyroxycarbamide for second line therapy in place of a TKI ..." The Committee also note, and do not dispute, the clinicians comments that HU would not "routinely be used as a 2nd line treatment" (4.3.3.) (iii) HU and CCyR & MMR The pervasive use of methodolgies that measure the degree of complete cytogenetic response (CCyR) and major molecular response (MMR) to interventions used in the management of the disease and their role as surrogates for progression free survival/overall survival renders HU to a position on the periphery of, rather than central to, CML management. HU is incapable of effecting a cytogenetic or molecular response and we fail to understand why it was ever introduced into the AG model as a line of treatment given every other intervention, including SCT, in all treatment lines in the four Scenarios developed has that very capability. (iv) HU treatment and progression The comment on the Novartis model that "People who were treated with hydroxyurea had a probability of progressing to advanced phase." (4.2.11 my emphasis). Given that there is a 100% certainty of progression to advanced phase and a fatal outcome if CML patients receive HU as their sole treatment; we view "probability" as a wildly inaccurate descriptor. It does not reflect Novartis' position as an examination of their response to the AR makes clear (see 2.2.2. "Time on HU in CP" in their AR comment). BMS in their response to the AR ("Hydroxyurea as a 2nd line treatment option" & "Reason Two" especially Table 2.) also comment on analytic failings in the AR on this issue. From industry responses to the AR it is clear that the AG also completely over estimated survival times on HU following TKI failure as a mean "of 7.00 years with a 5 year survival of 50%".	The description of the Novartis economic model, which states that: "People who were treated with hydroxyurea had a probability of progressing to advanced phase," was taken directly from Novartis' submission (p.82). However, given that people receiving hydroxyurea treatment in the chronic phase could only move to accelerated phase in the model (i.e. a probability of 100%), this sentence in section 4.2.11 of the FAD states that: "People for whom hydroxyurea therapy failed then progressed to accelerated phase". The Assessment Group's estimated survival time on second-line hydroxyurea following TKI failure of 7.00 years with a 5 year survival of 50% was derived from a single study (Kantarjian et al. 2007) and that survival on hydroxyurea in the AG's model (in the cumulative survival approach) was lower because patients started second-line hydroxyurea at a later age (approx 65 years) than the Kantarjian et al. study (median initial age of 54 years). It should also be noted that the same approach was used by Novartis to estimate survival on hydroxyurea following TKI failure for patients who were intolerant or resistant to imatinib as part of their submission for TA 241. For further details, see pages 161-163 of the Assessment Group report. In regard to the estimated time on second-line hydroxyurea using the surrogate survival approach, the Assessment Group have provided a detailed description of the rationale for this in section 8.1.3 (page 139) of their Assessment report. In summary, in order to model overall survival as predicted from the surrogate relationships, it was necessary to alter the estimated mean time on one or more intervening treatments. The mean time on TKIs were not altered because these were taken from high quality RCTs and the mean survival after stem cell transplantation was also not altered because it was not possible to replicate the overall survival from the surrogate relationships. Therefore, the only possibility was to alter the mean time on hydroxyurea, which resulted in an unrealistically high estimated time on hydroxyurea of approximately 15 years

Consultee	Comment	Response
CML Support Group UK	**(b) Stem cell transplantation (SCT)** (i) Size of the CML patient population for whom SCT is an treatment option The Committee noted that the manufacturers submissions note that "only a small number of patients would be eligible" (4.3.21.) for SCT as a treatment option. There are clinical grounds that limit the size of this population as there are limitations imposed by the size of the donor pool. As the Committee notes this raises equality issues although they note that because the provisional recommendations "...do not differentiate between any groups of people" there was "not considered to be an equalities issue" (4.3.21.) The extraordinary disadvantage Black and Minority Ethnic patients face in securing suitable donors is well documented as is the age related disadvantage for many patients in what is, on average, an older patient population. The Committee's refusal to incorporate their acknowledgement of this situation into their deliberative process which resulted in provisional recommendations authored by themselves betrays the lack of value they assign to these particular sections of the population. We believe, had they done so, the Committee would not have preferred the two Scenarios that were limited to SCT as the only treatment option, assuming HU has no status as a treatment, after 1st line. (ii) SCT as a 2nd line treatment option Our comments on interventions optioned for 2nd line use in current global good clinical practice and set out in guidelines in the previous HU section are pertinent here.	The Committee accepted that hydroxyurea and stem cell transplantation would not be routinely used in the second-line setting in place of a tyrosine kinase inhibitor. The Committee therefore considered the further analyses conducted by the Assessment Group, which modelled two additional scenarios – one comprising of first-line treatment with nilotinib followed by second-line standard-dose imatinib, and the other comprising of first-line treatment with dasatinib followed by second-line standard-dose imatinib. In both scenarios, hydroxyurea and stem cell transplantation were only considered as third-line treatments. See FAD sections 4.3.16-4.3.18.

Consultee	Comment	Response
CML Support Group UK	(iii) Cost of SCT The AG called for allocated research priority status to be assigned for both the incidence and cost of SCT ("Suggested Research Priorities"noted " 10.2. AR) and also noted considerable uncertainty surrounding survival and treatment costs following SCT (9.5.2. AR). Although they mention GvHD as a post SCT complication and indicate they recognize GvHD to be spectrum like with greater drug therapy costs for treating "more severe GvHD" (8.5.4.2. AR) all medical management costs assume out patient status for those treated. The higher grades (3 & 4) of GvHD, which can be chronic, more often than not, require hospitalization. Hospital readmission costs are not included for patients with higher grades of GVHD. The comments submitted by Healthcare Improvement Scotland in May 2011 in response to the ACD for the other ongoing MTA for CML cite the following concerning SCT costs. "...a procedure which costs £70,000 with approx £2,400 ongoing monthly cost thereafter (which includes a £21,000 readmission sum)." (my emphasis) This is vastly different than the £113 weighted mean cost per month quoted in the AR ('Table 50 Estimation of ongoing drug and monitoring costs after SCT' in 8.5.4.2. AR).	Comments noted. In its critique of the cost-effectiveness evidence submitted by Bristol-Myers Squibb, the Assessment Group noted that the model assumed an ongoing cost of £2400 per month following stem cell transplantation, which was significantly higher than the Assessment Group's estimate of £113 per month. The Assessment Group also noted that the Committee for TA 241 considered the ongoing cost of £2400 per month to be an unreasonably high estimate, given that only a minority of people who survive transplantation develop complications that incur high ongoing costs. See FAD section 4.2.10

Consultee	Comment	Response
CML Support Group UK	**(c) TKIs for the treatment of CML** <u>(i) Efficacy of the three appraisal TKIs relative to each other</u> We note the Committee agree that both nilotinib and dasatinib demonstrate superior efficacy to imatinib whilst also agreeing there is no statistical difference in the degree of efficacy between them (4.1.12., 4.3.5. & 4.3.6.). <u>(ii) The efficacy of imatinib</u> The ACD comments “However the progression of CML can be slowed by imatinib.” (2.6 my emphasis) We believe this is a misinterpretation of the available RCT (and other) evidence for a drug the Committee have previously described as a “step change” in the treatment of CML and worthy of innovative status. Imatinib, in approximately 60% of chronic phase patients, halts rather than slows disease progression and, on currently available data, ensures long term patient relevant outcomes including progression free and overall survival. In their comments on the AR Professors Clark (point 2) and Apperley (point 4) made observations concerning the IRIS trial data noting salient factors required to be kept in mind when interpreting the data sensitively but which nevertheless concur that imatinib use has the capability to halt disease progression.	Comments noted. Long-term data up to 6 years follow-up from the IRIS study suggests that progression-free survival with imatinib treatment (and according to complete cytogenetic response) declines over time. Therefore, it is more reasonable to state that the progression of CML can be slowed rather than halted by imatinib. Furthermore, no published evidence is provided in support of the statement:”imatinib, in approximately 60% of chronic phase patients, halts rather than slows disease progression...” The Committee therefore agreed that FAD section 2.6 should state that: “...the progression of CML can be slowed by imatinib”.

Consultee	Comment	Response
CML Support Group UK	(iii) Specialist clinicians experience in the used of the appraised TKIs The statement that ".... clinical experience of dasatinib and nilotinib for chronic phase CML is restricted to the context of clinical trials" (4.3.2. my emphasis) is not true. The observation in the Assessment Report that: "Anecdotal evidence suggests that dasatinib and nilotinib are currently widely used in the NHS in England and Wales following failure of treatment with imatinib" (2.9. AR) is pertinent here. Professor Apperley notes in her comments on the ACD for the other ongoing MTA appraisal: "These drugs have been readily available in the UK through clinical trials, expanded access and more recently through a variety of means including Regional Cancer Network and/or local Drug and Therapeutic Panel agreements, the Pan-London New Drug prioritization exercise, applications for exceptionality to relevant PCT or most recently from the Cancer Drugs Fund" We make the point to insure against any inference being made that specialist clinicians might lack experience in the use of the appraised drugs in clinical practice and that therefore their evidence should be treated with caution.	Comment noted. Section 4.3.2 of the FAD states that: ".... clinical experience of dasatinib and nilotinib for chronic phase CML is largely restricted to the context of clinical trials".

Consultee	Comment	Response
CML Support Group UK	**3. Small clearly defined sub groups of the total CML population** We were pleased that the Committee noted that: "... the clinical specialists stated that, for a very small proportion of people whose CML is resistant or intolerant to standard dose imatinib, there may be clinical reasons for the use of dasatinib, including comorbidities and disease resistance to nilotinib" (4.3.3.) <u>(a). Comorbidities:</u> (i) Long QT syndrome The most prominence granted in the ACD to the issue of comorbidities and their impact on therapeutic decision making concerns CML patients with a long QT syndrome diagnosis. The Committee note QT prolongation is listed in the "Special warnings and precautions for use" sections of the SPCs for both nilotinib and dasatinib although any warning for it is absent in the SPC for imatinib. They also note the consequent FDA decision to issue a 'black box' warning for nilotinib although there is no explicit reference in the ACD to the absence of a similar warning for dasatinib. We would argue that an inference that dasatinib, when compared to nilotinib, would be the most prudent and preferred clinical intervention in such cases would be reasonable. This would remain valid even though the Committee notes the views of clinical specialists that "there was no increased cardiovascular risk at licensed doses" for either drug (4.3.9.). (ii) Diabetes Similar reasoning would prevail in the case of patients with diabetes as a comorbidity given the much more exacting fasting requirements for nilotinib administration compared to dasatinib since the equally exacting dietary requirements for diabetics must also be considered by clinicians and patients in any decision making process.	The Committee noted that, for a small group of people with specific kinase domain mutations that would make their CML resistant to nilotinib, dasatinib would be offered as second-line treatment. However, the Committee considered that, because these mutations would be determined after first-line treatment failure, this would not be relevant to the first-line treatment decision for people presenting with chronic phase CML. Furthermore, this subgroup of people with specific kinase domain mutations was not distinguished in the evidence base for dasatinib. The Committee also heard from consultees after consultation on the ACD that there are other important subgroups for whom dasatinib would be used rather than nilotinib, including people with long QT syndrome or diabetes. However, the Committee noted that it had not been presented with any evidence to support this and therefore could not make any recommendations for dasatinib in these subgroups. See FAD section 4.3.26

Consultee	Comment	Response
	This view is supported by Professor Apperley who cites diabetes as an example of there being "good medical reasons" for the use of dasatinib over nilotinib. (Section1. of her comments on the AR). Given comorbidities are known, in most instances, prior to commencement of treatment and add to the burden of disease carried by CML patients we consider the relevant clinical evidence has not been taken into account for these two extremely small patient subgroups in considering first line treatment options. We would argue that specialist clinicians preference, assuming a lack of other conflicting comorbidities, would be for dasatinib as a first line treatment for both the above patient groups. On this basis we find the negative recommendation for dasatinib first line use to be unsound for such sub groups of the total CML patient population both of whom are clearly identifiable at naive to treatment stage given dasatinib's superior efficacy to imatinib. <u>(b) Disease resistance to nilotinib:</u> We limit ourselves only to those cases, defined as resistant, where nilotinib and imatinib lack activity against specific mutations. We recognize such cases, by definition, are detected as a result of first line treatment failure and note strong evidence of dasatinib's activity against a significant number of such mutations. The prominent CML specialist clinician Michael Mauro MD (Knight Cancer Institute OHSU) cites six studies that demonstrate that: "Mutations in the P- loop (including Y253H/F and E255K/V), a common site of mutations, 63 are sensitive to dasatinib but are often clinically insensitive to high-dose imatinib or nilotinib." 'Tailoring Tyrosine Kinase Inhibitor Therapy in Chronic Myeloid Leukemia (Cancer Control April 2009, Vol 16, No. 2, p. 113)	

Consultee	Comment	Response
	We would describe as deeply disingenuous the Committee's belated recognition in this appraisal that, for this small segment of the CML patient population, there is effectively no other treatment available other than dasatinib, that is able to halt disease progression but, configured as a subsequent line of treatment, is excluded from the remit of this appraisal which limits itself to first line TKI treatments (4.3.18.). The only exception would be for the even smaller group for whom stem cell transplantation (SCT) was a clinical possibility and the even smaller sub group able to access a willing matched donor (4.3.21.). This results from the same Committee's decision not to recommend dasatinib as a second line treatment in the appraisal for CML patients whose disease is resistant to (or intolerant of) the current first line treatment of standard dose imatinib. Amongst the resistant patients would be those with such mutations.	

Consultee	Comment	Response
CML Support Group UK	<u>(4) PAS and the efficient use of NHS resources</u> The DH considered that this PAS does not "constitute an excessive administrative burden on the NHS" (3.11) This statement was flatly contradicted by North Yorkshire & York PCT in their written submission on the AR. The PCT expressed generic reservations about PASs given they impose an additional administrative burden on PCTs with resultant increased costs and therefore fail to deliver expected efficiency savings. The North Yorkshire & York PCT response to the AR notes: ".... our experiences to date would advocate that historically such schemes are convoluted thus are not delivering the anticipated savings and indeed serve to cost the NHS in terms of staff resources to unpick the nuances and ensure payments are made to the commissioner for these PbR excluded drugs" In her oral evidence at the Committee hearing on the 8th November; the representative (Diane Tomlinson, a Senior Pharmacist) of the PCT consultee for this appraisal, North Yorkshire & York PCT, observed that, in this particular case (the PAS for nilotinib), the additional administration costs imposed would probably cancel out any savings made by the price reduction obtained under the PAS. In sum the savings would be illusory and hence the real cost to the NHS would be either no different from, or near to, the quoted net BNF (edition 62) price quoted (3.11.) The consideration of the evidence therefore did not take " into account the effective use of NHS resources" (4.3.1.).	Comment noted. The Committee were aware of the concerns raised by consultees about the additional administrative burden imposed on PCTs by an agreed patient access scheme for nilotinib. However, it was agreed that if these extra administrative costs (for example, a one-off fixed cost of £200-300) were included in the total costs of nilotinib treatment per patient within the economic model, this would have a marginal impact on the relative cost-effectiveness of nilotinib.

Consultee	Comment	Response
CML Support Group UK	**(5) Summary** The following discussion is limited to a consideration of chronic phase CML in adults. <u>(a) Current and provisional NICE guidance:</u> Current NICE guidance is limited to a provisional recommendation for nilotinib as an option in first line use and, subject to appeal in the other ongoing MTA for CML, for nilotinib in 2nd line use with standard dose imatinib also recommended as an option for 1st line use. Imatinib is already recommended for 1st line use (as part of TA guidance 70) with a part review of that recommendation being included in the current MTA for 1st line use. <u>(b) There is no guidance or recommendation for:</u> HU or SCT have never been the subject of appraisal. Given their prevailing use prior to the establishment of NICE their allocation in treatment lines is not open to procedural challenge. However their allocation to a comparator role at the appraisal scoping stage is possible although in this case this is not applicable since they are not comparators. None of the three TKIs, that are the subject of this MTA and all of which have marketing authorization for CML, are recommended for 3rd or any subsequent treatment line use in any NICE guidance. There is no recommendation for imatinib in 2nd line or, subject to appeal, for dasatinib in 2nd line in any NICE guidance.	The Committee accepted that hydroxyurea and stem cell transplantation would not be routinely used in the second-line setting in place of a tyrosine kinase inhibitor. The Committee therefore considered the further analyses conducted by the Assessment Group, which modelled two additional scenarios – one comprising of first-line treatment with nilotinib followed by second-line standard-dose imatinib, and the other comprising of first-line treatment with dasatinib followed by second-line standard-dose imatinib. In both scenarios, hydroxyurea and stem cell transplantation were only considered as third-line treatments. See FAD sections 4.3.16-4.3.18. It should also be noted that TA 241 does not recommend high-dose imatinib for the treatment of chronic, accelerated or blast-crisis phase Philadelphia-chromosome-positive CML that is resistant to standard-dose imatinib. However, no guidance currently exists that precludes the use of second-line standard-dose imatinib for the treatment of chronic phase CML that is resistant or intolerant to first-line nilotinib or dasatinib.

Consultee	Comment	Response
	(c) Consequences that follow from (a) and (b): The Committee accept, in its deliberations, HU as a treatment and accept its status, in its preferred Scenarios 1 & 2, as one of only two treatment options in 2nd line treatment. However when HU is used to control white blood counts (referred to in 2. (a) (i) above) its use often occurs at diagnosis whilst decisions are being made as to the therapy to be adopted to secure maximum efficacy against the underlying disease. In such cases, on this logic, HU would amount to a 1st line treatment with imatinib as a 2nd line. As already noted there is no recommendation for imatinib use in 2nd line. To the best of our knowledge there has never been any attempt by an AG to distinguish patients naive to treatment for CML that disqualifies those treated with HU. We are not of course arguing that such a situation should prevail only that, once appraisals depart from the real world of clinical practice, arbitrary decisions are taken and assumptions made that result in conclusions that are unable to be related to clinical practice which in itself of course constitutes an evidence source. It is little wonder that the Committee feel compelled to observe that "there is considerable uncertainty about which treatments would be given to people with chronic phase CML following first line treatment" (4.3.16) However admitting two treatment options (HU & SCT) not in clinical practice in 2nd line is tantamount to creating a parallel universe that exists alongside, rather than reflects in (simplified) model form, the real world.	

Consultee	Comment	Response
	(d) Changes to the regulatory landscape We recognize that the Committee is also constrained in its processes and procedures by procedural factors over which it has little control. Government and regulatory agencies are aware of inadequacies with the current situation. Recent policy initiatives, especially emerging policy on conditional authorization pathways, population data requirements and more generic regulatory issues, such as guideline adoption and compliance, relevant to health technology appraisals (HTA) are, we believe, the harbinger of what will be a much changed regulatory environment in the future. Public attention has focused on the Early Access Scheme (EAS) and the use of anonymized patient record data in clinical research but much less media attention has been given to implications that follow from the proposed proportionate risk benefit guiding principle underlying the EAS or that policy development should acknowledge the: "..era of 'stratified medicines' where new drugs may be effective in a small segment of patients with specific genetic characteristics" (Department of Business, Innovation & Skills "Strategy for UK Life Sciences" Nov 2011 p. 28) The plea underlying our comments on this ACD is that the Committee should be sensitive to the background noise of these developments to ensure their own public credibility, and more generally that of the HTA process, continues to be assured. (d) CMLSG suggestions We suggest that a constructive way forward would be for the Committee to commission further modelling work (as it did with SHTAC in the other ongoing MTA for CML) from another AG that: (i) Incorporates the outcome of the appeal of the FAD recommendations in the other ongoing MTA for CML since more rather than less certainty would prevail than is the case currently.	Comments noted. NICE can only provide recommendations in line with the marketing authorisations of the technologies being appraised (See FAD sections 3.2 and 3.6). The Committee accepted that hydroxyurea and stem cell transplantation would not be routinely used in the second-line setting in place of a tyrosine kinase inhibitor. The Committee therefore considered the further analyses conducted by the Assessment Group, which modelled two additional scenarios – one comprising of first-line treatment with nilotinib followed by second-line standard-dose imatinib, and the other comprising of first-line treatment with dasatinib followed by second-line standard-dose imatinib. In both scenarios, hydroxyurea and stem cell transplantation were only considered as third-line treatments. See FAD sections 4.3.16-4.3.18.

Consultee	Comment	Response
	(ii) For the reasons advanced we would argue that HU be removed entirely from any modelling. (iii) Likewise SCT should be modelled only in treatment lines other than 1st or 2nd. Post SCT costs should be adjusted to include hospital readmission costs for the patient cohort burdened with severe post SCT complications and then incorporated into the existing weighted mean cost per month figures. and that the Committee should also: (iv) Be mindful that, as the AR notes in 2.8., current clinical guidelines referred to in 1.(i) above are due for renewal in July of this year. It is likely that their revised contents might increase rather than diminish the current gulf between real world clinical reality and that presented in NICE guidance should current provisional negative recommendations become final. All the medical bodies that responded to the scope warned the Committee of the consequences of proceeding with an appraisal at this time, compromised the effectiveness of the decision making process. We accept NICE is constrained by the requirement to issue guidance as close as is possible to marketing authorization but reasonableness should prevail. See “Response to consultee and commentator comments on the draft scope” p.10 Response of NCRI/RCP/RCR/ACP/JCCO and the Royal College of Pathologists, BSH and RCP consultees. (v) Failure to recommend any TKI other than nilotinib as a 2nd line treatment will, we would argue, become increasingly untenable should the current ongoing STA for bosutinib in 1st line receive a positive recommendation. This would result in a situation where there are 3 TKIs available for 1st line use and only one for 2nd line with dasatinib, a drug of proven clinical efficacy including for mutations against which nilotinib and imatinib lack activity, unavailable in any line of treatment. The Committee’s acceptance of the principle of an alternative TKI being available in 1st line should logically apply in 2nd line with an alternative to nilotinib.	Comments noted.

Consultee	Comment	Response
Royal College of Nursing (RCN)	i) **Has the relevant evidence has been taken into account?** The evidence considered seems comprehensive. ii) **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with chronic myeloid leukaemia. The preliminary views on resource impact and implications should be in line with established standard clinical practice. iii) **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and do not have any other comments to add. The RCN would welcome guidance to the NHS on the use of this health technology. iv) **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 gender, race, disability, age, sexual orientation, religion or belief?** None that we are aware of.	Comments noted. An Equality Impact Analysis will also be published at the time of guidance publication for this appraisal. The Committee concluded that the recommendations do not differentiate between any groups of people, and therefore there was not considered to be an equalities issue. See FAD Section 4.3.28.

Consultee	Comment	Response
	v) **Are there any equality-related issues that need special consideration that are not covered in the appraisal consultation document?** We are not aware of any specific issue at this stage. However, it would be helpful to know if NICE will publish the equality analysis for this appraisal. We would also ask that any guidance issued should show that an analysis of equality impact has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.	
Royal College of Pathologists and British Society of Haematology (RCPath & BSH)	• Has all of the relevant evidence been taken into account? *Yes, more or less.* *The two key trials are ENESTnd (nilotinib vs. imatinib) and DASISION (dasatinib vs. imatinib). The appraisal took into account the latest available data on each of these, which were 12 months as published in NEJM in June 2010, and also 24 months data from ENESTnd that was presented at the American Society of Hematology (ASH) meeting in December 2010.* *In fact, 36 month data for ENESTnd and 24 month data for DASISION are now available, having been presented and therefore publically disclosed at the very recent ASH meeting in December 2011. There are no surprises, and the previous advantages of each second generation drug over imatinib are maintained. These advantages are in efficacy (for the same surrogate endpoints as in the appraisal document; still no benefit on survival) and risk of progression to advanced phase. These updated data are therefore highly unlikely to alter the appraisal document or the conclusions reached from it.*	Comments noted.

Consultee	Comment	Response
RCPath & BSH	• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? *Yes except for one important caveat.* *The NICE FAD appraisal of these two technologies for SECOND line use (i.e. where first-line imatinib at standard dose has failed) has supported nilotinib but not dasatinib. This is primarily because Novartis, the manufacturer of nilotinib, has offered a patient discount scheme whereby nilotinib is in effect the same cost as imatinib; Bristol-Myers-Squibb (BMS; manufacturers of dasatinib) has however not done so despite clear indications of the importance of price. BMS have appealed against this 2nd line FAD on procedural grounds and the results are expected on or before 23rd December 2011.* *This means that when considering these technologies as FIRST line agents, patients failing nilotinib cannot be considered to receive dasatinib 2nd line as it is not approved, and can only receive hydroxycarbamide or stem cell transplantation (SCT). In contrast, patients failing dasatinib could receive nilotinib as it is approved. As a second line agent, nilotinib is cumulatively far more expensive than hydroxycarbamide or one-off SCT. This means that the price comparison between 1st line dasatinib and nilotinib is intrinsically biased against dasatinib, because of a procedural ruling that NICE cannot consider a second line treatment that is not itself NICE approved.* *It may therefore be necessary to reconsider these price comparisons in the light of the results of the second line appeal, once available.*	The Committee considered that scenarios 1 and 2 of the Assessment Group's model did not reflect clinical practice and should not be used to inform the recommendations. The Committee accepted that hydroxyurea and stem cell transplantation would not be routinely used in the second-line setting in place of a tyrosine kinase inhibitor and that therefore scenarios 1 and 2 of the Assessment Group's model provided only relatively approximate estimates of the cost effectiveness of first-line treatment with tyrosine kinase inhibitors. The Committee therefore considered the further additional analyses carried out by the Assessment Group after the first appraisal committee meeting. It noted that the Assessment Group had modelled two additional scenarios – one comprising first-line treatment with nilotinib followed by second-line standard-dose imatinib, and the other comprising first-line treatment with dasatinib followed by second-line standard-dose imatinib. In both scenarios, hydroxyurea and stem cell transplantation were only considered as third-line treatments. See FAD Sections 4.3.16-4.3.18

Consultee	Comment	Response
RCPath & BSH	• Are the provisional recommendations sound and a suitable basis for guidance to the NHS? *Yes for nilotinib. The recommendations for dasatinib may be flawed as indicated in the response to the preceding question.* • 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 gender, race, disability, age, sexual orientation, religion or belief? *No apparent issues,* • Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document?" *No apparent issues,* If you wish to comment on the evaluation report, please do so under a separate heading to your comments on the ACD. *Minor points;* *In sections 3.2. and 3.9, the term chronic myelogenous leukaemia is used. This is rather transatlantic; the usual term for the disease in the UK is chronic myeloid leukaemia.*	Comments noted. The term 'chronic myelogenous leukaemia' in sections 3.2 and 3.9 was taken from the wording for the marketing authorisation for dasatinib and nilotinib.

Consultee	Comment	Response
NHS North Yorkshire and York	**Relevant evidence** We have nothing further to add **Clinical and cost effectiveness interpretations** We acknowledge the complexity of the economic evaluation undertaken by the evidence review group to consider the manufacturers comments, we have nothing further to add. **Provisional recommendation** I would consider the recommendation to offer nilotinib (with a patient access scheme) or imatinib as 1st line agents for the treatment of CML to be a rational and considered 1st line recommendation. To develop a pathway which only recommended nilotinib as the therapeutic agent of choice for 1st or one subsequent line of therapy (acknowledging draft recommendations following resistance or intolerance to the primary agent) would be unrealistic when considering current clinical practice for patients presenting in chronic phase within North Yorkshire and York routinely enables (for non trial patients) standard dose imatinib 1st line with either dasatinib or nilotinib 2nd line. It is suspected but unconfirmed that some clinicians may wish to continue with a 1st generation tyrosine kinase inhibitor and thus reserve nilotinib as a 2nd line second generation agent, which locally would represent no change to the current commissioning arrangements. It is considered realistic and appropriate that the recommendation enables a 1st line and different 2nd line agent. In the absence of an alternative choice, it is predicted that other new experimental agents soon to be licensed e.g. bosutinib would likely become a commissioning priority for this condition.	Comments noted.

Consultee	Comment	Response
NHS North Yorkshire and York	**Patient access scheme** Knowledge from earlier patient access schemes have resulted in commissioners being a little apprehensive regarding the real practical implications and resources required to ensure any financial savings a scheme may generate are reimbursed to the commissioner. It has been noted that more recent schemes offer a straightforward discount, commissioners would wish to reiterate that this represents the most practical and simple method of ensuring savings are generated within the NHS for these payment by results excluded drugs. Reading the appraisal consultation document, it would appear to represent a direct discount to invoices from the outset. I raise this as commissioners would not wish to pay the list price for nilotinib and the provider trust receive the discount as Novartis drug stock for example which inevitably would result in a more complex NHS transaction where any proposed savings may not materialise or would become a part of the growing list of 'gain sharing schemes' in that both the provider and the commissioner 'share' any resulting savings as a result of the staff time required to enable the savings to be generated. **Genetic mutations** It is noted that there are a number of genetic mutations reported and as such, there will be predictable occasions when a certain genetic mutation renders a particular drug technology being unsuitable. It is acknowledged that PCTs could evaluate such instances within the local decision making individual funding request framework, however, PCTs where possible prefer and indeed should make decisions based on polices as part of the annual commissioning prioritisation process. Commissioners would like NICE to consider such instances as appears within the scope of the technology, given that commissioners do not have the infrastructure to undertake complex detailed analysis of cost effectiveness, particularly when the mutation clearly drives the decision regarding choice of agent. This would provide clarity to commissioners and potentially minimise the opportunity for inconsistency of access to particular treatments across organisations.	The manufacturer of nilotinib (Novartis) has agreed a patient access scheme with the Department of Health which makes nilotinib available with a discount applied to all invoices. The size of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. See FAD section 3.11 The Committee heard from the clinical specialists and some consultees that, for a small group of people with specific kinase domain mutations that would make their CML resistant to nilotinib, dasatinib would be offered as second-line treatment. However, the Committee considered that, because these mutations would be determined after first-line treatment failure, this would not be relevant to the first-line treatment decision for people presenting with chronic phase CML. Furthermore, this subgroup of people with specific kinase domain mutations was not distinguished in the evidence base for dasatinib. See FAD section 4.3.26

Comments received from members of the public

Role*	Section	Comment	Response
Patient	1	I was diagnosed with CML 6 years ago & achieved a major molecular response after 2 years. At this time nilotinib was not available but dasatinib was soon afterwards. I think that now there is a possibility of 3 being available,clinicians should have the choice of which to use for their patients,particularly as a major molecular response is usually achieved more rapidly with dasatinib. I felt more than fortunate to be able to benefit from pioneering treatment and still do as I lead a completely normal life & contribute to the economy. I want other people who are diagnosed to have the benefit of whatever treatment their haematologist considers appropriate & therefore dasatinib should be among those choices.	Comment noted.
Patient	1	The recommendations in relation to Nilotinib and Imatinib are much welcomed. The failure to recommend dasatinib is of concern. It is accepted to be clinically as effective as nilotinib (and more effective than imatinib) but has been refused on the basis of a cost effectiveness assessment. Only if that assessment is factually robust (and based on appropriate and accurate modelling and assumptions) can that rejection be justified. It is far from clear that this is the case, and the difference seems entirely assoaciated with the patient access scheme for nilotinib. If as has been suggested PCTs will not exceptionally fund dasatinib for patients who need it (and cant take nilotinib), this recommedation has serious implications for a group of patients who would otherwise have normal life expectancy.	The Committee concluded that the ICERs for dasatinib were substantially outside the range normally considered a cost-effective use of NHS resources (that is, between £20,000 and £30,000 per QALY gained), and that dasatinib could not be recommended as a cost-effective use of NHS resources for the first-line treatment of adults with chronic phase CML. See FAD section 4.3.26

* 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.

Role*	Section	Comment	Response
Patient	2	CML is a heterogeneous condition and patients do not respond in identical ways. The summary of CML here does not make any mention of that, nor the resulting effect that patients will respond very differently to the various drugs. Imatinib can more than slow progression - this statement (2.6) should be expanded to indicate that this slowing is believed by clinicians to be potentially permanent in responding patients, and may even eradicate disease in a small percentage. This is important in the context of more potent second generation TKIs which bring better and faster responses - this will increase the percentage of patients for whom permanent remission or eradication will be the outcome. Imatinib has completely changed the way CML is treated - transplants are now very rarely carried out as first line therapy in any patient group. The 5 year survival data looks very out of date and a considerable underestimate - thus is a bit misleading as to the effectiveness of imatinib, and TKIs generally. More recent data should be quoted	Comments noted. Long-term data up to 6 years follow-up from the IRIS study suggests that progression-free survival with imatinib treatment (and according to complete cytogenetic response) declines over time. Therefore, it is more reasonable to state that the progression of CML can be slowed rather than halted by imatinib. Furthermore, no published evidence is provided in support of the statement:" imatinib, in approximately 60% of chronic phase patients, halts rather than slows disease progression..." The Committee therefore agreed that FAD section 2.6 should state that: "...the progression of CML can be slowed by imatinib".

Role*	Section	Comment	Response
Patient	4	This is a very complex appraisal as is demonstrated by no fewer than 6 different modelling scenarios (one each from the manufacturers and four from the assessment group). It seems right given the complexity to ignore scenarios where the outcome is so hugely dependent on factors not associated with the technologies themselves but the result of administrative decisions (eg the secondline appraisal). Having said that, I am concerned that those reading the "numbers" without considering fully how they were arrived at will read them as real. The data is too immature and several assumptions seem to be wrong. For example, why should time on treatment differ between any of the TKIs? (see 4.2.29).There is no basis for this. If no statistically relevant difference in CCyR and MMR as between dasatinib and nilotinib (4.3.7) why does dasatinib have fewer QALYs? That is not real. 4.3.9 - side effects for the majority are not a big problem - this should not be understood to mean that they are not a big problem for some. That is intolerance.4.3.18 - dasatinib may be the choice for other reasons (co-morbidities) not just mutations	Comments noted. The time on first-line TKI treatment duration in the Assessment Group's economic model was estimated from the relevant RCTs of dasatinib and nilotinib and adjusted upwards according to the long-term follow-up data available for time on imatinib treatment. As a result of indirect comparison between nilotinib and dasatinib, this resulted in longer treatment duration for nilotinib compared with dasatinib. See Assessment Report section 8.2.3 (pages 153-161) for further details. To estimate the mean duration of first-line tyrosine kinase inhibitor treatments in its economic model, the Assessment Group extrapolated treatment duration data using Weibull survival curves from the DASISION, ENESTnd and IRIS trials respectively. The estimated mean first-line treatment durations used in the economic model were imatinib 7.1 years, dasatinib 7.8 years and nilotinib 9.0 years. See FAD section 4.2.21 The Committee was made aware that there are other important subgroups for whom dasatinib would be used rather than nilotinib, including people with long QT syndrome or diabetes. However, the Committee noted that it had not been presented with any evidence to support this and therefore could not make any recommendations for dasatinib in these subgroups. See FAD section 4.3.26

Role*	Section	Comment	Response
Patient	6	Comments made by PCTs about the likely availability of dasatinib following either or both appraisals are of great concern. If dasatinib is going to be refused in either or both appraisals, that will, if PCTs do not eceptionally fund this drug for patients who need this option (because they cannot tolerate or wont respond to either nilotinib or imatinib - and these groups DO EXIST) lead to unnecessary and preventable deaths in the UK. NICE should recognise this possibility and address it, whether in express guidance to PCTs or in its commentary in either or both appraisal. Dasatinib is needed both where mutations indicate AND where co morbidities suggest it.	The Committee was aware that, for a small group of people with specific kinase domain mutations that would make their CML resistant to nilotinib, dasatinib would be offered as second-line treatment. However, the Committee considered that, because these mutations would be determined after first-line treatment failure, this would not be relevant to the first-line treatment decision for people presenting with chronic phase CML. Furthermore, this subgroup of people with specific kinase domain mutations was not distinguished in the evidence base for dasatinib. See FAD section 4.3.26
Patient	7	There should be flexibility. Â No doubt NICE will wish to take into account any price adjustments to any of these technologies. There is likely to be one for imatinib but not before 2016 when the patent expires. Â On this basis, 2015 may be too early. On the other hand, as this apprraisal is based on immature data as further long term benefit studies publish their results, if the body of evidence alters the clinical view of these and other technologies, NICE should respond to that.	The Committee concluded that the recommendations for first-line tyrosine kinase inhibitors should be reviewed in 2 years' time when the price of standard-dose imatinib may be affected by the entry of new manufacturers. See FAD section 4.3.21
Patient	1	I disagree with the preliminary recommendations. Dasatinib SHOULD be recommended. Clinical trials have proven its effectiveness and I see no reason for it not to be used by patients on the recommendation of a clinician This should not be the decision of a cost-cutting body that appears to be doing Government dirty work.	The Committee concluded that the ICERs for dasatinib were substantially outside the range normally considered a cost-effective use of NHS resources (that is, between £20,000 and £30,000 per QALY gained), and that dasatinib could not be recommended as a cost-effective use of NHS resources for the first-line treatment of adults with chronic phase CML. See FAD Section 4.3.26
Patient	2	You neglect to mention the very high mortality risk of bone marrow transplant and that most patients would want to avoid it at all costs if a less risky, but highly effective, treatment is available.	Comment noted.

Role*	Section	Comment	Response
Patient	4	To consider cost-effectiveness of drugs here is distasteful. They dont prolong lives, they save them! Thanks to dasatinib I look forward to a long & fruitful life with my wife and son. This decision should only be based on clinical effectiveness & dasatinib is effective. I object to the secrecy of PAH offered by the makers of nilotinib. I wish BMS would offer a similar scheme just to negate this argument. Any cost comparison between these 2 drugs is redundant because you cannot state the discounted cost. You criticism of trial data is out-of-touch with the real world. CML is a rare condition with only around 600 new diagnosis each year. You will NOT achieve your gold standard of research with CML, it is not achievable. I am disappointed that BOTH your patient experts came from CML Support Group. All 3 drugs work, some better than others, some better with different patients. How can you afford not to recommend all 3 when they have the potential to save life? Are you prepared to take the risk and limit these clinical advancements in the treatment of a form of cancer? When we have been looking for a cure for so long are you seriously considering limiting the treatment?	Comments noted. Recommendations are based on evidence of both clinical and cost effectiveness. For both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of economic considerations" (Social Value Judgements - Principles for the development of NICE guidance; principle 5). The manufacturer of nilotinib (Novartis) has agreed a patient access scheme with the Department of Health which makes nilotinib available with a discount applied to all invoices. It was also agreed that the size of the discount is commercial in confidence. See FAD section 3.11 The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Assessment Group's economic analysis and the manufacturers' submissions. It also carefully considered the comments received from consultees and commentators in response to the Assessment Report.

PenTAG reply to second batch of responses from Novartis and BMS on PenTAG report and NICE ACD on dasatinib, nilotinib and imatinib for 1st-line CML

For NICE 2nd Appraisal Committee Meeting, 8th February 2012

Sent by PenTAG to NICE on 2nd February 2012

Novartis present no new information which affects the assessment of the cost-effectiveness of any of the drugs. Having carefully considered the second batch of responses from BMS, we have neither substantially changed our opinion of the BMS model, nor have we changed the base case of our model. We believe that NICE and/or the Appraisal Committee are better placed to respond to BMS' assertions that

(1) we should model 2nd-line dasatinib, and

(2) that NICE should justify its recommendation in favour of 1st-line standard-dose imatinib.

First, a general response to comments relating to the choice of treatments sequences (and the omission of dasatinib as a 2nd line treatment following failure of nilotinib or dasatinib).

In multiple technology assessments for NICE, the specific comparators and scenarios chosen by an Assessment Group in any model-based analysis of cost-effectiveness have to try to:

- Be consistent with the NICE scope of the technology appraisal
- Be clinically plausible and feasible within the NHS
- Incorporate life-time treatment pathways which reflect current standard clinical practice in the NHS for the relevant patient groups
- Also be consistent with prevailing (mandatory) NICE Guidance on what treatments are recommended or not recommended
- Be based on research evidence as much as possible
- Allow exploration of the strengths and weaknesses of the (often substantially different) model-based analyses provided be different manufacturers

A key conflict between these goals arises when Draft NICE Guidance on 2nd or 3rd line treatments is (a) not yet finalised, and/or (b) recommends use of a narrower range of treatments than is currently considered "standard clinical practice in the NHS". We chose to model a number of scenarios which reflect both critical methodological choices in how to model long-term survival in CML and the treatment effects of TKIs, but which also reflected two of the possible outcomes of the NICE Guidance on 2nd line treatment (namely, not recommending any of the TKIs as 2nd line treatment – which was the draft decision at the ACD stage – or only recommending nilotinib for 2nd line following intolerance or resistance to 1st line imatinib – which was the draft guidance expressed in the FAD). The treatment sequences that we modelled in our assessment report represented our best estimates, at the time, of the combination of both current clinical best practice in the NHS, AND ALSO the likely range of TKIs that would ultimately be recommended by NICE for 2nd line use in CML. To have anticipated other combinations of possible outcome of the NICE Guidance for 2nd line TKIs would have significantly multiplied the number of possible treatment sequences that required modelling and grouping into relevant scenarios.

As it is, we have modelled 4 different scenarios using the Cumulative Survival approach (reflecting two possible outcomes of the NICE Guidance for 2nd line TKIs, and a modelled a further 4 scenario analyses on the basis of the Surrogate Survival approach. Note that the Surrogate Survival approach, as in the approach used by BMS, is based on data from studies where patients only received 1st line TKIs (imatinib). Therefore, we believe, the rationale for using such a Surrogate-based approach for estimating long-term survival in scenarios where patients receive TKIs both 1st and 2nd line TKIs seems substantially weakened: in essence, the model would then be ignoring any potential survival or quality of life advantages due to the 2nd line treatments.

Novartis

No comments are necessary.

BMS

1. *"The AC has not adequately considered the comments made by Bristol-Myers Squibb on the PenTAG Assessment Report."*

BMS assert that our Scenario 1 ,2, 3 and 4, which are based on the "Cumulative Survival" approach, also used by Novartis, "cannot be considered appropriate". We disagree, and note that BMS do not explain why they believe this to be true. Given that this is a difficult disease to model given the immaturity of the clinical data, and we have presented a range of scenario analyses. Some analyses are based on the Cumulative Survival method and some on the Surrogate Survival method. We refer BMS to our report and our reply to BMS' first comments for the advantages and disadvantages of the two different modelling approaches.

Next, BMS claim that we did not respond to their comments on the face validity of our estimates of overall survival. This is incorrect. Our responses are given in the section "Surrogate Survival method (p22, BMS Section 5.3)" in our first response document. Two particularly relevant sections of our response are given below;

"*Our identification and choice of historical data"* (for the surrogate survival relationship) *"was informed by a carefully conducted systematic review of the literature, to which we devote an entire chapter (Chapter 5, p101). Similar thoroughness is not shown by BMS in their choice of historical data, nor a suggestion made for a more scientifically defensible approach*."

"*BMS then correctly state that the difference in predicted OS between patients with a MMR and those without using our surrogate relationship is small, at 3 years. First, whilst these results may appear surprising, as stated above, they are calculated based on a thorough systematic review of historical trial data, and therefore should be respected. For example, in the IRIS trial, OS at 7 years for patients with MMR at 12 months was 92% which is very similar to the corresponding value for patients without a MMR, of 89% (Hughes et al 2010). Second, we can only speculate on the causes of such a small difference in OS, but we should remember that it is difficult to achieve a MMR, indeed more difficult than a CCyR. Therefore, there will doubtless be many patients who do not achieve a MMR, but who have good prognosis. Note that the difference in predicted OS using our cytogenetic surrogate relationship is much greater, at 10 years. Had we not presented MMR-based surrogate survival we would no doubt have also been criticised by BMS.*"

2. "*The Appraisal has not given fair consideration to the evidence for dasatinib*"

BMS claim that we should have modelled dasatinib as a 2nd-line treatment, despite NICE's (then) draft FAD guidance that dasatinib should not be reimbursed for 2nd-line use. We understand that the appeal process on 2nd-line dasatinib is now complete, and that as a result, NICE's FAD decision not to recommend 2nd-line dasatinib still holds. Our understanding is that it is not appropriate to model a treatment that NICE has explicitly not recommended. However, we believe that this issue is best addressed by the NICE Appraisal Committee.

3. "*The Appraisal Committee does not adequately justify its recommendation in favour of standard-dose imatinib*"

Again, we believe that NICE or the Appraisal committee are best placed to address this issue. However, we believe that BMS' allegation that NICE's recommendation in favour of 1st-line imatinib was made "without the presentation of any incremental costs and benefits" is incorrect. We presented such results for 1st-line imatinib followed by SCT/HU and for 1st-line imatinib followed by 2nd-line nilotinib followed by SCT/HU.

4. "*Given the scenarios the AC uses as the basis of its recommendation, the lack of Probabilistic Sensitivity Analysis (PSA), in particular, is not acceptable.*"

We have clearly explained our rationale for not providing a PSA both in our report, and in section "PSA (BMS Section 5.6)" in our response document. The main reason was "because of the unusually large amount of structural uncertainty that is inherent in the present decision problem(s). This structural uncertainty relates to both the variety of ways in which long-term survival might be estimated, and uncertainty surrounding the possible sequences and mixes of treatments post 1st line TKI failure. As a result, we believe that structural uncertainty would dominate total (structural and parameter) uncertainty, and therefore that if we presented PSAs based just on parameter uncertainty, this would be of little use to the committee. Furthermore, it might actually mislead users of our report who do not appreciate the substantial structural uncertainty."

Furthermore, while the NICE Guidance on the Methods of Health Technology Appraisal (2008) state that a PSA is preferred for exploring parameter uncertainty (section 5.9.8 and 5.9.10), it is not a part of the Reference Case, as claimed by BMS in their comments on the ACD.

5. "*The scenarios selected by the Appraisal Committee (AC) to form the basis of its recommendations are not adequate for this purpose.*"

First, BMS claim that the Surrogate Survival method is superior to the Cumulative Survival method. We repeat that we believe that there are advantages and disadvantages to the Cumulative Survival Method and to the Surrogate Survival Method, as we describe in great detail in Table 34, p145 of our report. One disadvantage of the Surrogate Survival method is that it assumes that overall survival is purely a function of response rate (at 12 months), and not a function of other factors, such as depth and duration of response or the nature of the drug. For example, if two patients take different drugs, but have the same response to the drugs, then BMS claim that their expected survival is equal. In Appendix A, BMS now claim that this assumption has been clearly demonstrated to be true. However, whilst they cite several studies that they claim support the predictive value of CCyR and MMR, they cite none that specifically demonstrate that overall survival is solely a function of response, independent of the drug. We repeat another criticism of the Surrogate Survival method that overall survival is dependent purely on response to 1st-line treatment, but no further lines of treatment. For example, overall survival for two patients, neither of whom achieved a response to 1st-line treatment, would be predicted to be equal, even if one patient subsequently achieved a

response on 2nd-line nilotinib, whereas the other did not. This issue is particularly relevant because BMS urge us to model 2nd-line TKIs.

Second, BMS claim that that analyses which assume hydroxyurea in place of 2nd-line TKIs are inappropriate as they do not reflect standard practice. However, this contradicts BMS' statement in Section 5.1 of their first response to the assessment report, "*the clinical community use this intervention*" (hydroxyurea) "*only when they have exhausted all TKI treatment options and when patients are ineligible for a SCT*." Indeed, our analyses do indeed model hydroxyurea only when patients have failed TKIs. Extending on this, can we remind the committee that our "HU" treatment is in fact a proxy for a range of possible post-TKI therapies, and that the time-of-treatment for this health state was not wholly based on data from patients taking HU. Novartis also model these range of treatments under the proxy of 'HU' but have received little criticism for this.

Third, state that the uncertainty in the use of 2nd-line dasatinib will soon be resolved. As noted above, we understand that BMS' appeal for use of 2nd-line dasatinib has failed.

Finally, BMS claim that the Committee's recommendations should be based on use of 2nd-line TKIs. In our original report, we presented a scenario using 2nd-line nilotinib. In response to a request from the Committee we now also present a scenario using 2nd-line imatinib.

Appendix A: Surrogate markers

See our response in Section 5 above.

Appendix B: Factual errors

Points 1 to 3 require no comment.

In point 4, BMS claim that our updated assumption of one visit to a haematologist/oncologist every 3 months is appropriate for patients who respond to treatment, but is not sufficiently frequent for patients who do not respond. Firstly, our model does not separately model responders and non-responders over time, because we did not judge the published clinical evidence sufficient to justify making our model more complex in this way. So we cannot, retrospectively, easily reflect this suggested change to our modelling. Second, the impact of the cost adjustment BMS are suggesting is very small compared to the cost of drugs while people are taking TKIs – especially when one considers that a minority of all patients who remain on TKIs will be complete cytogenetic non-responders (BMS's own modelling of responders and non-responders confirms this). Even assuming that as many as 20% of patient-years on TKIs are when they are not responding, the monthly difference in these costs per patient is very small, at £14 (= cost per visit to a haematologist x (0.90 visits per month – 0.33 visits per month) x 20% = 91 – 42 * 20%).

BMS further believe that patients who do not respond undergo more bone marrow biopsies than patients who do response. Again, our model does not retrospectively easily have different bone marrow aspiration costs for responders and non-responders. However, we believe our arguments

based on clinical advice (previous Addendum p.2), that to a large extent these costs would cancel out between treatment arms, still stand and therefore the impact on incremental costs would not be significant.

Appendix C: BMS model

1. **Formulae errors:**

   Error #1
   BMS concede that Formula Error #1 this is indeed an error. In response to their request, we corrected for this error as follows. The negative numbers associated with error 1 are because the health states utility formula is subtracting the number of SCT patients from the next cycle instead of the current cycle. For example, in cell IF7, the formula is subtracting from row 8 for SCT patients (LC8,LD8,LE8,LF8). In order to correct this we changed the formula to reference the current cell (LC7 to LF7). This corrected the issue of negative numbers.

   Error #2
   This issue has been discussed in detail in BMS' original response to our report and in our response to BMS' criticisms of our report. In summary, both BMS and us agree that there is an discrepancy between BMS' model and their report in their assumption for the probability that patients discontinue 1st-line imatinib if they have achieved less than a partial response on 1st-line imatinib. In BMS' model, this parameter is 100%, whereas in their report (p50, Table 25), it is 58%. BMS now argue that 100% is the appropriate value. In Point 3 of this Appendix, we present results for BMS' model separately assuming 100% and 58%.

2. **Alteration to 3rd-line treatments**: We still believe it would have been inappropriate to assume 3rd-line treatment with dasatinib (or other 2nd generation TKIs) as they are (a) beyond the scope of current NICE guidance and (b) do not have published research evidence to support any necessary effectiveness assumptions.

   In response to BMS' request for further information, we removed the use of 3rd-line dasatinib in BMS' model by changing cell D16 in worksheet "3rdLineResUse", the proportion of patients taking 3rd-line dasatinib, from 80% to 0%, changing cell D17, the proportion of patients taking "alternative single-agent TKI's", from 10% to 0% (although we note that this is has no impact on the model), and by changing cell D13, the proportion of patients taking hydroxyurea, from 10% to 100%.

3. **Additional analyses**: In this section, BMS present ICERs from their model under various updated assumptions. Here, for comparison, we also present the results from BMS' model after the following changes;

- All formulae Errors # 1-8 corrected, i.e. including changing the probability that patients discontinue 1st-line imatinib if they have achieved less than a partial response on 1st-line imatinib to 58%,
- Dasatinib not modelled 3rd-line. This is implemented as described in the previous point.
- Dasatinib not modelled 2nd-line. This is implemented in worksheet "Rx Sequence", by changing cell D12 to 0%, and cell D13 to 100%.

We also present the results with all these changes, except changing the probability that patients discontinue 1st-line imatinib if they have achieved less than a partial response on 1st-line imatinib from 100%.

First BMS' results where they change their assumptions for medical management costs according the changes we made to our model;

	Dasatinib		**Imatinib**		**ICER**
	Costs	QALYs	Costs	QALYs	
Base Case (with PAS) (updated resource use for responders and non-responders)	[redacted]	[redacted]	[redacted]	[redacted]	£46,300
Revised CP responder resource use estimates only +PAS	[redacted]	[redacted]	[redacted]	[redacted]	£34,400
Revised CP responder resource use estimates only + alternative imatinib dose intensity + PAS	[redacted]	[redacted]	[redacted]	[redacted]	£26,500

compared to the figures we estimate on the first basis above (including changing imatinib discontinuation rate to 58%) using BMS' model;

	Dasatinib		**Imatinib**		**ICER**
	Costs	QALYs	Costs	QALYs	
Base Case (with PAS) (updated resource use for responders and non-responders)	[redacted]	[redacted]	[redacted]	[redacted]	£97,000
Revised CP responder resource use estimates only +PAS	[redacted]	[redacted]	[redacted]	[redacted]	£87,000
Revised CP responder resource use estimates only + alternative imatinib dose intensity + PAS	[redacted]	[redacted]	[redacted]	[redacted]	£80,000

and compared to the results we estimate on the second basis above (leaving imatinib discontinuation rate at 100%) using BMS' model;

	Dasatinib		**Imatinib**		**ICER**
	Costs	QALYs	Costs	QALYs	
Base Case (with PAS) (updated resource use for responders and non-responders)	[redacted]	[redacted]	[redacted]	[redacted]	£91,000
Revised CP responder resource use estimates only +PAS	[redacted]	[redacted]	[redacted]	[redacted]	£81,000
Revised CP responder resource use estimates only + alternative imatinib dose intensity + PAS	[redacted]	[redacted]	[redacted]	[redacted]	£75,000

It is impossible to identify the causes of the substantial differences in our results and those produced by BMS, both using BMS' model. However, we believe it is likely that BMS' updated results still allow for dasatinib to be taken 2nd- and 3rd-line, which we believe is incorrect.

4. **PenTAG use of MMR and CCyR**: First, BMS repeat that they believe that the Cumulative Survival method is in appropriate. However, as we argue above, there are pros and cons of this method and of the Surrogate Survival method.

   Next, BMS present a graph showing the expected split of the dasatinib patient cohort by health state over time when we model overall survival according to cytogenetic response rate. BMS allege that we overestimate the time on hydroxyurea, as they did in their response to our assessment report. In response, we repeat the defence we presented before;

   "Next, under the Surrogate Survival methods, the mean time on HU for patients who reach treatment with HU is typically about 15 years. We discuss this in detail in Section 8.1.3, p139 of our report. In summary, in order to model OS as predicted from the surrogate relationships, it was necessary to alter the estimated mean time on one or more intervening treatments. The mean times on TKIs were not altered because these were taken from high quality RCTs. The mean survival after SCT was also not altered because it was not possible to replicate the OS from the surrogate relationships. This left only one possibility, to alter the mean time on HU. This gives the unrealistically high estimated mean time on HU of about 15 years.

   To be clear, we do not suggest that it is realistic to expect patients to spend 15 years on 2nd-line HU after failure of 1st-line TKI. Instead, we believe that this method still captures the essential features of the surrogate relationship, which is the overall survival advantage of dasatinib and nilotinib versus imatinib predicted by the response rates at 12 months. Furthermore, this highlights the extreme difficulty of modelling complex sequences of treatments given very limited, immature clinical evidence."

ADDENDUM #2 to Final Report for NICE

Dasatinib, Nilotinib, and standard dose Imatinib for the first-line treatment of chronic myeloid leukaemia

For NICE Appraisal Committee Meeting, 8th February 2012

Prepared and sent by PenTAG, 2nd February 2012

In our original report, we modelled the following treatment sequences;

In Scenarios 1 and 2 (and 1a, 1b, 2a, 2b)

- 1st-line Imatinib, 2nd-line SCT / HU,
- 1st-line Nilotinib, 2nd-line SCT / HU,
- 1st-line Dasatinib, 2nd-line SCT/HU,

In Scenarios 3 and 4

- 1st-line Imatinib, 2nd-line nilotinib, 3rd-line SCT / HU,
- 1st-line Nilotinib, 2nd-line SCT / HU,
- 1st-line Dasatinib, 2nd-line nilotinib, 3rd-line SCT / HU

In addition, the NICE Appraisal Committee has recently asked us to model;

- 1st-line nilotinib, 2nd-line imatinib, 3rd-line SCT / HU
- 1st-line dasatinib, 2nd-line imatinib, 3rd-line SCT / HU

First, we describe how we parameterised the model for 2nd-line imatinib. Second, we present our corresponding cost-effectiveness results.

Parameters for 2nd-line standard dose imatinib

Time on 2nd-line imatinib

We are aware of no clinical data for time on 2nd-line standard dose imatinib after failure of 1st-line nilotinib or dasatinib. For simplicity, and given the lack of evidence to the contrary, we assumed the same mean time on 2nd-line imatinib following 1st-line nilotinib or 1st-line dasatinib. We estimated;

Mean time on 2nd-line imatinib =

Mean time on 2nd-line nilotinib

x (Mean time on 1st-line imatinib / Mean time on 1st-line nilotinib)

= 2.4 years x (7.0 years / 8.9 years)

= 1.9 years

All figures in this calculation are based on evidence from high-quality trials. We assume a constant rate of failure of 2nd-line imatinib over time, as we do for 2nd-line nilotinib.

Dose intensity of 2nd-line imatinib

We are aware of no clinical evidence for the dose intensity of 2nd-line standard dose imatinib following failure of 1st-line nilotinib or dasatinib. For simplicity, we set this quantity equal to our assumption for the dose intensity of 1st-line imatinib, 100%.

Cost of treating adverse events on 2nd-line imatinib

We are aware of no clinical evidence for the incidence of adverse events on 2nd-line standard dose imatinib following failure of 1st-line nilotinib or dasatinib. For simplicity, we set the cost of treating these equal to our assumption for the cost of treating adverse events on 1st-line imatinib, £166 per patient.

Cost-effectiveness results involving 2nd-line standard dose imatinib

In all these analyses, patients additionally take 3rd-line HU or SCT.

1st-line imatinib, 2nd-line nilotinib vs. 1st-line nilotinib, 2nd-line imatinib

Results under the full (non-simplified) method;

	1st-line imatinib, 2nd-line nilotinib, 3rd-line SCT / HU	1st-line nilotinib, 2nd-line imatinib, 3rd-line SCT / HU	1st-line nilotinib arm – 1st-line imatinib arm
Undiscounted life years	17.3	18.0	0.7
Discounted QALYs	9.53	9.82	0.29
Discounted costs	£188,480	£191,701	£3,222
ICER (£ per QALY)			**£11,000**

For comparison, the results for 1st-line nilotinib followed by 2nd-line SCT / HU are;

Undiscounted life years: 17.4
Discounted QALYs: 9.43
Discounted costs: £169,932

Undiscounted life years are greater for 1st-line nilotinib - 2nd-line imatinib compared to 1st-line nilotinib alone obviously because we now model the additional 2nd-line imatinib. One might expect the difference in mean life years between these treatment arms (18.0 – 17.4 = 0.6 years) to equal the mean time on 2nd-line imatinib (1.9 years). This is not so for two reasons. First when we introduce 2nd-line imatinib, the mean age of starting HU / SCT increases from 66 to 68 years, and the probability of having a life-extending SCT decreases with age. Second, not all patients (84%) survive long enough to receive 2nd-line imatinib. When we add 2nd-line imatinib, discounted costs increase substantially, from £169,932 to £191,701. On the one hand, costs increase because of the time on 2nd-line imatinib, and on the other hand, costs decrease because fewer patients are predicted to have an expensive SCT.

The ICER is now low because we predict more QALYs in the 1st-line nilotinib arm at similar total cost.

Results under the simplified method (setting HU and SCT per patient costs and QALYs equal in both treatment arms);

	1st-line imatinib, 2nd-line nilotinib, 3rd-line SCT / HU	1st-line nilotinib, 2nd-line imatinib, 3rd-line SCT / HU	1st-line nilotinib arm – 1st-line imatinib arm
Undiscounted life years	n/a	n/a	n/a
Discounted QALYs	9.53	9.90	0.37
Discounted costs	£188,480	£192,699	£4,219

ICER (£ per QALY)	**£11,000**

1st-line imatinib, 2nd-line nilotinib vs. 1st-line dasatinib, 2nd-line imatinib

Results under the full (non-simplified) method;

	1st-line imatinib, 2nd-line nilotinib, 3rd-line SCT / HU	1st-line dasatinib, 2nd-line imatinib, 3rd-line SCT / HU	1st-line dasatinib arm – 1st-line imatinib arm
Undiscounted life years	17.3	17.4	0.1
Discounted QALYs	9.53	9.57	0.04
Discounted costs	£188,480	£247,171	£58,691
ICER (£ per QALY)			**£1,364,000**

For comparison, the results for 1st-line dasatinib followed by 2nd-line nilotinib, followed by 3rd-line SCT / HU are;

Undiscounted life years: 17.6
Discounted QALYs: 9.67
Discounted costs: £252,208

Undiscounted life years are slightly lower for 1st-line dasatinib - 2nd-line imatinib compared to 1st-line dasatinib, 2nd-line nilotinib because we predict a slightly lower mean time on 2nd-line imatinib (1.9 years) compared to 2nd-line nilotinib (2.4 years). With 2nd-line imatinib rather than 2nd-line nilotinib, discounted costs decrease slightly, from £252,000 to £247,000, for the same reason.

The ICER is now extremely high because we predict similar QALYs but much higher costs in the 1st-line dasatinib arm.

Results under the simplified method;

	1st-line imatinib, 2nd-line nilotinib, 3rd-line SCT / HU	1st-line dasatinib, 2nd-line imatinib, 3rd-line SCT / HU	1st-line dasatinib arm – 1st-line imatinib arm
Undiscounted life years	n/a	n/a	n/a
Discounted QALYs	9.53	9.55	0.02
Discounted costs	£188,480	£246,962	£58,482
ICER (£ per QALY)			**£3,159,000**

Sensitivity analyses for ICERs for 1st-line imatinib, 2nd-line nilotinib vs. 1st-line nilotinib, 2nd-line imatinib

Parameter	Base case	Sensitivity analysis	Full, unsimplified method	Simplified method
Base case	n/a	n/a	**£11,000**	**£11,000**
General				
Discounting costs & benefits	3.5% p.a.	0% p.a.	£21,000	£19,000
Treatment pathways				
Proportion receiving SCT	Mean 26% nilotinib, 23% imatinib, decreases with age	31% at all ages (BMS assumption)	£12,000	£11,000
		75% if age < 65 (Novartis)	£10,000	£11,000
		Halve % at all ages	£12,000	£12,000
Effectiveness				
Time on 1st-line TKI	8.9 years nilotinib, 7.0 years imatinib	7.0 years nilotinib, 7.0 years imatinib	nilotinib dominates	nilotinib dominates
		13.8 years nilotinib, 11.7 years imatinib (IRIS)	£1,000	£2,000
Time on 2nd-line nilotinib	Mean 2.5 years	Same as mean time on 1st-line nilotinib = 8.9 years	£63,000	£41,000
Time on 2nd-line imatinib	Mean 2.0 years	Same as mean time on 1st-line imatinib = 7.0 years	£42,000	£31,000
Survival after SCT	Mean approximately 17 years	Mean 5.7 years (Novartis)	£8,000	£10,000
Time in CP on HU	Mean 5 years	Mean 1.6 years (Novartis)	£9,000	£10,000
OS estimated by Cumulative Survival or Surrogate Survival	Cumulative Survival	Cumulative survival means, MMR survival difference	n/a as 2 lines of TKI	
		Cumulative survival means, CCyR survival difference	n/a as 2 lines of TKI	
		Surrogate survival means, MMR survival difference	n/a as 2 lines of TKI	
		Surrogate survival means, CCyR survival difference	n/a as 2 lines of TKI	
Costs				
Drug price reduction on patent expiry	0% nilotinib, 0% imatinib	0% nilotinib, 25% imatinib	£47,000	£39,000
		25% nilotinib, 25% imatinib	£29,000	£25,000
Dose intensities	[redacted] 1st-line nilotinib, 100% 1st-line imatinib, 99% 2nd-line nilotinib, 100% 2nd-line imatinib	100% 1st-line nilotinib, rest unchanged	£52,000	£42,000
		106% 1st- and 2nd-line imatinib, rest unchanged	Nilotinib dominates	Nilotinib dominates
		[redacted] 2nd-line nilotinib, rest unchanged	£20,000	£18,000
Cost SCT	£81,603	£40,801	£15,000	£13,000
		£163,205	£5,000	£8,000
Medical management	£113 per month	£226 per month	£11,000	£11,000

Parameter	Base case	Sensitivity analysis	Full, unsimplified method	Simplified method
Base case	n/a	n/a	**£11,000**	**£11,000**
costs after SCT				
Medical management costs in CP	£56 per month TKIs, £106 per month HU	£28 per month TKIs, £53 per month HU	£11,000	£11,000
		£112 per month TKIs, £211 per month HU	£13,000	£12,000
Medical management costs in AP and BC	£1,113 per month	£2,227 per month	£10,000	£10,000
AEs costs	£166 per patient 1st-line and 2nd-line imatinib, £119 1st-line nilotinib, £299 2nd-line nilotinib	All costs multiplied by 10	£6,000	£7,000
Utilities				
Utilities		Equal to Novartis	£11,000	£11,000
		Reduce all utilities by 0.10	£10,000	£11,000

Sensitivity analyses for 1st-line imatinib, 2nd-line nilotinib vs. 1st-line dasatinib, 2nd-line imatinib

Parameter	Base case	Sensitivity analysis	Full, unsimplified method	Simplified method
Base case	n/a	n/a	**£1,364,000**	**£3,159,000**
General				
Discounting costs & benefits	3.5% p.a.	0% p.a.	£748,000	£1,064,000
Treatment pathways				
Proportion receiving SCT	Mean 25% dasatinib, 26% imatinib, decreases with age	31% at all ages (BMS assumption)	£1,798,000	£2,587,000
		75% if age < 65 (Novartis)	£1,352,000	£4,996,000
		Halve % at all ages	£1,439,000	£2,325,000
Effectiveness				
Time on 1st-line TKI	7.7 years dasatinib, 7.0 years imatinib	7.0 years dasatinib, 7.0 years imatinib	Imatinib dominates	Imatinib dominates
		12.5 years dasatinib, 11.7 years imatinib (IRIS)	£979,000	£1,030,000
Time on 2nd-line nilotinib	Mean 2.5 years	Same as mean time on 1st-line nilotinib = 8.9 years	£4,000¶	£7,000¶
Time on 2nd-line imatinib	Mean 2.0 years	Same as mean time on 1st-line imatinib = 7.0 years	£110,000	£75,000
Survival after SCT	Mean approximately 17 years	Mean 5.7 years (Novartis)	£1,468,000	£1,639,000
Time in CP on HU	Mean 5 years	Mean 1.6 years (Novartis)	£959,000	£1,677,000
OS estimated by Cumulative Survival or Surrogate Survival	Cumulative Survival	Cumulative survival means, MMR survival difference	n/a as 2 lines of TKI	
		Cumulative survival means, CCyR survival difference	n/a as 2 lines of TKI	
		Surrogate survival means, MMR survival difference	n/a as 2 lines of TKI	
		Surrogate survival means, CCyR survival difference	n/a as 2 lines of TKI	
Costs				
Drug price reduction on patent expiry	0% dasatinib, 0% imatinib	25% dasatinib, 25% imatinib	£1,304,000	£3,020,000
Dose intensities	100% 1st- and 2nd-line imatinib, 99% 1st-line dasatinib, 99% 2nd-line nilotinib	106% 1st- and 2nd-line imatinib, rest unchanged	£1,238,000	£2,866,000
		[redacted] 2nd-line nilotinib, rest unchanged	£1,422,000	£3,294,000
Cost SCT	£81,603	£40,801	£1,364,000	£3,166,000
		£163,205	£1,363,000	£3,145,000
Medical management costs after SCT	£113 per month	£226 per month	£1,364,000	£3,158,000
Medical management		£28 per month TKIs,	£1,364,000	£3,156,000

Parameter	Base case	Sensitivity analysis	Full, unsimplified method	Simplified method
Base case	n/a	n/a	**£1,364,000**	**£3,159,000**
costs in CP	£56 per month TKIs, £106 per month HU	£53 per month HU		
		£112 per month TKIs, £211 per month HU	£1,364,000	£3,161,000
Medical management costs in AP and BC	£1,113 per month	£2,227 per month	£1,361,000	£3,154,000
AEs costs	£166 per patient 1st- and 2nd-line imatinib, £282 1st-line dasatinib, £299 2nd-line nilotinib	All costs multiplied by 10	£1,360,000	£3,151,000
Utilities				
Utilities		Equal to Novartis	£1,353,000	£3,151,000
Utilities		Reduce all utilities by 0.10	£1,210,000	£3,058,000

¶ dasatinib arm provides fewer QALYs at less cost than imatinib arm

ADDENDUM #3 to Final Report for NICE

Dasatinib, Nilotinib, and standard dose Imatinib for the first-line treatment of chronic myeloid leukaemia

Information considered at NICE Appraisal Committee Meeting, 8th February 2012

Prepared and sent by PenTAG, 15th February 2012

The following two analyses were produced and sent on 7th February to NICE in response to a query (by e-mail) from Prof Matt Stevenson (ScHARR, and Lead committee member for cost-effectiveness on this MTA).

1st-line nilotinib, 2nd-line imatinib, 3rd-line HU/SCT *versus* 1st-line nilotinib, 2nd-line HU/SCT

Results under the full (non-simplified) method;

	1st-line nilotinib, 2nd-line SCT / HU	1st-line nilotinib, 2nd-line imatinib, 3rd-line SCT / HU	Col 2 – col 1
Undiscounted life years	17.4	18.0	0.6
Discounted QALYs	9.43	9.82	0.38
Discounted costs	£169,932	£191,701	£21,770
ICER (£ per QALY)			**£57,000**

Results under the simplified method (setting HU and SCT per patient costs and QALYs equal in both treatment arms);

	1st-line nilotinib, 2nd-line SCT / HU	1st-line nilotinib, 2nd-line imatinib, 3rd-line SCT / HU	Col 2 – col 1
Undiscounted life years	n/a	n/a	n/a
Discounted QALYs	9.43	10.27	0.84
Discounted costs	£169,932	£196,066	£26,135
ICER (£ per QALY)			**£31,000**

Notice that incremental QALYs are greater under the simplified method. This is caused by the QALY difference between treatment arms in respect of SCT. In the full model, there are 0.58 fewer SCT QALYs in the nilotinib – imatinib treatment arm compared to the nilotinib arm (not shown in table above). This is because we assume that the proportion of patients who get a SCT declines with age, and people become eligible for SCT later in the nilotinib – imatinib treatment arm. However, in the simplified method, there are just 0.08 fewer SCT QALYs in the nilotinib – imatinib treatment arm. This difference is less because the simplified method – by standardising the costs and QALYs' post-TKI - does not allow for the declining proportion of patients receiving a SCT with age.

ERRATUM: Corrections to final Assessment Group report for NICE

Dasatinib, Nilotinib, and standard dose Imatinib for the first-line treatment of chronic myeloid leukaemia

Prepared and sent by PenTAG, 28th February 2012

In this Erratum, we make some corrections to our original report concerning response rates to treatment. Please note that the errors noted in this document do not impact the ICERs that were presented in the report or any of the other cost-effectiveness analyses conducted.

<table>
<tr><th>AG report page ref</th><th>Error (noted in red text)</th><th>Correction (noted in orange text)</th></tr>
<tr><td>Table 12 Complete cytogenic response (Section 4.2.3.1, page 78)</td><td>
<table>
<tr><td colspan="4">ENESTnd</td></tr>
<tr><td>Intervention</td><td>Nilotinib (300 mg)</td><td>Nilotinib (400 mg)</td><td>Imatinib (400 mg)</td></tr>
<tr><td colspan="4">Risk group CCyR rates 12 mths[a] (%)</td></tr>
<tr><td>Low
Intermediate
High</td><td></td><td></td><td>[redacted]
38/78 (49)</td></tr>
</table>
a = ITT analysis
</td><td>
<table>
<tr><td colspan="4">ENESTnd</td></tr>
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High</td><td></td><td></td><td>[redacted]
38/78 (49)</td></tr>
</table>
</td></tr>
<tr><td>Section 4.2.3.2, page 80</td><td>At 24-months follow-up, MMR rates continued to be significantly higher for patients receiving nilotinib 300 mg (62%) compared to patients receiving imatinib (37%) (p=0.001; RR 2.02, 95% CI 1.56-2.65).</td><td>At 24-months follow-up, MMR rates continued to be significantly higher for patients receiving nilotinib 300 mg (62%) compared to patients receiving imatinib (37%) (p=0.001; RR 1.67, 95% CI 1.40–2.00).</td></tr>
<tr><td>Section 4.2.3.2, page 80</td><td>..., 24-months follow-up (71% vs 44%, p=0.001; RR 1.67, 95% CI 1.40–1.89).</td><td>..., 24-months follow-up (71% vs 44%, p=0.001; RR 1.63, 95% CI 1.37–1.84).</td></tr>
<tr><td>Table 13 Major molecular response (Section 4.2.3.2, page 83)</td><td>
<table>
<tr><td colspan="7">ENESTnd</td></tr>
<tr><td></td><td>Nilotinib (300 mg)</td><td>RR (95% CI)[d, #]</td><td>Nilotinib (400 mg)</td><td>p-value</td><td>RR (95% CI)[d, #]</td><td>Imatinib (400 mg)</td></tr>
<tr><td colspan="7">MMR at any time (12-months)[a,b] (%)</td></tr>
<tr><td></td><td>[redacted] (57)</td><td></td><td>[redacted] (54)</td><td></td><td></td><td>[redacted] (30)</td></tr>
<tr><td colspan="7">MMR at any time (24 months)[a,b] (%)</td></tr>
<tr><td></td><td></td><td>1.67 (1.40–1.89)</td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="7">Risk group MMR rates 18-months[c] (%)</td></tr>
<tr><td>Low</td><td>71/103 (70)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Intermed</td><td>69/101 (67)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>High</td><td>46/78 (59)</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
a = ITT analysis; b = cumulative (MMR may be lost by timepoint); c = Hasford risk Kantarjian, Sokal risk, Saglio; d = PenTAG calculated; # = relative risk compared with imatinib
</td><td>
<table>
<tr><td colspan="7">ENESTnd</td></tr>
<tr><td></td><td>Nilotinib (300 mg)</td><td>RR (95% CI)[d, #]</td><td>Nilotinib (400 mg)</td><td>p-value</td><td>RR (95% CI)[d, #]</td><td>Imatinib (400 mg)</td></tr>
<tr><td colspan="7">MMR at any time (12-months)[a,b] (%)</td></tr>
<tr><td></td><td>[redacted] (55)</td><td></td><td>[redacted] (51)</td><td></td><td></td><td>[redacted] (27)</td></tr>
<tr><td colspan="7">MMR at any time (24 months)[a,b] (%)</td></tr>
<tr><td></td><td></td><td>1.63 (1.37–1.84)</td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="7">Risk group MMR rates 18-months[c] (%)</td></tr>
<tr><td>Low</td><td>71/103 (69)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Intermed</td><td>69/101 (68)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>High</td><td>46/78 (59)</td><td></td><td></td><td></td><td></td><td></td></tr>
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a = ITT analysis; b = cumulative (MMR may be lost by timepoint); c = Hasford risk Kantarjian, Sokal risk, Saglio; d = PenTAG calculated; # = relative risk compared with imatinib
</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td></tr>
<tr><td>Section 4.2.3.3, page 84</td><td>... receiving dasatinib (13%, p=0.04; RR 1.79, 95% CI 1.00–3.24) compared to patients receiving imatinib (7%). ...</td><td>... receiving dasatinib (13%, p=0.04; RR 1.90, 95% CI 1.00–3.24) compared to patients receiving imatinib (7%). ...</td></tr>
<tr><td>Table 14 Complete molecular response (Section 4.2.3.3, page 85)</td><td>
<table>
<tr><th colspan="3">DASISION</th><th colspan="3">ENESTnd</th><th></th></tr>
<tr><td></td><td></td><td>RR (95% CI)[d, #]</td><td></td><td></td><td></td><td>Nilotinib (400 mg)</td></tr>
<tr><td colspan="7">CMR 18-months[a] (BCR-ABL ≤0.0032(%) (%)</td></tr>
<tr><td></td><td></td><td>1.79 (1.00–3.24)</td><td></td><td></td><td></td><td>48/233 (17)</td></tr>
</table>
a = ITT analysis
</td><td>
<table>
<tr><th colspan="3">DASISION</th><th colspan="3">ENESTnd</th><th></th></tr>
<tr><td></td><td></td><td>RR (95% CI)[d, #]</td><td></td><td></td><td></td><td>Nilotinib (400 mg)</td></tr>
<tr><td colspan="7">CMR 18-months[a] (BCR-ABL ≤(0.0032%) (%)</td></tr>
<tr><td></td><td></td><td>1.90 (1.00–3.24)</td><td></td><td></td><td></td><td>48/281 (17)</td></tr>
</table>
a = ITT analysis
</td></tr>
</table>

Comments from Bristol-Myers Squibb on the Appraisal Consultation Document (ACD)

Dasatinib, nilotinib and standard-dose imatinib for the first line treatment of chronic myeloid leukaemia (incl part-review of TA 70)

Thank you for the opportunity to comment on this ACD. We have structured our reply as follows:

1. A summary of the main issues with the ACD.
2. A more detailed consideration of the issues, structured as requested by the Institute:
    - Has all of the relevant evidence been taken into account?
    - Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
    - Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
    - Are there any aspects of the recommendation that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?
3. Correction of factual errors and further clarification / presentation of results from the Bristol-Myers Squibb model.

Summary of the Main Issues with the ACD

1. The Appraisal Committee (AC) has not adequately considered the comments made by Bristol-Myers Squibb on the PenTAG Assessment Report (AR).
2. The Appraisal has not given fair consideration to the evidence for dasatinib.
3. The Appraisal Committee does not adequately justify its recommendation in favour of standard-dose imatinib
4. The lack of probabilistic sensitivity analysis (PSA), especially given the scenarios the AC uses as the basis of its recommendation, is not acceptable
5. The scenarios selected by the Appraisal Committee to form the basis of its recommendations are not adequate for this purpose.

Detailed Consideration of the Issues with the ACD

Has all of the relevant evidence been taken into account?

No, we do not believe all of the relevant evidence has been taken into account.

1. **The AC has not adequately considered the comments made by Bristol-Myers Squibb on the PenTAG Assessment Report**.
   The ACD is clear that the Committee carefully considered comments received by Bristol-Myers Squibb (4.3.14) and, furthermore, were satisfied that the Assessment Group had adequately addressed the issues raised by presenting a range of scenarios rather than a single base-case cost-effectiveness analysis.

We assert that Scenarios 1 and 2 are basically flawed, and so we question how the Committee can be satisfied that these scenarios are an adequate basis for making its recommendations. Furthermore, as noted in the ACD, our comments on the Assessment Report highlighted fundamental issues with the PenTAG model – such as its inability to reflect the underlying nature of the disease, and its estimation of unreliable treatment durations (See Appendices).

Scenarios 1, 2, 3 and 4 cannot be considered appropriate as the basis for the Committee's recommendations as they are all reliant on the cumulative survival approach.

Furthermore, our response to the AR highlighted issues with the AG model in estimating survival via the surrogate approach:

> *"Consequently, even when adjusting for background non-CML mortality, the predicted mean survival (especially for those who do not respond) is far too high (CCR; 24.4 years, Non-CCyR: 14.3 years, MMR: 24.2 years, No MMR: 21.3 years). The figures for MMR are striking, suggesting that achieving the highest possible level of response to treatment only offers an additional 3 years of life – and that if this level is not achieved, a patient will still live for over 20 years!*
>
> *These small differences in a patient's prognosis, with and without response, clearly diminish the importance of the proportion of patients who respond overall. A recent indirect comparison meta-analysis of first line treatments concluded that treatment with dasatinib was significantly associated with achieving MMR (Odds ratio 2.23 dasatinib compared to imatinib: Table 12 BMS submission document).*
>
> *Despite the superior performance on this key clinical endpoint the predicted difference for dasatinib compared to imatinib is a mere 0.6 years. The approach used in the AG model, therefore, is not in line with the clinical evidence and strongly biases all results against dasatinib."*

As the Assessment Group did not respond to this point in their commentary, we would invite the Committee to re-evaluate whether the analyses using the surrogate approach (as implemented by the AG) should be considered reliable or adequate given the issues we have (once again) highlighted. In addition, in Appendix C, we raise further concerns regarding the validity of the AG approach to estimating survival via surrogate markers.

If the Committee had adequately considered our comments and the evidence available, it would recognise that such concerns cannot simply be addressed by the range of scenarios presented. We feel the cumulative survival approach lacks clinical validity, while the surrogate survival approach (as implemented by the AG) lacks face validity.

2. **The Appraisal has not given fair consideration to the evidence for dasatinib**.

The Committee justifies its exclusion of dasatinib in the 2nd line setting with reference to its FAD in the ongoing appraisal for chronic and accelerated phase CML in adults whose CML is resistant to or intolerant to standard-dose imatinib. However, as the Committee will be aware, this FAD is subject to appeal and so is not final.

As noted in our response to the Assessment Report, it is inappropriate to exclude consideration of dasatinib (as well as imatinib) in the 2nd line setting from this appraisal because correct consideration of the evidence in the 1st line setting requires accurate consideration of the evidence in 2nd line.
Notwithstanding our comments about the validity of Scenarios 1 and 2, the exclusion of data for dasatinib in the 2nd line setting has unnecessarily reduced the accuracy of this appraisal.

To avoid the perception that the Committee's unratified recommendation in the 2nd line setting may be driving its approach to the 1st line setting and to ensure the accuracy of the 1st line evaluation, the assessment should have comprehensively included all relevant comparators in both settings.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
We believe the summary of clinical effectiveness is a reasonable interpretation of the evidence; however, the summaries of cost effectiveness are not.

3. **The Appraisal Committee does not adequately justify its recommendation in favour of standard-dose imatinib**.

In Section 4.3.17, the AC concludes nilotinib represents a cost effective use of NHS resources and should be recommended as a 1st-line treatment option for people with chronic-phase CML. This is a conclusion based on comparison with standard-dose imatinib.

In Section 4.3.19, the Committee go on to recommend standard-dose imatinib in this setting based on the long-term data from the IRIS trial and the importance of having an alternative TKI for people for whom nilotinib is inappropriate. This recommendation is made despite recognition of the borderline cost-effectiveness results, and without the presentation of any incremental costs and benefits. In short, the Committee consider standard-dose imatinib to be a cost effective use of NHS resources despite not presenting any comparative data for costs and benefits.

Even without any other considerations, this explanation for the Committee's recommendation is perverse. However, given the recent price increase for imatinib, and because this appraisal serves (in part) as an update to TA70, the Committee must provide greater justification for its recommendation in favour of standard-dose imatinib.

4 **Given the scenarios the AC uses as the basis of its recommendation, the lack of Probabilistic Sensitivity Analysis (PSA), in particular, is not acceptable**.

We previously commented on the importance of a PSA, noting it is a requirement of the NICE reference case for economic analysis. We again highlight this significant omission.

- The Committee has chosen to base its draft recommendation on Scenarios 1 and 2, and does so partly to reduce the uncertainty associated with subsequent lines of treatment. Given this approach, the Committee has effectively removed the structural uncertainty referred to by the Assessment Group as a barrier to conducting a PSA.

- As noted, the decision to recommend standard-dose imatinib in this setting is not adequately justified. In the context of the aforementioned reliance on Scenarios 1 and 2, it is essential that a PSA is published to support this decision, to ensure that the Committee has reached a robust assessment

If the Committee decide to continue to base their recommendations on these Scenarios, they must present a PSA as support to their decision.

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

The provisional recommendations are neither sound, nor a suitable basis for guidance to the NHS, given the comments made above. In addition, we believe the scenarios used by the AC are a not suitable basis for their recommendations.

5. **The scenarios selected by the Appraisal Committee (AC) to form the basis of its recommendations are not adequate for this purpose**.

   While we respect the logic applied by the Committee to decide which treatment scenarios give the most realistic estimates of cost effectiveness (4.3.16), we request that on review, and during discussions at the second appraisal committee meeting, the Committee reflect on the following issues:

   - The extensive amount of published data demonstrating the predictive value of surrogate markers means any analyses based on a cumulative survival approach must be considered obsolete. We provide an up to date summary of published data for the predictive value of surrogate markers in Appendix A.
   - Analyses which consider the use of hydroxyurea (HU) in place of 2nd-line TKIs are inappropriate as they do not reflect standard clinical practice.
   - The uncertainty referred to by the Committee (4.3.16) for 2nd-line use of TKIs in the treatment of chronic and accelerated phase CML will be resolved in a matter of weeks (as the Appeal decision is due in early January 2012).

We realise that the Committee has chosen PenTAG Scenarios 1 and 2 because it considers these minimise the uncertainty associated with assessing TKIs in the 1st line setting. However, on reflection, and for the reasons outlined above, we hope the Committee also recognises these scenarios are not an adequate basis for making its recommendations. To be considered valid by the clinical community, the Committee's recommendations must be based on an assessment of overall survival using surrogate markers, and must include 2nd line use of TKI's.

We look forward to the Committee's detailed consideration of the points we raise and we are of course on hand to provide additional analyses or model outputs if these would help the Committee in its further deliberations.

Yours sincerely,

[redacted]

Appendix A

Surrogate Markers. It is widely accepted by the clinical community that the estimation of long term clinical benefit is most appropriately based on surrogate clinical markers, not cumulative survival. Numerous peer reviewed publications, both historic (Schrover et al 2006, Druker et al 2006, Kantarjian et al 2006, Anstrom et al 2004) and more recent (Marin et al 2011, Jabbour et al 2011, as well as data presented at the 2011 American Society of Hematology (ASH) (Milojkovic et al, Nicolini et al, Hochhaus et al, Hanfstein etal, Marin et al, Latagliata et al) demonstrate the predictive value of CCyR and MMR on long term outcomes (including PFS and OS).

Importantly, it has been clearly demonstrated that any effects on these surrogate endpoints are not dependent upon the action of a particular drug (or even class of drug). Rather, achieving an effect on the surrogate marker *per se* is what is essential – and is predictive of long term clinical effectiveness (whatever the drug).

For example, IFN- α can (historically) be shown to have induced cytogenetic responses, which were predictive of a positive long term outcome. This predictive long term effect can also be applied to imatinib – but is not limited to imatinib alone. Any other agent achieving a cytogenetic response can, just as legitimately, be predicted to have a positive effect on long term clinical outcomes.

Thus, historical data shows that achieving a cytogenetic response with IFN- α is predictive of a long term outcome, and this predictive nature extends to cytogenetic responses achieved with imatinib.

In addition, some of the more recent data referred to above also supports the predictive value of these surrogates when achieved with 2GTKIs (Jabbour et al 2011 and data from ASH 2011: Hochhaus et al, Marin et al, Nicolini et al)

In light of the fact that the surrogate markers of outcome used in CML are relevant to all treatments, BMS submit that a surrogate marker model should be use to generate the base case ICERs, not a cumulative survival model.

Appendix B

Factual Errors

1. Dasatinib is not just a SRC inhibitor: it inhibits the activity of the BCR-ABL kinase and SRC family kinases, along with a number of other selected oncogenic kinases including c-KIT, ephrin (EPH) receptor kinases, and PDGFβ receptor. Thus, dasatinib is a potent, subnanomolar inhibitor of the BCR-ABL kinase and this ability to inhibit BCR-ABL is likely to be key to its clinical effectiveness in CML.

2. Ponatinib not panitumab – page 49

3. "At" or "By" for response rates: the AG have the following to say in their response to Novartis comments: "*...however, the response rates were not always reported simply as 'at' and 'by' and interpretation of whether the values were 'at' or 'by' was based on all sources of information for a specified time-point."* BMS use meta-analysis data for MMR as inputs into their model, as it is not possible (from a number of the studies published) to identify whether responses were 'at' or 'by' a given time point. Therefore, by not using the response rates from one particular study we hope to minimise any potential bias.

4. Resource use reduction: BMS only partially agree with the resource use reductions applied to the PenTAG analysis as a result of comments made by Novartis.

   In general terms BMS agree that the resource use should be lower than that used initially by PenTAG. However, we are concerned that the same reduction has been applied not only to patients who have responded to TKIs, but also those who have <u>not responded</u> to TKIs. BMS agree with the reduction of the number of visits to one visit to a haematologist/oncologist every 3 months (i.e. 0.33 visits per month) for patients responding to therapy (as per ELN recommendations). However, we suggest that for the patients who have not responded, the number of visits per month should be based on the same assumptions used for HU (i.e. one visit every 6 weeks, or 0.72 visits per month) as it is clear that neither therapy is producing an adequate disease response.

   Furthermore, with regard to bone marrow aspiration, this too would vary depending on whether a patient had responded (in this case by achievement of a CCyR) or not responded (CCyR not achieved); in other words, if a patient does not respond, they will undergo more bone marrow biopsies. Hence, resource use would be significantly greater for patients who do not achieve a CCyR, or in whom it is delayed.

Appendix C

Additional Modelling (BMS model)

The Assessment Group has responded to BMS comments on the Assessment Report and their model, and here we make additional points in response to that document. This is important because we are confident the BMS modelling approach remains methodologically stronger than the other models considered by the AC.

1. **Further comment on formulae errors**:

    a. **Formulae Error #1:** the "error" identified by the AG relates to one component of the formula in the identified column. In the example cited by the AG (part of the Evaluation Report) the component of the calculation (ED7 – LF8) is indeed negative. However, this problem does not make itself apparent in the next row (ED8-LF9= 1.60), the one after (ED9-LF10 = 3.32), the one after that (ED10-EF11 = 4.68) and so on. The problem only returns during the final few (heavily discounted) years in a small number of cells. Hence, the problem arises in a small selection of calculations, and is not apparent for the greatest proportion of the model.

    It is not clear how this error was 'fixed' by PenTAG, but using a crude approach (whereby a floor of zero was applied to all calculations) resulted in the generation of an ICER of approximately £33,100 per QALY gained for the comparison of dasatinib with imatinib, and £158,600 per QALY gained for dasatinib compared with nilotinib (with the caveat that dasatinib is less efficacious and less costly than nilotinib, and so the usual interpretation of these results does not apply).

    b. **Formulae Error #2:** we maintain that the model is correct. While we concede there is a discrepancy between the model and the report, the rationale for using 100% for this parameter value is solid and supported by major international guidelines. In the context of additional second generation treatments, if a patient has less than a partial response they can be viewed as having 'failed' treatment. We therefore reiterate that the error lies in the reporting and not the model, and so no wiring or formulae error exists.

2. **Comment on alteration to 3rd line treatment composition**: the AG generated ICERs with the removal of dasatinib based combinations from 3rd line therapy. It should be noted that in no way does this relate to monotherapy treatment with dasatinib (the subject of all on-going appraisals) but rather to combination treatment (which is outside of the scope of all on-going appraisals). The values used in our model (and also the PenTAG 1st line and 2nd line models) were derived via a survey of practicing haematologists.

    We would be grateful for further clarification to confirm how PenTAG removed this from the costing sheet and the rationale for alternative choices. Our concerns are as follows:

    a. What alterations to the case mix were made? Currently ~70% of patients are assumed to receive chemo/ combination therapy, and if the principle treatment option is removed is this assumed to hold? If not, this will have major cost implications?

b. What other treatment options were used? If all patients are assumed to switch to alternative single agent TKIs the cost of these in the model is zero (since they are rarely used and assumed only available to those in a clinical trial). Without altering the price this would significantly alter the cost of therapy. If this is not the case and patients are moved to other chemotherapy based agents, what was the split and how was it decided?

c. Was there an assumed alteration to: the proportion receiving; or the composition of in-hospital palliative care?

d. Was there an alteration to the proportion receiving stem cell transplantation?

To summarise, dasatinib monotherapy is not used as 3rd line treatment in our model. In relation to the PenTAG alterations to the BMS model, in the absence of any evidence based re-allocation of the patients from the dasatinib combination box to other boxes, we would strongly advise the Committee to disregard the ICER of £96,000 per QALY gained generated by PenTAG with this change in place (see ACD 4.3.16).

In the worst case scenario patients were simply moved onto "other single agent TKi's," so the ICERs assume that all of these patients enter a clinical trial – which is clearly an unrealistic assumption. The lack of a treatment cost allocated to these patients strongly biases the analysis in favour of interventions which either have more patients on 3rd line, or arrive there sooner (i.e. in favour of imatinib).

3. **Additional analyses - correction of the ICER's for the BMS model presented by the AG:** because we assert the BMS model is methodologically stronger than the PenTAG and Novartis models, and to ensure the AC have to hand a complete range of ICERs on which to base their decision making, we have incorporated the changes PenTAG made to their model (based on feedback from Novartis), into the BMS model. We are happy to provide a copy of the model to the AG for further review to ensure they are happy with the approaches used to implement the changes.

Dose Intensity: we note with interest the discussion concerning imatinib dose intensity. Given PenTAG were willing to undertake an analysis using a value of 106% applied to the Novartis model, we have undertaken a similar analysis with the BMS model. The results are presented in the following table using the fully revised BMS model (i.e. with the correction to wiring error #1 included as discussed above). The revised ICER is approximately £25,000 per QALY gained.

	Dasatinib		**Imatinib**		**ICER**
	Costs	QALYs	Costs	QALYs	
Dose intensity (imatinib)=100%	£498,200	10.65	£477,200	10.01	£33,200
Dose intensity (imatinib)=106%	£498,200	10.65	£482,200	10.01	£25,300

Medical Management Costs: given that the costing template used in the PenTAG model was almost identical to that in the BMS model, we are very interested in the latest results from the clinical advisor. Careful comparison with the values reported in the PenTAG and BMS models confirms that these relate to the resource use patterns for patients who are chronic phase responders in the BMS model.

We therefore performed an analysis using the revised values for this group in our model, and the results are presented in the following table. The ICER generated is close to £20,000 per QALY gained.

	Dasatinib		**Imatinib**		**ICER**
	Costs	QALYs	Costs	QALYs	
Base Case	£498,200	10.65	£477,200	10.01	£33,200
Revised CP responder resource use estimates	£468,600	10.65	£455,100	10.01	£21,300

Combining the revised resource use estimates and alternative imatinib dose intensity estimates leads to the ICER reported below. The ICER is now below £15,000 per QALY gained.

	Dasatinib		**Imatinib**		**ICER**
	Costs	QALYs	Costs	QALYs	
Base Case	£498,200	10.65	£477,200	10.01	£33,200
Revised CP responder resource use estimates and alternative imatinib dose intensity (106%)	£468,600	10.65	£460,100	10.01	£13,400

Inclusion of assumed nilotinib PAS into revised model: If we assume the discount to the price for nilotinib under the PAS is [redacted] including this value in the BMS model for both 1st and 2nd line nilotinib, generates the results presented in the following table.

	Dasatinib		**Imatinib**		**ICER**
	Costs	QALYs	Costs	QALYs	
Base Case (no PAS)	£498,200	10.65	£477,200	10.01	£33,200
Base Case (with PAS)	[redacted]	[redacted]	[redacted]	[redacted]	£46,300
Revised CP responder resource use estimates +PAS	[redacted]	[redacted]	[redacted]	[redacted]	£34,400
Revised CP responder resource use estimates + alternative imatinib dose intensity + PAS	[redacted]	[redacted]	[redacted]	[redacted]	£26,500

These analyses include correction of all outstanding wiring / formulae errors.

In the base case, the ICER for dasatinib compared with imatinib remains above the usual decision threshold of £30,000 per QALY gained. However, when the alternative assumptions for key parameters discussed above are included (i.e. revised medical management costs and revised dose intensity for

imatinib) the BMS model generates ICERs that are within the acceptability thresholds typically used by the Institute.

Please note that all of these alternative assumptions were agreed as relevant by the AG and were discussed at the 1st Appraisal Committee meeting (see Sections 4.2.37 and 4.2.42).

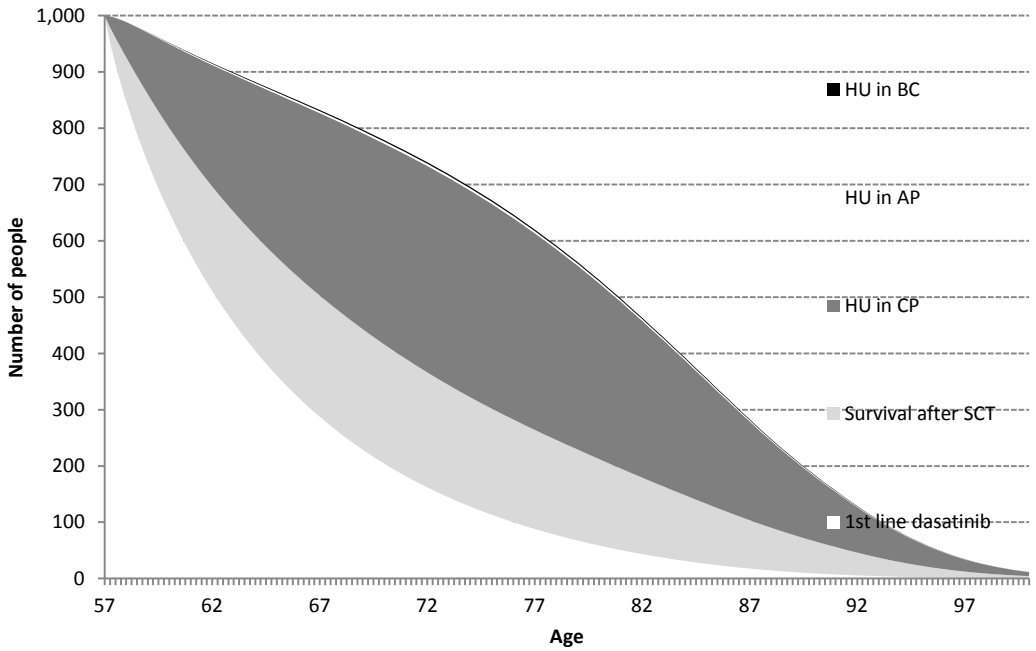
4. **Comment on PenTAG approach to including MMR and CCyR into their model:** as we have stressed, any plausible model of 1st line TKI treatment in CML will of necessity have to be predicated on the concept of treatment response (either MMR or CCyR).

   The AG generated results predicated on response to treatment; however these are relegated to sensitivity analyses in the Assessment Report and are the subject of a single slide in the presentation to the Committee at the 1st AC meeting *[slide #17, presented by Dr. Matt Stevenson]*).

   We noted in our response to the AR these analyses are not reliable, and do so again here, and also provide graphical outputs from the AG model to further clarify our concerns.

   In the AR, the AG present graphical output to show the proportion of the cohort on each treatment for Scenarios 1 and 3 by treatment arm *(see ERG report P188 and 201)*. These plots are included to provide a visual representation of the outputs of the model and the validity of the approach. However, these plots are not presented for the surrogate marker approach.

   We include an example here to allow the Committee to see why we believe there are fundamental flaws with the approach taken by the AG. The plot shown below is for the dasatinib arm and is generated by selecting the "Surrogate mean, CCyR difference". Very similar plots are generated for the imatinib and nilotinib arm and for the MMR endpoint for all treatment options.



Interpretation of this plot is very simple. The X-axis shows the age of the cohort, and reading vertically, the Y-axis shows the count of patients on each treatment option (the very top line corresponds to the number of patients predicted to be alive). The pale grey section shows the number of patients on 2nd line SCT (a curative treatment option) and the dark grey section the number of patients on 1st line HU (a purely palliative treatment).

From this graph we can see that as time progresses the number of patients on 1st line dasatinib is ever decreasing. In contrast, the number of patients on 1st line HU is increasing, with the 'bulge' effect showing that more patients are arriving than leaving. Interpretation of the shaded areas gives the user some idea of the expected time on each treatment option.

We have previously highlighted the issues with the AG model (and these were noted by the AG and the AC). However, the Committee have felt the issues were adequately addressed by the AG – we disagree.

Here, we highlight that the AG model does not generate clinically plausible *time on treatment* results and would certainly not be considered reliable in critique if the same model had been submitted by a manufacturer. The above plot should show a very thin dark grey slice representing the small amount of time patients are likely to spend on treatment with HU alone.

We have repeatedly stressed the validity of modelling survival via a surrogate endpoint approach; however, we hope it is clear to the committee that (as implemented by the AG) the analyses presented are not usable. We hope the Committee are able to reflect on the adequacy of the modelling work submitted to this appraisal and should, in our opinion, retest the BMS model for the same results.

The BMS model provides clinically appropriate time on treatment scenarios using the surrogate approach and is therefore a more reliable basis for decision making.

References

Anstrom KJ et al. Cancer 2004 Volume 101 / Number 11

Druker BJ et al. New England Journal of Medicine 2006;355:2408-17.

Hanfstein B et al. ASH 2011 Abs 783 (Oral)

Hochhaus A et al. ASH 2011 Abs 2767.

Kantarjian HM et al. Blood 2006;108:1835-40.

Jabbour E et al Blood 2011 Prepublished online July 29, 2011 as doi:10.1182/blood-2011-04-348110

Latagliate et al, ASH 2011 Abs 3783

Marin D et al. ASH 2011 Abs 785 (oral)

Marin D et al. JCO Published Ahead of Print on November 7, 2011 as 10.1200/JCO.2011.38.6565

Milojkovic D et al. ASH 2011 Abs 1680

Nicolini FE et al. ASH 2011 Abs 1684

Schrover RJ et al. Leukemia & Lymphoma 2006;47:1069-81.

Multiple technology appraisal (MTA)

Dasatinib, nilotinib and standard-dose imatinib for the first line treatment of chronic myeloid leukaemia (incl part-review of TA 70)

Comments from Novartis on the ACD

Novartis are pleased that the committee have given a positive preliminary recommendation to approve Tasigna as a treatment for first-line Ph+ CML. The ACD provides a good overview of CML and a fair summary of the interventions being assessed.

We have a few comments we would like to make, as detailed below:

Section 3.10, 4.1.16, 4.3.9 – in our response to the Assessment Report, we explained that QT prolongation, which is listed as a side effect for nilotinib, is in fact a class effect. We are therefore pleased to note that in section 4.3.9, the Committee clarify that QT prolongation was listed in the special warnings and precautions for use in the SPC for both dasatinib and nilotinib. We feel the summary in this ACD portrays a fairer representation of the nilotinib safety profile than previous reports.

Section 4.1.3 – the ACD discusses the ENESTnd trial design and states: 'all study participants had a minimum follow-up of 12 months, with a median duration of 14 months of treatment'. We would like to re-iterate that the latest published data (Kantarjian 2011 – Blood, as referenced in previous responses) reports a minimum follow-up of 24 months, which is correctly referred to later in the report.

In addition, 36 month follow-up data has just been presented at ASH 2011. The data continues to support nilotinib as a potential standard of care in CML with superior MMR and CMR by 36 months, significantly lower progression to AP/BC and significantly lower deaths following progression in the nilotinib arms vs the imatinib arms.

Section 4.3.6 and 4.3.9 – We are pleased to read that the committee has noted the views of the clinical specialists and patients experts that nilotinib and dasatinib are more effective drugs than imatinib, and that the committee has noted from the clinical trials that all three drugs were well tolerated.

Comments from the Chronic Myeloid Leukaemia Support Group (CMLSG) on the NICE Appraisal Consultation Document (ACD) for dasatinib, nilotinib and standard dose imatinib for the first line treatment of chronic myeloid leukaemia (CML).

Introduction

CMSLG welcomes this ACD as representing a more coherent and closely argued body of work than any of the outputs for the other ongoing MTA for CML.

The ACD contains comments on important issues concerning the underlying disease, treatment strategies available to secure favourable outcomes for patients diagnosed with CML and markers used to measure such outcomes.

The decision to include these comments combined with an absence of rebuttal or qualification we assume indicates an acceptance of their veracity by the Committee.

We find it both disappointing and disconcerting that this acceptance has not been proactively transported into the Committee's consideration of the economic modelling work undertaken by the Assessment Group (AG).

By this we mean the treatment lines in the economic modelling scenarios preferred by the Committee do not reflect either current specialist clinical practice or clinical guidance for the treatment of CML.

Structure of our comments

We have noted the criteria governing the call for comments on the ACD.

Our comments are organized as follows:

1.Treatment lines in Scenarios 1 & 2

2.Treatments for the underlying disease

3. Small clearly defined sub groups of the CML patient population

4. Patient Assistance Schemes (PAS) and the efficient use of NHS resources

5. Summary

1. Treatment lines in Scenarios 1 & 2

(i) Second line treatment: current clinical practice and guidelines

Both the specialist clinician evidence and the recommendations of two leading organizations of clinicians are clear on recommended practice.

"This reviewer cannot see a time in which any UK physician will routinely use hyroxycarbamide for second line therapy in place of a TKI ..." from Section 2 Professor Apperley's comments on the Assessment Report (AR)

In the same section Professor Apperley mentions the use of TKIs as the only interventions in 2nd line treatment, following 1st line imatinib, thus excluding SCT as a possible 2nd line option.

The Committee do not offer a rebuttal of the clinicians comments that HU would not "routinely be used as a 2nd line treatment" (4.3.3.)

The treatment guidelines approved by the European Leukaemia Net and the British Committee for Standards in Haematology guidelines both recommend only TKIs as 2nd line treatments.

These recommendations are specifically mentioned in the 'Current Service Provision' section of the AR (2.8. AR).

Scenarios 1 & 2 are described by the Committee as their "preferred scenarios" (4.3.18) and do not model any TKI beyond first line.

It is clear the Committee have not therefore 'taken all the relevant evidence' into account.

(ii) The logic deployed by the Committee in their decision making

Scenarios 1 & 2 are limited to a single subsequent line of treatment with the options in 2nd line being limited to hydroxycarbamide (HU) or stem cell transplantation (SCT).

The justification given for abandoning scenarios 3 & 4 was because it resulted in a dual, rather than single, treatment strategy where 1st line nilotinib use was not followed by a 2nd line TKI whereas there was a 2nd line TKI (nilotinib) used after 1st line dasatinib and imatinib.

Since this situation is absent in Scenarios 1 & 2, the Committee has defaulted to them as their "preferred scenarios" (4.3.18.) to avoid the "uncertainty associated with subsequent lines of treatment" (4.3.16.)

Given the Committee's commitment to the principle of modelling treatment lines beyond a 1st line, we would argue that preferring the **unreality** of

Scenarios 1 & 2 over the **uncertainty** of Scenarios 3 & 4 does not represent a prudent trade off.

To favour some set of events that does not occur over a set that does in part, but is complicated, can hardly be said to be a worthy example of evidence based decision making.

Their summary of the clinical evidence is therefore flawed in that their interpretation of the evidence is not reasonable.

(iii) Second line treatment lines in current practice

(a) As the Committee note (4.3.16.) imatinib was not modelled as a 2nd line treatment following 1st line 2nd generation TKI use in cases were patients are intolerant of a 2nd generation TKI used in 1st line.

(b) Neither was dasatinib modelled as a 2nd treatment line to 1st line nilotinib by the AG in any of the four scenarios developed. If the AG had done so this would not have conflicted with the recommendations of the FAD for the other ongoing MTA appraisal mentioned in 4.3.16.since this is restricted to standard dose imatinib treatment failure.

(iv) Treatment lines in current practice in 3rd and subsequent lines

(a) Dasatinib was also not modelled as a 3rd line treatment following 2nd line nilotinib failure following 1st line imatinib failure. Again, as noted in (b) above, there would be no conflict with the FAD recommendations of the other ongoing MTA.

Professor Apperley (Section 2 of her comment on the AR) notes "one or more" TKIs being optioned following 1st line imatinib failure which permits dasatinib to represent a rational 3rd line choice in such situations.

(b) TKIs lacking marketing authorization (bosutinib and ponatinib) available in the UK on clinical trial would, notes Professor Apperley (in Section 2 of her AR comment), be options in situations of what she describes as "upfront" (ie 1st line) dasatinib and nilotinib failure. In the same section she also mentions the availability of imatinib being a further TKI, post 1st line, option.

In this scenario there are 5 TKIs currently available together with the option of an SCT.

It is therefore unsurprising that the AR refers to there being "extensive structural uncertainty" (8.1. AR) in the modelling due in part to availability of "very heterogenous treatment and care pathways" (1.8.8.2. AR) for CML patients.

This is reflected more broadly in the "unusually large amount of structural uncertainty that is inherent in the present decision problem(s)" (1.7.3. AR).

The Committee recognize these issues i(4.3.12. & 4.3.16.) and also acknowledge their linkage with subsequent AG economic modelling when they refer to the "wide variation in the cost-effectiveness results across the scenarios presented" (4.3.13.) by the AG.

In short model outputs (ICER and cost per QALY gained) are directly related to the number of treatment lines, the particular interventions allocated to each treatment line and a host of additional factors that generate the significant levels of uncertainty all acknowledged to be present even after further analytic work (sensitivity analyses) was undertaken.

The Committee's summaries of the cost effectiveness evidence are therefore constrained by a consideration of a highly restricted base of evidence on which their decisions were then made. As such all the relevant evidence was not taken into account.

2. Treatments for the underlying disease.

(a) HU

(i) The role of HU in the management of CML

The Committee seem to haver on whether to accord HU status as a "treatment" for CML or simply as a "measure" or "agent" available to clinicians in much the same way as other agents are available for the control of clinical events that are a consequence of the underlying disease.

We find the AG's decision to include HU as a treatment line in their modelling perplexing given that they recognize that:

"Hyroxycarbamide can be used to control the white blood count but does not alter the natural history of the disease"

("Natural history and clinical presentation" section of the AR under the sub heading: Chronic Phase)

We find their decision even more perplexing given they do not accord HU a place in the relevant AR section describing CML treatments ("Treatment" 2.4. AR). All other interventions allocated to treatment lines in all four Scenarios developed appear in this section of the AR.

The Committee note, and do not reject or qualify, the clinicians comments (in 4.3.3.) that HU "...does not affect the progression of the disease" and that its use is for "palliative purposes" or "as a short term measure **between** lines of treatment" (my emphasis).

We find it perverse that the Committee then limit themselves to scenarios that contain HU as an option in the second of only two treatment lines.

(ii) HU as a 2nd line treatment in current clinical practice.

As Professor Apperley notes (Section 2 in her comments on the AR)

"This reviewer cannot see a time in which any UK physician will routinely use hyroxycarbamide for second line therapy in place of a TKI ..."

The Committee also note, and do not dispute, the clinicians comments that HU would not "routinely be used as a 2nd line treatment" (4.3.3.)

(iii) HU and CCyR & MMR

The pervasive use of methodolgies that measure the degree of complete cytogenetic response (CCyR) and major molecular response (MMR) to interventions used in the management of the disease and their role as surrogates for progression free survival/overall survival renders HU to a position on the periphery of, rather than central to, CML management.

HU is incapable of effecting a cytogenetic or molecular response and we fail to understand why it was ever introduced into the AG model as a line of treatment given every other intervention, including SCT, in all treatment lines in the four Scenarios developed has that very capability.

(iv) HU treatment and progression

The comment on the Novartis model that "People who were treated with hydroxyurea had a **probability** of progressing to advanced phase." (4.2.11 my emphasis)

Given that there is a 100% certainty of progression to advanced phase and a fatal outcome if CML patients receive HU as their sole treatment; we view "probability" as a wildly inaccurate descriptor.

It does not reflect Novartis' position as an examination of their response to the AR makes clear (see 2.2.2. "Time on HU in CP" in their AR comment).

BMS in their response to the AR("Hydroxyurea as a 2nd line treatment option" & "Reason Two" especially Table 2.) also comment on analytic failings in the AR on this issue.

From industry responses to the AR it is clear that the AG also completely over estimated survival times on HU following TKI failure as a mean "of 7.00 years with a 5 year survival of 50%".

(b) Stem cell transplantation (SCT)

(i) Size of the CML patient population for whom SCT is an treatment option

The Committee noted that the manufacturers submissions note that "only a small number of patients would be eligible" (4.3.21.) for SCT as a treatment option.

There are clinical grounds that limit the size of this population as there are limitations imposed by the size of the donor pool.

As the Committee notes this raises equality issues although they note that because the provisional recommendations "...do not differentiate between any groups of people" there was "not considered to be an equalities issue"(4.3.21.)

The extraordinary disadvantage Black and Minority Ethnic patients face in securing suitable donors is well documented as is the age related disadvantage for many patients in what is, on average, an older patient population.

The Committee's refusal to incorporate their acknowledgement of this situation into their deliberative process which resulted in provisional recommendations authored by themselves betrays the lack of value they assign to these particular sections of the population.

We believe, had they done so, the Committee would not have preferred the two Scenarios that were limited to SCT as the only treatment option, assuming HU has no status as a treatment, after 1st line.

(iii) SCT as a 2nd line treatment option

Our comments on interventions optioned for 2nd line use in current global good clinical practice and set out in guidelines in the previous HU section are pertinent here.

(iv) Cost of SCT

The AG called for allocated research priority status to be assigned for both the incidence and cost of SCT ("Suggested Research Priorities"noted " 10.2. AR) and also noted considerable uncertainty surrounding survival and treatment costs **following** SCT (9.5.2. AR).

Although they mention GvHD as a post SCT complication and indicate they recognize GvHD to be spectrum like with greater drug therapy costs for treating "more severe GvHD" (8.5.4.2. AR) all medical management costs assume out patient status for those treated.

The higher grades (3 & 4) of GvHD, which can be chronic, more often than not, require hospitalization.

Hospital readmission costs are not included for patients with higher grades of GVHD.

The comments submitted by Healthcare Improvement Scotland in May 2011 in response to the ACD for the other ongoing MTA for CML cite the following concerning SCT costs.

"...a procedure which costs £70,000 with approx £2,400 ongoing monthly cost thereafter (which **includes** a £21,000 readmission sum)." (my emphasis)

This is vastly different than the £113 weighted mean cost per month quoted in the AR ('Table 50 Estimation of ongoing drug and monitoring costs after SCT' in 8.5.4.2. AR).

(c) TKIs for the treatment of CML

(i) Efficacy of the three appraisal TKIs relative to each other

We note the Committee agree that both nilotinib and dasatinib demonstrate superior efficacy to imatinib whilst also agreeing there is no statistical difference in the degree of efficacy between them (4.1.12., 4.3.5. & 4.3.6.).

(ii) The efficacy of imatinib

The ACD comments " However the progression of CML can be **slowed** by imatinib." (2.6 my emphasis)

We believe this is a misinterpretation of the available RCT (and other) evidence for a drug the Committee have previously described as a "step change" in the treatment of CML and worthy of innovative status.

Imatinib, in approximately 60% of chronic phase patients, halts rather than slows disease progression and, on currently available data, ensures long term patient relevant outcomes including progression free and overall survival.

In their comments on the AR Professors Clark (point 2) and Apperley (point 4) made observations concerning the IRIS trial data noting salient factors required to be kept in mind when interpreting the data sensitively but which nevertheless concur that imatinib use has the capability to halt disease progression.

(iii) Specialist clinicians experience in the used of the appraised TKIs

The statement that ".... clinical experience of dasatinib and nilotinib for chronic phase CML is **restricted** to the context of clinical trials" (4.3.2. my emphasis) is not true.

The observation in the Assessment Report that:

"Anecdotal evidence suggests that dasatinib and nilotinib are currently widely used in the NHS in England and Wales following failure of treatment with imatinib" (2.9. AR) is pertinent here.

Professor Apperley notes in her comments on the ACD for the other ongoing MTA appraisal:

"These drugs have been readily available in the UK through clinical trials, expanded access and more recently through a variety of means including Regional Cancer Network and/or local Drug and Therapeutic Panel agreements, the Pan-London New Drug prioritization exercise, applications for exceptionality to relevant PCT or most recently from the Cancer Drugs Fund"

We make the point to insure against any inference being made that specialist clinicians might lack experience in the use of the appraised drugs in clinical practice and that therefore their evidence should be treated with caution.

3. Small clearly defined sub groups of the total CML population

We were pleased that the Committee noted that:

"... the clinical specialists stated that, for a very small proportion of people whose CML is resistant or intolerant to standard dose imatinib, there may be clinical reasons for the use of dasatinib, including comorbidities and disease resistance to nilotinib" (4.3.3.)

(a). Comorbidities:

(i) Long QT syndrome

The most prominence granted in the ACD to the issue of comorbidities and their impact on therapeutic decision making concerns CML patients with a long QT syndrome diagnosis.

The Committee note QT prolongation is listed in the "Special warnings and precautions for use" sections of the SPCs for both nilotinib and dasatinib although any warning for it is absent in the SPC for imatinib.

They also note the consequent FDA decision to issue a 'black box' warning for nilotinib although there is no explicit reference in the ACD to the absence of a similar warning for dasatinib.

We would argue that an inference that dasatinib, when compared to nilotinib, would be the most prudent and preferred clinical intervention in such cases would be reasonable.

This would remain valid even though the Committee notes the views of clinical specialists that "there was no increased cardiovascular risk at licensed doses" for either drug (4.3.9.).

(ii) Diabetes

Similar reasoning would prevail in the case of patients with diabetes as a comorbidity given the much more exacting fasting requirements for nilotinib administration compared to dasatinib since the equally exacting dietary requirements for diabetics must also be considered by clinicians and patients in any decision making process.

This view is supported by Professor Apperley who cites diabetes as an example of there being "good medical reasons" for the use of dasatinib over nilotinib. (Section1. of her comments on the AR).

Given comorbidities are known, in most instances, **prior** to commencement of treatment and add to the burden of disease carried by CML patients we consider the relevant clinical evidence has not been taken into account for these two extremely small patient subgroups in considering first line treatment options.

We would argue that specialist clinicians preference, assuming a lack of other conflicting comorbidities, would be for dasatinib as a first line treatment for both the above patient groups.

On this basis we find the negative recommendation for dasatinib first line use to be unsound for such sub groups of the total CML patient population both of whom are clearly identifiable at naive to treatment stage given dasatinib's superior efficacy to imatinib.

<u>(b) Disease resistance to nilotinib:</u>

We limit ourselves only to those cases, defined as resistant, where nilotinib and imatinib lack activity against specific mutations.

We recognize such cases, by definition, are detected as a result of first line treatment failure and note strong evidence of dasatinib's activity against a significant number of such mutations.

The prominent CML specialist clinician Michael Mauro MD (Knight Cancer Institute OHSU) cites six studies that demonstrate that:

"Mutations in the P- loop (including Y253H/F and E255K/V), a common site of mutations, 63 are sensitive to dasatinib but are often clinically insensitive to high-dose imatinib or nilotinib."

'Tailoring Tyrosine Kinase Inhibitor Therapy in Chronic Myeloid Leukemia (Cancer Control April 2009, Vol 16, No. 2, p. 113)

We would describe as deeply disingenuous the Committee's belated recognition in this appraisal that, for this small segment of the CML patient population, there is effectively no other treatment available other than dasatinib, that is able to halt disease progression but, configured as a subsequent line of

treatment, is excluded from the remit of this appraisal which limits itself to first line TKI treatments (4.3.18.).

The only exception would be for the even smaller group for whom stem cell transplantation (SCT) was a clinical possibility and the even smaller sub group able to access a willing matched donor (4.3.21.).

This results from the **same** Committee's decision not to recommend dasatinib as a second line treatment in the appraisal for CML patients whose disease is resistant to (or intolerant of) the current first line treatment of standard dose imatinib.

Amongst the resistant patients would be those with such mutations.

(4) PAS and the efficient use of NHS resources

The DH considered that this PAS does not "constitute an excessive administrative burden on the NHS" (3.11)

This statement was is flatly contradicted by North Yorkshire & York PCT in their written submission on the AR.

The PCT expressed generic reservations about PASs given they impose an additional administrative burden on PCTs with resultant increased costs and therefore fail to deliver expected efficiency savings.

The North Yorkshire & York PCT response to the AR notes:

".... our experiences to date would advocate that historically such schemes are convoluted thus are not delivering the anticipated savings and indeed serve to cost the NHS in terms of staff resources to unpick the nuances and ensure payments are made to the commissioner for these PbR excluded drugs"

In her oral evidence at the Committee hearing on the 8th November; the representative (Diane Tomlinson, a Senior Pharmacist) of the PCT consultee for this appraisal, North Yorkshire & York PCT, observed that, in this particular case (the PAS for nilotinib), the additional administration costs imposed would probably cancel out any savings made by the price reduction obtained under the PAS.

In sum the savings would be illusory and hence the real cost to the NHS would be either no different from, or near to, the quoted net BNF (edition 62) price quoted (3.11.)

The consideration of the evidence therefore did not take " into account the effective use of NHS resources" (4.3.1.).

(5) Summary

The following discussion is limited to a consideration of chronic phase CML in adults.

(a) Current and provisional NICE guidance:

Current NICE guidance is limited to a provisional recommendation for nilotinib as an option in first line use and, subject to appeal in the other ongoing MTA for CML, for nilotinib in 2nd line use with standard dose imatinib also recommended as an option for 1st line use.

Imatinib is already recommended for 1st line use (as part of TA guidance 70) with a part review of that recommendation being included in the current MTA for 1st line use.

(b) There is no guidance or recommendation for:

HU or SCT have never been the subject of appraisal. Given their prevailing use prior to the establishment of NICE their allocation in treatment lines is not open to procedural challenge.

However their allocation to a comparator role at the appraisal scoping stage is possible although in this case this is not applicable since they are not comparators.

None of the three TKIs, that are the subject of this MTA and all of which have marketing authorization for CML, are recommended for 3rd or any subsequent treatment line use in any NICE guidance.

There is no recommendation for imatinib in 2nd line or, subject to appeal, for dasatinib in 2nd line in any NICE guidance.

(c) Consequences that follow from (a) and (b):

The Committee accept, in its deliberations, HU as a treatment and accept its status, in its preferred Scenarios 1 & 2, as one of only two treatment options in 2nd line treatment.

However when HU is used to control white blood counts (referred to in 2. (a) (i) above) its use often occurs at diagnosis whilst decisions are being made as to the therapy to be adopted to secure maximum efficacy against the underlying disease.

In such cases, on this logic, HU would amount to a 1st line treatment with imatinib as a 2nd line.

As already noted there is no recommendation for imatinib use in 2nd line.

To the best of our knowledge there has never been any attempt by an AG to distinguish patients naive to treatment for CML that disqualifies those treated with HU.

We are not of course arguing that such a situation should prevail only that, once appraisals depart from the real world of clinical practice, arbitrary decisions are taken and assumptions made that result in conclusions that are unable to be related to clinical practice which in itself of course constitutes an evidence source.

It is little wonder that the Committee feel compelled to observe that "there is considerable uncertainty about which treatments would be given to people with chronic phase CML following first line treatment" (4.3.16)

However admitting two treatment options (HU & SCT) not in clinical practice in 2nd line is tantamount to creating a parallel universe that exists alongside, rather than reflects in (simplified) model form, the real world.

(c) Changes to the regulatory landscape

We recognize that the Committee is also constrained in its processes and procedures by procedural factors over which it has little control.

Government and regulatory agencies are aware of inadequacies with the current situation.

Recent policy initiatives, especially emerging policy on conditional authorization pathways, population data requirements and more generic regulatory issues, such as guideline adoption and compliance, relevant to health technology appraisals (HTA) are, we believe, the harbinger of what will be a much changed regulatory environment in the future.

Public attention has focused on the Early Access Scheme (EAS) and the use of anonymized patient record data in clinical research but much less media attention has been given to implications that follow from the proposed proportionate risk benefit guiding principle underlying the EAS or that policy development should acknowledge the:

"..era of 'stratified medicines' where new drugs may be effective in a small segment of patients with specific genetic characteristics" (Department of Business, Innovation & Skills "Strategy for UK Life Sciences" Nov 2011 p. 28)

The plea underlying our comments on this ACD is that the Committee should be sensitive to the background noise of these developments to ensure their own public credibility, and more generally that of the HTA process, continues to be assured.

(d) CMLSG suggestions

We suggest that a constructive way forward would be for the Committee to commission further modelling work (as it did with SHTAC in the other ongoing MTA for CML) from another AG that:

(i) Incorporates the outcome of the appeal of the FAD recommendations in the other ongoing MTA for CML since more rather than less certainty would prevail than is the case currently.

(ii) For the reasons advanced we would argue that HU be removed entirely from any modelling.

(iii) Likewise SCT should be modelled only in treatment lines other than 1st or 2nd. Post SCT costs should be adjusted to include hospital readmission costs for the patient cohort burdened with severe post SCT complications and then incorporated into the existing weighted mean cost per month figures.

and that the Committee should also:

(iv) Be mindful that, as the AR notes in 2.8., current clinical guidelines referred to in 1.(i) above are due for renewal in July of this year.

It is likely that their revised contents might increase rather than diminish the current gulf between real world clinical reality and that presented in NICE guidance should current provisional negative recommendations become final.

All the medical bodies that responded to the scope warned the Committee of the consequences of proceeding with an appraisal at this time, compromised the effectiveness of the decision making process.

We accept NICE is constrained by the requirement to issue guidance as close as is possible to marketing authorization but reasonableness should prevail.

See "Response to consultee and commentator comments on the draft scope" p.10 Response of NCRI/RCP/RCR/ACP/JCCO and the Royal College of Pathologists, BSH and RCP consultees.

(v) Failure to recommend any TKI other than nilotinib as a 2nd line treatment will, we would argue, become increasingly untenable should the current ongoing STA for bosutinib in 1st line receive a positive recommendation.

This would result in a situation where there are 3 TKIs available for 1st line use and only one for 2nd line with dasatinib, a drug of proven clinical efficacy including for mutations against which nilotinib and imatinib lack activity, unavailable in any line of treatment.

The Committee’s acceptance of the principle of an alternative TKI being available in 1st line should logically apply in 2nd line with an alternative to nilotinib.

National Institute for Health and Clinical Excellence

Dasatinib, nilotinib and standard-dose imatinib for the first line treatment of chronic myeloid leukaemia (including part-review of TA 70)

Royal College of Nursing

Introduction

The Royal College of Nursing (RCN) was invited to review the second Appraisal Consultation Document (ACD) for Dasatinib, nilotinib and standard-dose imatinib for the first line treatment of chronic myeloid leukaemia (including part-review of TA 70).

Nurses caring for people with chronic myeloid leukaemia reviewed the documents on behalf of the RCN.

Appraisal Consultation Document – RCN Response

The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the four questions on which comments were requested is set out below:

i) **Has the relevant evidence has been taken into account?**

The evidence considered seems comprehensive.

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

We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with chronic myeloid leukaemia. The preliminary views on resource impact and implications should be in line with established standard clinical practice.

iii) **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and do not have any other comments to add.

The RCN would welcome guidance to the NHS on the use of this health technology.

Iv) **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 gender, race, disability, age, sexual orientation, religion or belief?**

None that we are aware of.

v) **Are there any equality-related issues that need special consideration that are not covered in the appraisal consultation document?**

We are not aware of any specific issue at this stage. However, it would be helpful to know if NICE will publish the equality analysis for this appraisal. We would also ask that any guidance issued should show that an analysis of equality impact has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.

The Royal College of Pathologists and BSH comments on the Appraisal Consultation Document (ACD) produced for the NICE multiple technology appraisal of *dasatinib, nilotinib and standard-dose imatinib for the first line treatment of chronic myeloid leukaemia (incl part-review of TA 70)*

The Appraisal Committee is interested in receiving your comments on the ACD under the following general headings:
The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?

Yes, more or less.

The two key trials are ENESTnd (nilotinib vs. imatinib) and DASISION (dasatinib vs. imatinib). The appraisal took into account the latest available data on each of these, which were 12 months as published in NEJM in June 2010, and also 24 months data from ENESTnd that was presented at the American Society of Hematology (ASH) meeting in December 2010.

In fact, 36 month data for ENESTnd and 24 month data for DASISION are now available, having been presented and therefore publically disclosed at the very recent ASH meeting in December 2011. There are no surprises, and the previous advantages of each second generation drug over imatinib are maintained. These advantages are in efficacy (for the same surrogate endpoints as in the appraisal document; still no benefit on survival) and risk of progression to advanced phase. These updated data are therefore highly unlikely to alter the appraisal document or the conclusions reached from it.

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

Yes except for one important caveat.

The NICE FAD appraisal of these two technologies for SECOND line use (i.e. where first-line imatinib at standard dose has failed) has supported nilotinib but not dasatinib. This is primarily because Novartis, the manufacturer of nilotinib, has offered a patient discount scheme whereby nilotinib is in effect the same cost as imatinib; Bristol-Myers-Squibb (BMS; manufacturers of dasatinib) has however not done so despite clear indications of the importance of price. BMS have appealed against this 2nd line FAD on procedural grounds and the results are expected on or before 23rd December 2011.

This means that when considering these technologies as FIRST line agents, patients failing nilotinib cannot be considered to receive dasatinib 2nd line as it is not approved, and can only receive hydroxycarbamide or stem cell transplantation (SCT). In contrast, patients failing dasatinib could receive nilotinib as it is approved. As a second line agent, nilotinib is cumulatively far more expensive than hydroxycarbamide or one-off SCT. This means that the price comparison between 1st line dasatinib and nilotinib is intrinsically biased against dasatinib, because of a procedural ruling that NICE cannot consider a second line treatment that is not itself NICE approved.

It may therefore be necessary to reconsider these price comparisons in the light of the results of the second line appeal, once available.

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

Yes for nilotinib. The recommendations for dasatinib may be flawed as indicated in the response to the preceding question.

- 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 gender, race, disability, age, sexual orientation, religion or belief?

No apparent issues,

- Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document?"

No apparent issues,

If you wish to comment on the evaluation report, please do so under a separate heading to your comments on the ACD.

Minor points;

In sections 3.2. and 3.9, the term chronic myelogenous leukaemia is used. This is rather transatlantic; the usual term for the disease in the UK is chronic myeloid leukaemia.

No additional comments are necessary.

[redacted]

Thank you for providing the opportunity to comment on this technology. I have sought to address the points you wish answered within the appraisal consultation document with additional commentary which I felt relevant arising from the 1st appraisal meeting.

Relevant evidence
We have nothing further to add

Clinical and cost effectiveness interpretations
We acknowledge the complexity of the economic evaluation undertaken by the evidence review group to consider the manufacturers comments, we have nothing further to add.

Provisional recommendation
I would consider the recommendation to offer nilotinib (with a patient access scheme) or imatinib as 1st line agents for the treatment of CML to be a rational and considered 1st line recommendation. To develop a pathway which only recommended nilotinib as the therapeutic agent of choice for 1st or one subsequent line of therapy (acknowledging draft recommendations following resistance or intolerance to the primary agent) would be unrealistic when considering current clinical practice for patients presenting in chronic phase within North Yorkshire and York routinely enables (for non trial patients) standard dose imatinib 1st line with either dasatinib or nilotinib 2nd line.

It is suspected but unconfirmed that some clinicians may wish to continue with a 1st generation tyrosine kinase inhibitor and thus reserve nilotinib as a 2nd line second generation agent, which locally would represent no change to the current commissioning arrangements. It is considered realistic and appropriate that the recommendation enables a 1st line and different 2nd line agent. In the absence of an alternative choice, it is predicted that other new experimental agents soon to be licensed e.g. bosutinib would likely become a commissioning priority for this condition.

Patient access scheme
Knowledge from earlier patient access schemes have resulted in commissioners being a little apprehensive regarding the real practical implications and resources required to ensure any financial savings a scheme may generate are reimbursed to the commissioner. It has been noted that more recent schemes offer a straightforward discount, commissioners would wish to reiterate that this represents the most practical and simple method of ensuring savings are generated within the NHS for these payment by results excluded drugs. Reading the appraisal consultation document, it would appear to represent a direct discount to invoices from the outset. I raise this as commissioners would not wish to pay the list price for nilotinib and the provider trust receive the discount as Novartis drug stock for example which inevitably would result in a more complex NHS transaction where any proposed savings may not materialise or would become apart of the growing list of ‘gain sharing schemes’ in that both the provider and the commissioner

‘share’ any resulting savings as a result of the staff time required to enable the savings to be generated.

Genetic mutations
It is noted that there are a number of genetic mutations reported and as such, there will be predictable occasions when a certain genetic mutation renders a particular drug technology being unsuitable. It is acknowledged that PCTs could evaluate such instances within the local decision making individual funding request framework, however, PCTs where possible prefer and indeed should make decisions based on polices as part of the annual commissioning prioritisation process. Commissioners would like NICE to consider such instances as appears within the scope of the technology, given that commissioners do not have the infrastructure to undertake complex detailed analysis of cost effectiveness, particularly when the mutation clearly drives the decision regarding choice of agent. This would provide clarity to commissioners and potentially minimise the opportunity for inconsistency of access to particular treatments across organisations.

Best wishes

[redacted]

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

Name	[redacted]
Role	Patient
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I was diagnosed with CML 6 years ago & achieved a major molecular response after 2 years. At this time nilotinib was not available but dasatinib was soon afterwards. I think that now there is a possibility of 3 being available,clinicians should have the choice of which to use for their patients,particularly as a major molecular response is usually achieved more rapidly with dasatinib. I felt more than fortunate to be able to benefit from pioneering treatment and still do as I lead a completely normal life & contribute to the economy. I want other people who are diagnosed to have the benefit of whatever treatment their haematologist considers appropriate & therefore dasatinib should be among those choices.
Section 2 (Clinical need and practice)	
Section 3 (The technologies)	
Section 4 (Evidence and interpretation)	
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date for review of guidance)	
Date	1/10/2012 9:12:00 PM

Name	[redacted]
Role	Patient
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	the recommendations in relation to Nilotinib and Imatinib are much welcomed. Â The failure to recommend dasatinib is of concern. Â It is accepted to be clinically as effective as nilotinib (and more effective than imatinib) but has been refused on the basis of a cost effectiveness assessment. Only if that

	assessment is factually robust (and based on appropriate and accurate modelling and assumptions) can that rejection be justified. It is Â far from clear that this is the case, and the difference seems entirely assoaciated with the patient access scheme for nilotinib. Â If as has been suggested PCTs will not exceptionally fund dasatinib for patients who need it (and cant take nilotinib), this recommedation has serious implications for a group of patients who would otherwise have normal life expectancy.
Section 2 (Clinical need and practice)	CML is a heterogeneous condition and patients do not respond in identical ways. The summary of CML here does not make any mention of that, nor the resulting effect that patients will respond very differently to the various drugs. Imatinib can more than slow progression - this statement (2.6) should be expanded to indicate that this slowing is believed by clinicians to be potentially permanent in responding patients, and may even eradicate disease in a small percentage. This is important in the context of more potent second generation TKIs which bring better and faster responses - this will increase the percentage of patients for whom permanent remission or eradication will be the outcome. Imatinib has completely changed the way CML is treated - transplants are now very rarely carried out as first line therapy in any patient group. The 5 year survival data looks very out of date and a considerable underestimate - thus is a bit misleading as to the effectiveness of imatinib, and TKIs generally. More recent data should be quoted
Section 3 (The technologies)	
Section 4 (Evidence and interpretation)	This is a very complex appraisal as is demonstrated by no fewer than 6 different modelling scenarios (one each from the manufacturers and four from the assessment group). It seems right given the complexity to ignore scenarios where the outcome is so hugely dependent on factors not associated with the technologies themselves but the result of administrative decisions (eg the secondline appraisal). Having said that, I am concerned that those reading the "numbers" without considering fully how they were arrived at will read them as real. The data is too immature and several assumptions seem to be wrong. Â For example, why should time on treatment differ between any of the TKIs? (see 4.2.29).There is no basis for this. Â If no statistically relevant difference in CCyR and MMR as between dasatinib and nilotinib (4.3.7) why does dasatinib have fewer QALYs? That is not real. 4.3.9 - side effects for the majority are not a big problem - this should not be understood to mean that they are not a big problem for some. That is intolerance.4.3.18 -dasatinib may be the choice for other reasons (co-morbidities) not just mutations
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	Comments made by PCTs about the likely availability of dasatinib following either or both appraisals are of great concern. If dasatinib is going to be refused in either or both appraisals, that will, if PCTs do not eceptionally fund this drug

	for patients who need this option (because they cannot tolerate or wont respond to either nilotinib or imatinib - and these groups DO EXIST) lead to unnecessary and preventable deaths in the UK. NICE should recognise this possibility and address it, whether in express guidance to PCTs or in its commentary in either or both appraisal. Dasatinib is needed both where mutations indicate AND where co morbidities suggest it.
Section 7 (Related NICE guidance)	There should be flexibility. Â No doubt NICE will wish to take into account any price adjustments to any of these technologies. There is likely to be one for imatinib but not before 2016 when the patent expires. Â On this basis, 2015 may be too early. On the other hand, as this apprraisal is based on immature data as further long term benefit studies publish their results, if the body of evidence alters the clinical view of these and other technologies, NICE should respond to that.
Section 8 (Proposed date for review of guidance)	CML is a heterogeneous condition and patients do not respond in identical ways. The summary of CML here does not make any mention of that, nor the resulting effect that patients will respond very differently to the various drugs. Imatinib can more than slow progression - this statement (2.6) should be expanded to indicate that this slowing is believed by clinicians to be potentially permanent in responding patients, and may even eradicate disease in a small percentage. This is important in the context of more potent second generation TKIs which bring better and faster responses - this will increase the percentage of patients for whom permanent remission or eradication will be the outcome. Imatinib has completely changed the way CML is treated - transplants are now very rarely carried out as first line therapy in any patient group. The 5 year survival data looks very out of date and a considerable underestimate - thus is a bit misleading as to the effectiveness of imatinib, and TKIs generally. More recent data should be quoted
Date	1/9/2012 2:03:00 PM

Name	[redacted]
Role	Patient
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I disagree with the preliminary recommendations. Dasatinib SHOULD be recommended. Clinical trials have proven its effectiveness and I see no reason for it not to be used by patients on the recommendation of a clinician This should not be the decision of a cost-cutting body that appears to be doing Government dirty work.
Section 2 (Clinical need and practice)	You neglect to mention the very high mortality risk of bone marrow transplant and that most patients would want to avoid it at all costs if a less risky, but highly effective, treatment is available.

Section 3 (The technologies)	
Section 4 (Evidence and interpretation)	To consider cost-effectiveness of drugs here is distasteful. They dont prolong lives, they save them! Thanks to dasatinib I look forward to a long & fruitful life with my wife and son. This decision should only be based on clinical effectiveness & dasatinib is effective. I object to the secrecy of PAH offered by the makers of nilotinib. I wish BMS would offer a similar scheme just to negate this argument. Any cost comparison between these 2 drugs is redundant because you cannot state the discounted cost. You criticism of trial data is out-of-touch with the real world. CML is a rare condition with only around 600 new diagnosis each year. You will NOT achieve your gold standard of research with CML, it is not achievable. I am disappointed that BOTH your patient experts came from CML Support Group. All 3 drugs work, some better than others, some better with different patients. How can you afford not to recommend all 3 when they have the potential to save life? Are you prepared to take the risk and limit these clinical advancements in the treatment of a form of cancer? When we have been looking for a cure for so long are you seriously considering limiting the treatment?
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date for review of guidance)	You neglect to mention the very high mortality risk of bone marrow transplant and that most patients would want to avoid it at all costs if a less risky, but highly effective, treatment is available.
Date	1/3/2012 6:27:00 PM