NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance

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

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Bristol Myers Squibb
   - Novartis
   - Royal College of Nursing
   - Royal College of Pathologists / British Society for Haematology / NCRI CML Working Group
   - Royal College of Physicians
   - Commissioning Support Appraisals Service
   - Healthcare Improvement Scotland

3. **Comments on the Appraisal Consultation Document from experts:**
   - Jane Apperley, Royal College of Physicians
   - Sandy Craine, The CML Support Group

4. **Critique on the Patient Access Scheme submitted by Novartis by** Southampton Health Technology Assessment Centre

5. **Comments on the Appraisal Consultation Document:**
   - Report to the Appraisal Committee summarising public comments on the Appraisal Consultation Document (ACD) issued in May 2011 (including comments from patients, carers and health professionals)

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, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance

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
Royal College of Pathologists (RCPath)	Unfortunately, this is not good news for CML patients who are currently receiving imatinib at the standard dose (400 mg daily), nor for future patients yet to be diagnosed. This decision denies access to the second generation agents dasatinib and nilotinib, for patients whose leukaemia becomes resistant to imatinib. This is approximately 40% of CML patients, which is about 300 patients per annum across the UK. We have very recently been carrying out a population study of CML outcome in the geographically contiguous area of Merseyside, Cheshire, Isle of Man and the North Wales coastal strip (total population = 2.0 million). During the 7 year period 2003-2009, 192 patients were newly diagnosed, of whom 9 presented with advanced disease, 3 did not receive a tyrosine kinase inhibitor (TKI) because of extreme age, and 20 received a second generation TKI as first line treatment as part of a clinical trial. A total of 160 therefore received first line imatinib, and 123 are assessable at 36 months, of which 69 (56%) have achieved adequate responses (at least complete cytogenetic remission). Thirty-three patients (which are approx. 40% of cases diagnosed since second generation TKI became locally available in Jan 2006) required switching to a second generation TKI because of imatinib resistance (18 cases) or intolerance (15 cases). Of these, 21 of 30 (70%) assessable cases have achieved not only complete cytogenetic remission but major molecular response, and no patient has lost this response at latest follow-up. It is known from the IRIS study that the progression rate to advanced disease for patients unable to achieve complete cytogenetic response on imatinib is substantial, of the order of 10% over the subsequent 3-5 years. However, the progression rate for patients in major molecular response is less than 1%. In this population study, second generation TKI have therefore converted 70% of imatinib resistant/intolerant patients from a progression risk of 10% to <1%. It is too soon to detect an effect on progression free survival (though a trend is currently apparent), but the overall rate of complete cytogenetic response is superior for patients diagnosed since 1/1/2006 (p = 0.04), which is when second generation TKI became locally available for imatinib resistance/intolerance. In summary, these very recent population data provide evidence that second generation TKI benefit 70% of the 40% of CML patients in whom they are indicated.	The Committee concluded that it is clear that dasatinib, high-dose imatinib and nilotinib provide clinical benefit for people with imatinib-resistant CML. However, the Committee agreed that the limited evidence base means that the magnitude of the benefit is uncertain. See FAD section 4.3.9

Consultee	Comment	Response
RCPath	There are problems with all of the 4 health economic models used in the NICE assessment. In addition, each of these has used the wrong comparator; either hydroxycarbamide, interferon or stem cell transplantation. In earlier meetings and documentation (and in the response from this college to the first appraisal meeting), it was recommended that the appropriate comparator should be high-dose imatinib. This has however been included as an appraisal technology instead. In this case, assuming that high-dose imatinib were also unavailable, then the relevant comparator should be maintaining the patients on standard dose imatinib. A detailed discussion of these points is given in the attached response to NICE from the NCRI CML subgroup (attached).	The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care. The Committee also heard from the clinical specialists that bone marrow stem cell transplantation could be used. The Committee concluded that any one of these treatments could be considered a comparator with high-dose imatinib, nilotinib or dasatinib. See FAD section 4.3.3
RCPath	The appraisal committee has acknowledged that the appraisal technologies provide clinical benefit in imatinib-resistant CML (paragraph 4.3.6). We of course agree with this. It is therefore plausible that these technologies (especially dasatinib and nilotinib) may well achieve an ICER below the £30,000 threshold, if their NHS price were reduced. Novartis have recently dropped the effective NHS price of nilotinib for first line use (at a dose of 300mg twice daily) to match that of imatinib, whilst leaving the price of the licensed dose for second line use (400mg twice daily) unaltered. If there were downward movement of the price also for second line use, and a similar move from Bristol Myers Squibb for dasatinib, these drugs may then achieve the NICE model of cost-effectiveness. It is however difficult for the College or for individual clinicians to take a view on the detail of this; discussion between the manufacturers and the Department of Health are therefore required. One suggestion is that this could be pegged to the establishment of a CML registry across the UK, as already in place for the North of England and Wales; the UK clinical CML community would welcome and support this.	The Committee noted that the manufacturer of nilotinib had agreed a patient access scheme with the Department of Health. The Committee recommended the use of nilotinib for the treatment of adults with chronic and accelerated phase CML that is resistant to standard-dose imatinib or who have imatinib intolerance, if the manufacturer makes nilotinib available with the discount agreed as part of the patient access scheme. See FAD section 4.3.21–4.3.23 The Committee noted that, given the patient access scheme for nilotinib and the assumed equivalence of effectiveness of dasatinib and nilotinib, dasatinib is considerably more expensive but no more effective than nilotinib. See FAD section 4.3.25
Royal College of Nursing (RCN)	The evidence considered seems comprehensive.	Comment noted

Consultee	Comment	Response
RCN	Nurses caring for people with chronic myeloid leukaemia have reviewed the recommendations of the Appraisal Committee. It is a bit confusing to understand the rationale for the draft recommendations. We note that the document does not recommend the use of dasatininb/nilotinib for treatment of imatinib-resistant CML. However it acknowledges that clinical specialists report that the drug is effective in those patients who have shown themselves to be imatinib-resistant, whilst noting that there is little in the way of hard evidence from clinical trials. The report also notes that treatment is £30,000 per annum for dasatinib/noliotinib and that, because it works, the patient is likely to be taking it until they die (from other causes). So it appears that this technology is not being recommended because it is too expensive as patients are likely to live too long! We also note that it is recommended that patients already on it should stay on it. The alternatives for the treatment of people with this condition are either inadequate drugs or stem cell transplant. The latter has higher upfront costs, but is potentially curative; however only suitable for the younger, fitter patients. What is not stated in the document is the increase in mortality rate by up to 20% during the treatment and subsequent mortality and ongoing complications at 3, 6, 12 months and ongoing. Further, it is now standard routine practice to use both of these drugs in imatinib resistant/refractory patients. In view of the points raised, we consider that the provisional recommendations do not sound or constitute suitable basis for guidance to the NHS. They seem to have paid more emphasis on cost than on the clinical effectiveness of the technology.	Comment noted. The Committee heard from the clinical specialists that bone marrow stem cell transplantation could be used, although it carries high risks and is restricted to fit, younger people. See FAD section 4.3.3 The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care. The Committee also heard from the clinical specialists that bone marrow stem cell transplantation could be used. The Committee concluded that any one of these treatments could be considered a comparator with high-dose imatinib, nilotinib or dasatinib.. See FAD section 4.3.3
RCN	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 equality impact assessment report will be published on the NICE website.

Consultee	Comment	Response
Royal College of Physicians (RCP)	The ACD makes the point, several times, that there are insufficient data. In fact, there are 11 studies available, which were considered by the SHTAC assessment group; four of these are new since the earlier PENTAG assessment of 2009. Whilst these data are not ideal (there are no phase III RCT with survival outcomes), several clinical study groups including the NCRI Haematological Oncology (CML subgroup) Clinical Studies Group have felt it impossible to design an RCT of the appraisal technologies against standard dose imatinib, in a population of patients in whom the latter has already failed. It is therefore highly unlikely, and probably unethical, to design further studies to investigate the efficacy of these technologies. The appraisal committee has acknowledged this problem, since it supports the view that the appraisal technologies provide clinical benefit in imatinib-resistant CML (paragraph 4.3.6). We would of course agree with this.	The Committee concluded that it is clear that dasatinib, high-dose imatinib and nilotinib provide clinical benefit for people with imatinib-resistant CML. However, the Committee agreed that the limited evidence base means that the magnitude of the benefit is uncertain. See FAD section 4.3.9
RCP	The analysis considered four different models, all of which are considered flawed by our experts. That from Bristol Myers Squibb assumes that chronic phase patients can only progress; there is no possibility of progressing patients being able to achieve a second chronic phase (which is achievable clinically in approximately 30% of cases). This model uses 5 'disease states' linked to prognosis; these do not reflect real clinical practice, as they assume that once a response is achieved, it does not change until disease progression. For example, it does not encompass slow responding patients who may take time to move from no response to cytogenetic response and then molecular response. The treatment options at imatinib failure were obtained from a postal survey, but it is not clear whether continuance of standard dose imatinib was presented as an option if none of the appraisal technologies were available. Interferon was used as the comparator, apparently using first-line efficacy data from the 1990s. Apart from being an inappropriate comparator, these data are likely to be overoptimistic when applied to imatinib resistant patients, who are 'selected' for having unfavourable disease. Interestingly, the costs of nilotinib and high-dose imatinib in this model are more than double that in the other models.	The Committee considered that the model developed by Bristol-Myers Squibb had a number of limitations, of which the most important were that it estimated the cost for people receiving interferon alfa to be higher than (in some cases double) that of all the other economic models, and it did not include a comparison with hydroxycarbamide. See FAD section 4.3.14
RCP	The model from Novartis compared nilotinib and high dose imatinib against the comparators stem cell transplantation (SCT) and hydroxycarbamide. Apart from being inappropriate comparators, this model also assumed that CML phases are only consecutive (ie that second chronic phase is not possible). The assumption that 75% of patients under 65 can undergo allogeneic SCT, and that all other patients receive hydroxycarbamide is considered unrealistic.	The Committee considered the economic model for chronic-phase CML that is resistant to standard-dose imatinib in the model developed by Novartis. The Committee noted that if the treatment duration and overall survival as observed in clinical practice were more accurately modelled and if hydroxycarbamide alone was a comparator, the base-case ICER would be likely to increase. See FAD section 4.3.22

Consultee	Comment	Response
RCP	That from PENTAG uses a model in which chronic phase patients have only 2 states; those with a major cytogenetic response and those without. There is no distinction between a patient with only a partial (ie not complete) cytogenetic response at say 18 months and beyond (who has failed according to ELN recommendations and has a significant probability of disease progression) and a patient who achieves not only complete cytogenetic response but also a deep molecular response (in whom the risk of progression is very low, <1%). Interferon is again used as a comparator, to derive ICERs that are in each case well in excess of a £30,000 threshold. However, our experts believe that the interferon data appear highly unusual (treatment for 2.04 years with interferon is associated with 10.75 years of survival; paragraph 4.2.19). This analysis also predicts overall survival of 12.98 and 13.4 years of survival with nilotinib and dasatinib respectively, despite the fact that neither drug was available in any trial until 2004/5, so long term survival is unknown. It also does not take account of the clinical observation that responses to dasatinib/nilotinib vary from minimal right through to complete molecular remissions, which are likely to have very different resultant survivals.	The Committee noted the PenTAG model did not link treatment duration with overall survival and that some of the results were not plausible. It understood that the SHTAC base-case treatment durations still did not reflect the fact that in clinical practice, people will receive treatment until progression or death. See FAD section 4.3.17
RCP	The final model is from SHTAC, and addresses some of the deficiencies in the other models (eg the PENTAG assumption that treatment duration is twice as long for nilotinib as for dasatinib). However, the derivations of overall survival are made 'by a pragmatic approach' which is not made clear. No allowance is made for varying depths of response, in which long term outcome varies widely. How would this model look if patients with minimal response ceased treatment after say 12 months, with only those in complete cytogenetic remission or better continuing treatment after this time? The comparators used for deriving the ICERs of the appraisal technologies (paragraph 4.2.26) are considered inappropriate; hydroxycarbamide, interferon and SCT. It appears that at a threshold of £30,000 per QALY gained, nilotinib and dasatinib have probabilities of being cost effective of 60% and 28% respectively.	The Committee noted the PenTAG model did not link treatment duration with overall survival and that some of the results were not plausible. It understood that the SHTAC base-case treatment durations still did not reflect the fact that in clinical practice, people will receive treatment until progression or death. See FAD section 4.3.17

Consultee	Comment	Response
RCP	Our experts believe that the wrong comparator has been used in each of the models. If none of the appraisal technologies were available, it is highly likely that the majority of patients would simply remain on standard dose imatinib. The statement that hydroxycarbamide is associated with a median survival of 5 years in the setting of imatinib resistance (paragraph 4.3.3) is not based on any data and appears extremely overoptimistic. We note that the issue of comparators is incorrectly summarised at point 4.3.2. We are aware that in the written evidence to the committee from the Royal College of Pathologists, it is stated that if neither dasatinib nor nilotinib were available, then most clinicians would opt for high-dose imatinib. However, hitherto the question had not arisen of what to do if high-dose imatinib were also not available. In this case, we believe that most clinicians would advise remaining on standard dose imatinib. We understand that this was also stated at the appraisal meeting. There are several reasons why continuing standard dose imatinib in imatinib resistance may be reasonable: a) In the majority, haematological response is maintained. Most would be reluctant to change to therapies that need to be given by injection and associated with many side effects (interferon) or risk cytogenetic deterioration (hydroxycarbamide). b) There is laboratory evidence to support the notion that disease progression may commonly arise in a mature progenitor cell compartment, rather than the leukaemic stem cell. Whilst imatinib does not target the latter, it does reduce the progenitor cell compartment, unlike hydroxycarbamide. This observation may explain the paradox that imatinib decreases progression rates whilst being ineffective against leukaemic stem cells. The only other treatment that is logical is stem cell transplantation (SCT). However, this is only feasible for fewer than 30% of patients, because of age and donor availability. Even if feasible, SCT is associated with significant permanent morbidity and some mortality, and some patients will opt to wait until clear evidence of disease progression before accepting SCT	The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care. The Committee also heard from the clinical specialists that bone marrow stem cell transplantation could be used. The Committee concluded that any one of these treatments could be considered a comparator with high-dose imatinib, nilotinib or dasatinib.. See FAD section 4.3.3
RCP	Once patients progress to blast crisis, the only option likely to achieve long term good health is SCT. This is typically preceded by acute leukaemia style chemotherapy (usually 2 courses) with a concurrent second generation TKI, rather than the TKI alone. Unfortunately, SCT in this situation has a mortality approaching 50% (partly due to relapse), and is in any case only feasible in about 30% of patients, as above. The outlook for those who cannot receive SCT is grave, with a median survival of less than 24 months; those who are too unfit to withstand acute leukaemia treatment fare particularly badly. Only dasatinib has a product licence for blast crisis, but clinical experience suggests that it may palliate the unpleasant symptoms of blast crisis for many months, ensuring reasonable quality of life for the majority of patients. This is especially important for the considerable number of patients who cannot undergo acute leukaemia-style treatment. It appears that blast crisis may therefore meet NICE criteria for ‘end of life’, and indeed this point was made at the April appraisal committee meeting.	The Committee heard from the clinical specialists that treatment strategy in the blast-crisis phase of the disease is different from that in the accelerated or chronic phases, with dasatinib and high-dose imatinib given as adjuvant treatment with intensive chemotherapy for acute leukaemia. See FAD section 4.3.12 and 4.3.27

Consultee	Comment	Response
RCP	The appraisal committee has 'concluded that it is clear that dasatinib, high-dose imatinib and nilotinib provide clinical benefit for …imatinib-resistant CML' [paragraph 4.3.6]. We agree that these drugs may be effective in 50-75% of patients. However, since none of the technologies pass below the ICER threshold of £30,000 per QALY, the issue may centre on the drugs price, especially for dasatinib and nilotinib. For example, if the effective price to the NHS of each drug were to drop by say 30% (eg to the current price of imatinib), it may well be that the ICER for both drugs would fall below the £30,000 threshold. Whilst we appreciate that NICE is not in a position to negotiate pricing directly with manufacturers, it is possible that the effective price could be reduced through patient access schemes. Of note, Novartis have recently dropped the effective NHS price of nilotinib for **first line** use (at a dose of 300mg twice daily) to match that of imatinib, whilst leaving the price of the licensed dose for second line use (400mg twice daily) unaltered. We agree that these drugs offer valuable options in imatinib resistant CML, but understand that at current prices, these do not meet the standard NICE cost-effectiveness thresholds. We would suggest that the appraisal panel consider the following: • an interval for the manufacturers to consider patient access scheme options that may in effect reduce the drug price, perhaps linked to a national register for imatinib-resistant patients. • that patients with advanced phase disease (accelerated phase and blast crisis) meet the 'end of life' criteria.	The Committee noted that the manufacturer of nilotinib had agreed a patient access scheme with the Department of Health. The Committee recommended the use of nilotinib for the treatment of adults with chronic and accelerated phase CML that is resistant to standard-dose imatinib or who have imatinib intolerance, if the manufacturer makes nilotinib available with the discount agreed as part of the patient access scheme. See FAD section 4.3.21–4.3.23 The Committee noted that, given the patient access scheme for nilotinib and the assumed equivalence of effectiveness of dasatinib and nilotinib, dasatinib is considerably more expensive but no more effective than nilotinib. See FAD section 4.3.25
Bristol-Myers Squibb (BMS)	Bristol-Myers Squibb (BMS) has reviewed the Appraisal Consultation Document (ACD) relating to dasatinib for the treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance to standard dose imatinib. BMS is disappointed with the preliminary recommendation of the ACD that does not recommend dasatinib for use on the NHS in this setting. BMS has concerns about the Appraisal Committee's (AC) conclusions relating to dasatinib due to what are agreed difficulties in producing a robust economic model on which to make informed conclusions. We have noted before that we are aware of the difficulties in undertaking modelling with any certainty in this setting, because of the lack of comparative data. BMS is obviously keen that an informed decision point is reached based on the best information possible. There are two possible ways to achieve this, namely: 1. the Institute commissions an independent re-modelling exercise to develop an economic model that all parties feel is credible or 2. the appraisal should be referred to the Decision Support Unit (DSU).	Comment noted.

Consultee	Comment	Response
BMS	There is no question that, for patients who are imatinib-resistant, both dasatinib and nilotinib are transformational treatments. They may offer a real chance of full life expectancy for a significant group of patients who would otherwise have reached the end of the road with regard to their treatment options, other than a bone marrow transplant. This last point appears to be accepted by all. The AC acknowledges also that, even in the advanced stages of the disease, there is likely to be real clinical benefit and that there is merit in the view of clinicians that patients in a real-life setting are likely to perform better than those in trials. This is because they will access treatment earlier and are likely to be in better overall physical state than trial patients. Whilst accepting that this benefit cannot be accurately quantified, and given the impossibility of generating new comparative data (what we have is realistically all that can ever - ethically - be generated), this is surely a situation where the potential benefits of the improved real-life performance and the clinical support for these benefits should be given greater weight than the uncertainty. This is doubly the case, given that any effective alternative for patients at this stage is likely to be associated with a substantially sub-optimal side-effect profile. We have noted below the areas where we feel that the model has significant shortcomings, which have the effect of increasing of the ICER. Correction of these would offset many of the increases in the ICERs that the AC believes result from assuming a longer duration of treatment, and would provide more overall certainty. Our modelling leads us to believe that it should be possible to end up with ICER values that, with greater certainty, are in the normal range considered acceptable under the end of life criteria	Comment noted.

Consultee	Comment	Response
BMS	Our main points of contention with the ACD are as follows: • The original (and revised) Assessment Group (AG) economic model contains fundamental shortcomings and cannot be reliably used for decision-making. These relate both to the assumptions on which the model is built and the methods used in its construction. The model allows for individuals to spend longer in one health state than they do alive, and uses inconsistent approaches to modelling key parameters for different drugs. The approach also allows for individuals on the older, less effective interventions to have a lower rate of disease progression than those on newer and more effective drugs. • The interpretation of 'continuation of treatment until death' is flawed. Whilst we accept that treatments are given until death for patients who continue to respond to treatment, however, importantly, they are also given until disease progression, or until the development of intolerance. It is incorrect to assume that the same treatment is always given until death. • The AC's interpretation of methods and outputs of BMS modelling is incorrect, as discussed in detail in section 2.3. This results in conclusions that are unfair and unrepresentative of the true value of these technologies. • Additional evidence does, in fact, exist beyond that considered by the AC. For example, in order to make an informed decision around the comparative cost effectiveness of hydroxycarbamide (on the assumption that the AC insists it is "...probably the most appropriate comparator", a position with which BMS and clinical experts disagree), an in-depth analysis of the efficacy and cost of this treatment, should surely be required from the AG and manufacturers. The current conclusion about hydroxycarbamide is based on the contested AG model. • 'face validity' check of model outputs represents an over-simplification of the real-life clinical situation. The AC has disregarded the overall treatment costs that should include much more expensive and more complicated post-failure treatments such as Bone Marrow Stem Cell Transplantation (BMSCT), (predominately a 3rd line therapy). If, as implied by the ACD, dasatinib and nilotinib were not available more patients would need to receive these high cost 3rd line treatments at increased cost to the NHS. Such an outcome seems counter-intuitive. The practical reality of this is, that in the absence of TKIs in the 2nd line setting at a rough estimate a minimum of 300 patients each year will be left with a BMSCT as their only realistic treatment option. This is likely to stretch the bone marrow transplant infrastructure in England and Wales to breaking point and to impose significant extra costs onto the NHS. • Where BMSCT is the only credible treatment option it is likely to exclude many patients who are not Caucasian, young and healthy. This is due to the lack of suitable donors, so that the effect of this guidance is to discriminate against anyone who is of an ethnic minority, old and with multiple co-morbidities.	The Committee noted the PenTAG model did not link treatment duration with overall survival and that some of the results were not plausible. It understood that the SHTAC base-case treatment durations still did not reflect the fact that in clinical practice, people will receive treatment until progression or death. See FAD sections 4.3.17 and 4.3.18. 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. The reliability of the available evidence is also considered by the Committee when formulating its recommendations. The Committee noted the argument that if dasatinib, high-dose imatinib or nilotinib are not recommended for the treatment of imatinib-resistant CML and that this could raise issues in relation to race, age (the elderly), and comorbidities. However, the Committee concluded that allowing for clinical decisions relating to a range of possible treatments based on individual assessment of risk and benefit does not limit access to the technology for any specific protected group compared with other people. See FAD section 4.3.31

Consultee	Comment	Response
BMS	This preliminary recommendation, if carried forward into the Final Appraisal Determination, would therefore have serious negative consequences for patients. Dasatinib and nilotinib have become standard treatments for patients with CML, in the 4 years they have been available, improving the quality and quantity-of-life of CML patients over alternative treatments. Dasatinib is currently used in the majority of cancer networks in the UK, with an estimated 450 patients currently benefiting from treatment with it. Virtually all Primary Care Trusts in the NHS who have received funding applications have agreed to fund it.	Comment noted.
BMS	Patients in England will receive care that is poor by EU standards, given that European recommendations embrace the use of dasatinib. There is also the making of a new UK postcode lottery, since dasatinib has been approved by HTA agencies in Scotland and Wales and the London Cancer New Drugs Group (LCNDG). The preliminary negative decision also raises fundamental ethical and human right issues in that it prevents doctors from prescribing, and patients from having access to, potentially life-saving treatment. This outcome seems disproportionate when one considers the ultra-orphan nature of the disease.	Comment noted
BMS	We are keen to collaborate fully with NICE and its Appraisal Committee to develop a credible independent economic model and to seek to generate robust outcomes that are understood and ratified by all stakeholders at NICE, BMS and the wider community. We believe the best way to move forward on this is by utilising one of the two approaches set out above and we look forward to hearing the Institute's views on this suggestion. Given the meaningful and high quality extra years of life that these treatments offer, it must be right to explore all avenues to find an acceptable solution and ensure that patients are able to access these treatments.	Comment noted.
BMS	*Paragraph 4.1.4: 'Four studies provided data on dasatinib for imatinib-resistant chronic-phase CML. All of these studies had been identified by PenTAG and* ***one was updated with the SHTAC Assessment Group review'.*** **Comments**: The SHTAC did not include an update of a pivotal study of dasatinib (i.e. the dose-ranging study BMS-034). The PenTAG and the SHTAC assessment reports only included the 6-month follow-up data of this study (Shah et al 2008), whilst the 2-year follow up data was presented in the American Society of Haematology in 2008 (Shah et al 2008a) and then published early 2010 (Shah et al 2010), and the 4-year follow-up data has been presented in the American Society of Clinical Oncology (Shah et al 2010a). These data (BMS-034 2 year follow-up along with the BMS-017 data) formed the basis of EMA approval of dasatinib.	Comment noted. This section has been amended (accordingly, for clarity).

Consultee	Comment	Response
BMS	*Paragraph 4.1.5: 'PenTAG provided pooled summary results for three outcomes. A complete cytogenetic response was reported in 37.4% of participants (95% confidence interval [CI] 34.2 to 40.5), 50.9% had a major cytogenetic response (95% CI 47.6 to 54.1) and 89.2% had a complete haematological response (95% CI 87.2 to 91.3)'.* **Comments**: Pooled complete cytogenic response (CCyR) (37.4%) is reported in PenTAG report (Table 15) that includes 6-month follow-up data from BMS-034 (33.9%). The 24-month follow-up data of this study shows a much higher CCyR (50%) (Shah et al 2010), and this has not been taken account. There are similar discrepancies regarding the pooled major cytogenetic response (MCyR) and complete haematological response (CHR) (see PenTAG report: Table 16 and Table 25).	Comment noted. This section has been amended (accordingly, for clarity).
BMS	*Paragraph 4.1.16: 'One dose-ranging RCT and one single-arm cohort study were identified that reported results for dasatinib in participants with accelerated-phase CML. The Assessment Groups considered that the RCT was of low methodological quality as it **did not report allocation concealment** and had an open-label design.'* **Comments**: The highlighted statement has not taken into account the evidence of the allocation concealment reported in the clinical study report (CSR). The allocation concealment is reported as: Each site enrolled subjects into the study at the time of eligibility screening by accessing a call-in interactive voice response system (IVRS) after informed consent had been obtained. A subject number was assigned at this time. After completion of all screening evaluations, all eligible subjects were then randomly assigned to one of two treatment arms (dasatinib or imatinib) in a 2:1 ratio. To enrol a subject, a phone call was made by the site to the central randomization centre using a 24-hour toll-free number. The randomisation procedure dynamically minimized the imbalance between treatment arms within each of the following stratification factors: 1) site and 2) cytogenetic response on imatinib (cytogenetic response (minimal, minor, partial or complete) vs no cytogenetic response). Upon completion of randomisation, the first dose of study therapy was administered within three days.	Comment noted. The FAD has been amended to reflect that this was a consideration of the Assessment Groups - see FAD section 4.1.18

Consultee	Comment	Response
BMS	*Paragraph 4.3.3: 'The Committee heard from the clinical specialists that people whose CML does not respond to dasatinib or nilotinib within 12 months* ***would receive treatment with hydroxycarbamide*** *or, if suitable, stem cell transplantation. For people receiving hydroxycarbamide, the prognosis is poor,* ***with a median life expectancy of around 5 years'****.* **Comments**: The clinical evidence, and clinical experts' opinions, have clearly been misinterpreted. All the extensive, senior clinical advice that BMS has received and that NICE has received as part of this appraisal (e.g. see comments from Dr Patrick Cadigan, RCP Registrar on behalf of: NCRI/RCP/RCR/ACP/JCCO) clearly show that patients who do not respond to dasatinib or nilotinib within 12 months, would NOT receive hydroxycarbamide (considered obsolete in this indication). Instead they would receive another 2nd generation TKI, and then proceed to BMSCT. Historically, hydroxycarbamide has only been used in the 1st line setting. The evidence relating to hydroxycarbamide in the 2nd line setting is minimal. It is safe to assume however that patients resistant to 2nd generation TKIs are unlikely to respond to hydroxycarbamide and the median survival is likely to be significantly less than the 5 years cited above (in the 1st line setting). In this respect, the Chronic Myeloid Leukemia Trialists' Collaborative Group (1997) state that, in newly diagnosed patients, the survival rate is only 44% at 5-years.	The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care. The Committee also heard from the clinical specialists that bone marrow stem cell transplantation could be used. The Committee concluded that any one of these treatments could be considered a comparator with high-dose imatinib, nilotinib or dasatinib. See FAD section 4.3.3.
BMS	*Paragraph 4.3.4: 'The Committee noted that the economic models available to them had used major cytogenetic response as a surrogate for overall survival and heard from the clinical specialists that* ***the strongest link was between major molecular response and overall survival****.'* **Comments**: The highlighted statement is not a reflection of current clinical knowledge. As noted in the ELN guideline (Baccarani et al 2009) and Marin et al (2008), complete cytogenetic response is the most important response-related prognostic factor since Marin's et al (2008) concluded that 'At 12 months, the only independent predictors for PFS were: (1) being in CCyR (complete cytogenetic response)..... and (2) prior loss of CCyR ……; At 18 months, the only independent predictor for PFS was being in CCyR'. Furthermore, Marin et al (2008) stated that 'the achievement of MMR (major molecular response) at 12 or 18 months **failed to** confer any benefit in 5-year PFS or OS'. The ELN guideline stated that: 'In these patients (treated with dasatinib and nilotinib), the response-related prognostic factors that have been identified for imatinib may apply as well to dasatinib and nilotinib, but it should not be overlooked that the response to these drugs is more rapid' (Baccarani et al 2009).	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.

Consultee	Comment	Response
BMS	*Paragraph 4.3.4: 'The Committee noted the **poor evidence base** for all interventions for people whose CML is resistant to standard-dose imatinib'* **Comments**: This statement is not a reasonable interpretation of the evidence. There is sufficient evidence demonstrating the safety and efficacy of dasatinib from 7 phase 2 and phase 3 clinical trials that include over 2,000 patients. Whilst we appreciate the issue regarding the paucity of comparative data, the majority of the available evidence supports dasatinib as an effective intervention. Such trials were considered sufficiently robust for the European Medicines Agency to grant a marketing authorisation and therefore we fail to see how the AC can consider the evidence base poor.	This information was included in the ACD, but has been amended following comments from other consultees.
BMS	*Paragraph 4.3.5: 'The Committee was aware that no evidence was presented on the use of dasatinib, high-dose imatinib and nilotinib (accelerated phase only) in this way (i.e. **as adjuvant treatment with intensive chemotherapy for acute leukaemia**) and that the evidence base in this advanced stage of the disease was very limited'.* **Comments**: This statement is not a reasonable interpretation of the evidence. In advanced phase CML there is evidence regarding the clinical efficacy of dasatinib monotherapy ((Apperley et al 2009, Kantarjian et al 2009, Cortes et al 2008). It should be remembered that this appraisal is to assess the clinical and cost-effectiveness of dasatinib used in CML patients as monotherapy (as defined in the final scope). It is not to assess dasatinib used in the neo-adjuvant/adjuvant setting (TKI initiated before and/or after BMSCT) and any such discussions or opinions in this ACD are procedurally unfair.	See FAD 4.3.12 and 4.3.27 – It has been clarified that this comment relates to the blast phase crisis only. The Committee noted that usual treatment for the blast-crisis phase is different from that used in the other phases.

Consultee	Comment	Response
BMS	*Paragraph 4.3.8: 'The Committee was aware that,* ***for people who respond, these treatments (dasatinib and nilotinib) are given daily, very often until death****, and that this results in high treatment costs for every year of life lived with CML'* **Comments**: This statement is not a reasonable interpretation of the evidence and oversimplifies the clinical situation. The interpretation of 'continuation of treatment until death' is flawed. Whilst we accept that treatments are given until death for patients who continue to respond to treatment, however, importantly, they are also given until disease progression, or until the development of intolerance. It is incorrect to assume that the same treatment is always given until death. In clinical practice, for those people with CML, and who cannot be treated with dasatinib and nilotinib, the treatment options are other TKIs, various combination of treatments, and finally (only if they are suitable), BMSCT. These post-failure treatments are likely to attract high costs (such as treating Graft versus Host Disease; managing co-morbidities and serious adverse effects; hospitalisation; blood tests; weekly visits to the GP; blood transfusion; hospital based out-patient visits etc). All these costs, not only the initial drug or transplantation costs, should be taken into account. It is too simplistic to conclude that only treatments such as dasatinib and nilotinib will result in high treatment costs for every year of life lived with CML. Should dasatinib and nilotinib be unavailable, the alternative treatments will result in even higher treatment costs.	Comment noted. This section has been amended (accordingly, for clarity). See FAD section 4.3.6

Consultee	Comment	Response
BMS	*Paragraph 4.3.8: 'The Committee also considered that if each year of life were adjusted by quality of life the resulting costs per QALY would be likely to be higher than the annual costs of the drugs. The Committee agreed that these considerations would be important in checking the face validity of each of the economic models and outputs……'* **Comments**: The argument above is intuitive and does seem to have 'face value' If an intervention costs £1, and gives a year of life, the ICER would be £1 per life year gained. If that year was given a utility weight (i.e. QALY weight - quality adjusted life years) of 0.5 the ICER becomes £2 per QALY gained. However, BMS requests clarification of the Committee's logic on this point, since a drug's acquisition costs are only one component of the total treatment costs. It is important to recognise that any 3rd line intervention for CML includes a combination of drugs, chemotherapeutic agents and BMSCT. Thus, if a patient 'fails' treatment more quickly, or has a poorer prognosis, on treatment A compared with treatment B, it can be expected that treatment A will incur far greater third line costs than treatment B. Consider the following case study. If most patients on hydroxycarbamide will be classified as failures at 1 year, then a large proportion of them will receive BMSCT. However, if a much smaller proportion of patients fail dasatinib at 1 year, then much fewer patients will receive BMSCT. Therefore, the difference in front line acquisition costs is offset. In summary, in the presence of significant cost offsets, the TOTAL incremental lifetime cost per patient can be a lot lower than the incremental lifetime acquisition costs.	This information was included in the ACD, but has been amended following comments from consultees.

Consultee	Comment	Response
BMS	*Paragraph 4.2.4: 'The published data from the dasatinib trial were limited to 48 months of follow-up and the manufacturer extrapolated longer-term progression-free survival* ***by assuming that the monthly rate of progression after 48 months was equal to that observed during the final year of the published data.'*** *Paragraph 4.3.9: 'the Committee noted that the transition probabilities were extrapolated* ***by taking the rate of progression from months 36 to 48 forward****; the Committee was concerned that this* ***implied no one would progress from the (healthy) complete cytogenetic response state after 3 years****. It considered that this is not plausible, given that it had heard from the clinical experts that a proportion of people with CML will experience disease progression'.* **Comments**: The highlighted parts of the above sentences are not a reasonable interpretation of the evidence. Firstly, in our economic model (Excel format), we actually extrapolated longer-term progression-free survival based on the progression rate observed from months 6 and 48, not the final year of the trial data (i.e. not by taking the rate of progression from month 36 and 48 forward). Secondly, the AC suggests that BMS model extrapolation implies no one ever progressed from the CCyR state after 4 years, this is incorrect. Firstly, during the trial period, there is not progression observed in the trial from month 23 to month 47 for patients who achieved CCyR (Table 1 [not reproduced here]). Secondly, while there is no progression at the last year in the trial (see Table 1), we have not used this information to inform the extrapolation process. Instead, earlier data was used to derive the progression rates (i.e. data from months 6 and 48) and hence there is increasing progression at 48 months onwards, especially with CCyR patients. Sample proportions from the model are reproduced below to support this statement (**Error! Reference source not found.**2 [not reproduced here]).	This information was included in the ACD, but has been amended following comments from consultees.

Consultee	Comment	Response
BMS	*Paragraph 4.2.4: 'The rates of progression with the other treatments were taken from other clinical studies and assumptions'* **Comments**: The above sentence is not a reasonable interpretation of the evidence. The rates of progression were based on the initial best response levels. For example, patients with CCyR would have a certain rate of progression, whilst patients do not respond to treatment would have another rate of progression. In this case, the relationship between progression and response levels are the same for all treatments. This relationship (rates of progression) is based on dasatinib 4-year follow up trial data. Therefore, the rates of progression with the other treatments were the same as those of dasatinib. However, since the initial best response levels vary of different treatments, the progression free survival become different.	This information was included in the ACD, but has been amended following comments from consultees.
BMS	*Paragraph 4.3.9: 'First, the (BMS) model estimated that the cost for people receiving interferon alfa was higher (in some cases double) than that of all of the other economic models……'* **Comments**: As noted in the summary of product characteristics for Interferon alfa-2a (Roferon A): "Roferon-A should be administered under the supervision of a qualified physician experienced in the management of the respective indication" As such, the total monthly cost must include not only the cost of treatment, but also all outpatient/ administration costs relating to treatment administration. Assuming that treatment is needed three times per week, this would result in 13 outpatient visits per month (3 per week * 4.33 weeks per month). Thus, administration costs would range from £325 per month (if all were performed via a GP nurse at the practice) to £1,400 per month (if all were performed via a hospital based oncology outpatient visit). In terms of drug costs, assuming a body surface area of 1.7m2, and a dose of 6 MIU, the monthly cost of treatment (including inevitable wastage due to lack of vial sharing) is £550 if 1ml vials are used, and £1,376 if 2.5ml vials are used (vial dose 10MU/ml). Therefore BMS would argue that the cost of interferon used in our model is likely to be at the lower end of the costs range, and as a result all ICERs represent values close to or on the upper threshold for this comparison.	Comment noted. 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. See FAD section 4.3.14

Consultee	Comment	Response
BMS	*Paragraph 4.3.9: '(the BMS model) did not include a comparison with hydroxycarbamide. The Committee noted the testimony of the clinical specialists that hydroxycarbamide was probably the most appropriate comparator (along with stem cell transplantation if possible) '.* **Comments**: BMS does not consider hydroxycarbamide as a valid comparator because clinical evidence suggests that this would be obsolete clinical practice (see comments above). Therefore, data on hydroxycarbamide, and in particular best initial response to treatment, were not included in the original BMS model. Nevertheless, we have conducted the following exploratory exercise by estimating: 1. Efficacy of dasatinib: based on clinical trial data (Shah et al 2008a), at 12 months, 8.1% patients were non-responders 2. Discontinuation of dasatinib: 10.2% (quoting PenTAG report) 3. Efficacy of hydroxycarbamide: since hydroxycarbamide is given largely to modify white blood cell counts, the efficacy of this product as a treatment for CML was assumed to be the same as observed for interferon. For example, 100% patients were non-responders. 4. Discontinuation rates of hydroxycarbamide: it is assumed that the premature discontinuation rate is the same as the IFN (55.5% as reported in IRIS, quoting PenTAG report). 5. The cost of hydroxycarbamide: it was calculated on the basis of information in the product SPC and includes all tests, doctor visits etc. The following statements are notes in the Summary of Product Characteristics for Hydrea 500 mg Hard Capsules	The Committee examined the assumptions that had been used in the additional analysis. See FAD section 4.3.15.

Consultee	Comment	Response
BMS	Hence, given that hydroxycarbamide is an oral medication, the following need to be included into the calculation of treatment costs: ▪ Weekly blood tests ▪ Weekly visits to the GP of the purposes of provision of a blood sample ▪ A proportion of individuals requiring a blood transfusion ▪ This proportion also requiring a hospital based out-patient visit For the purposes of calculation, the following values have been used to calculate the cost of hydroxycarbamide treatment (Table 3 [not reproduced here]). When the additional costs are included, the **total** monthly cost for hydroxycarbamide is £150.62. We also note that for patients who fail 2nd line treatment (non-responders and early discontinuation), 31% patients are eligible for BMSCT (Oxford Outcomes 2009). The costs of BMSCT in 3rd line use were calculated as below: ▪ The one-off cost of BMSCT is £80,000 (the lower-end estimated from clinical experts) ▪ The ongoing cost of post BMSCT (31% * £2,400) = £744 per month, according to clinical experts' estimates ▪ % patients treated with BMSCT and alive at one year = % eligible * (% non-responders + % early discontinuation). Thus, for patients treated with dasatinib, the calculation is as follows: % BMSCT's = 30.8%* (8.1%+ 10.2%) = 5.7%. The results generated using these assumptions are presented in Table 4 [not reproduced here] Thus, the cost-effectiveness ratio generated for dasatinib compared to hydroxycarbamide is at the upper end of the costs range used by NICE in their decision making process. In this regard, we would argue that the additional benefits of treatment (in particular the additional 8.6 years in the progression free state) should be taken into account when making a reimbursement decision.	The Committee examined the assumptions that had been used in the additional analysis. See FAD section 4.3.15.
BMS	*Paragraph 4.3.9: 'The Committee concluded that the base-case ICER resulting from the Bristol-Myers Squibb model of £38,900 per QALY gained is an underestimate and would be substantially higher* ***if the relevant comparator (hydroxycarbamide) and more plausible assumptions about progression were used'****.* **Comments**: As noted above, the AC misinterprets the progression assumptions used in the BMS model, therefore BMS disagrees with the hypothesis that any alternative approach would result in an increase in the ICER. This statement is not evidence based and is misleading.	The Committee concluded that the additional analysis from the Bristol-Myers Squibb's analysis was not reliable and could not form a suitable basis for a recommendation. See FAD section 4.3.15.

Consultee	Comment	Response
BMS	*Paragraph 4.3.11: 'The Committee noted that the (PenTAG) model* ***does not link treatment duration and overall survival*** *and that some of the results are not plausible. In particular, it noted the overall survival for interferon alfa is implausible and the treatment duration for people receiving nilotinib is lower than would be seen given the estimated overall survival. The Committee therefore concluded that PenTAG's model underestimated the most optimistic ICER; that of £44,600 for nilotinib compared with interferon alfa.'* *Paragraph 4.3.12: 'The Committee understood that the (SHTAC) model attempted to correct PenTAG's overestimate of survival on interferon alfa and the discrepancy between the nilotinib and dasatinib treatment durations. However, the Committee noted that* ***the SHTAC Assessment Group's model also had the major limitation of PenTAG's model of assessing treatment duration and overall survival by unrelated methods'****.* **Comments:** As BMS have noted consistently throughout all the appraisals of 2nd line CML interventions, the simple, fundamental rule of any health economic model is that it is an accurate representation of the underlying disease process. We are pleased that some of the inaccuracies in the model have been acknowledged by the AC. However, the 'PenTAG model does not link treatment duration and overall survival' is the consequence of a fundamental flaw in the model structure, that is, the response rate is not used as a common surrogate outcome measure for OS and PFS. It is important to note that by changing the 'treatment duration' alone will not improve or correct the model. Indeed, BMS are deeply concerned that no effort has been made to change the flawed modelling approach. As noted by the AC, the base-case of SHTAC analysis is based a revised version of the PenTAG model, and it did not fix the fundamental problem, but merely altered some data outputs (for example, PFS). It would therefore seem perverse of NICE to make a reimbursement decision for a whole class of interventions based on a flawed economic model. The model initially developed by PenTAG, and slightly modified by SHTAC, have not addressed this fundamental issue. Serious and fundamental flaws exist in both the assumptions on which the model is built and the methods used in the construction. In particular, the model allows for individuals to spend longer in one health state than they do alive, and uses inconsistent approaches to modelling key parameters for different drugs (implicitly stating that they act in a biologically different manner). The approach also allows for individuals on the older, less effective, interventions to have a lower rate of disease progression than those on newer and more effective drugs.	The Committee understood that the model updated by SHTAC attempted to correct PenTAG's overestimate of survival on interferon alfa and the discrepancy between the nilotinib and dasatinib treatment durations, but the SHTAC base-case treatment durations still did not reflect the fact that in clinical practice, people will receive treatment until progression or death (this was confirmed by the clinical specialists; see section 4.3.6). See FAD section 4.3.18. The Committee did not consider that a plausible ICER had been presented in any of the economic models, but agreed that the least implausible analysis was the SHTAC scenario in which the treatment durations of dasatinib, high-dose imatinib and nilotinib were set to 10 years with overall survival estimates of 12.4–13.4 years. See FAD section 4.3.19

Consultee	Comment	Response
BMS	**Implications of not using a common surrogate outcome measure for OS and PFS** The lack of link between response rates and PFS means that altering the value for the chosen surrogate marker (Major Cytogenetic response – MCyR) has no impact on time in Progression Free Survival (PFS). In other words, regardless of whether the MCyR response rate is set to 0% or 100%, the amount of time spent on therapy in chronic phase ('CP on-treatment') remains constant (Table 5 [not reproduced here]).	The Assessment relies on the available evidence submitted to the Institute and that retrieved from the published literature by the assessment group. 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.
BMS	In the model, individuals are also assumed to spend time in chronic phase without any treatments ('CP off-treatment'), and the time spent in 'CP off-treatment' is set as the difference between Overall Survival (OS) and the amount of time spent in 'CP on-treatment'. As a result of this approach, even when a patient does not respond to the treatment (response rate is set to 0%), he/she can still remain in chronic phase without receiving any treatment – for as long as 6 years! This is not supported by clinical data and fundamentally undermines the clinical credibility of the model. As noted by PenTAG in their original report, there is a body of evidence supporting the hypothesis that a complete cytogenic response (CCyR) (defined as no Ph+ chromosomes in the bone marrow) is a predictor of both OS and PFS (Figure 1 [not reproduced here]). It is important to note that (a) both plots were derived from individuals in the same clinical trial (IRIS) and (b) other authors have identified the same relationship (Druker et al 2006, Roy et al 2006).	The Assessment relies on the available evidence submitted to the Institute and that retrieved from the published literature by the assessment group. 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.

Consultee	Comment	Response
BMS	BMS consider it extremely unlikely, given the proven causal link between CCyR and PFS, that no such link exists between MCyR (defined as ≤35% Ph+ chromosomes in the bone marrow). The PenTAG/SHTAC model is therefore fundamentally flawed in the way it represents the underlying disease, and as such the model cannot form the basis of rational decision making. In addition to the problem of 'no link between response rates and PFS', another issue with PenTAG/SHTAC model is the counter-intuitive and inconsistent methods used to model OS and PFS of different treatments. Given the Committee's desire to include face validity checks into the decision making process it is worthwhile reflecting, in abstract terms, on the nature of CML. In general, for people who do not have CML, the rate of death will increase over time by virtue of the natural aging process. For people with CML, because of natural disease progression, loss of response, intolerance to treatment, time, etc, the rate of death would also be expected to increase over time. This leads to the conclusion that an increasing rate of death should be observed in any parametric function used to model OS and PFS. The PenTAG approach used to model OS is based on a Weibull model with a gamma value (the parameter controlling the rate of change) being set to less than one. This means that the rate of death decreases over time. In terms of PFS, with the exception of high dose imatinib (HDI) where a Weibull function is used (and the fitted progression rate increases over time), all interventions are modelled using exponential distributions. This approach is flawed on three levels: 1. It assumes a constant rate of disease progression over time. That is, if a patient has had CML for 20 years, the rate of progression is the same as if the patient has had it for one day. 2. By using a different method to model high dose imatinib (HDI) and IFN, the result is that after a short period of time (from model cycle 10 onwards), patients on HDI have a higher rate of progression than those on interferon (IFN). 3. As a direct consequence of this mixed modelling approach, individuals in the IFN arm can expect to spend longer in the PFS state than alive (predicted undiscounted PFS state occupancy: 3.47 years, predicted overall survival: 3.41 years), see Table 6 [not reproduced here].	The Assessment relies on the available evidence submitted to the Institute and that retrieved from the published literature by the assessment group. 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.

Consultee	Comment	Response
BMS	*Paragraph 4.3.12: 'the SHTAC Assessment Group's base-case treatment durations did not reflect what the Committee had heard from the clinical specialists that in clinical practice, people will receive treatment until progression or death (see section 4.3.3). It noted, however, that two main scenario analyses as well as a sensitivity analysis of survival versus treatment duration had been developed to reflect this problem.'* **Comments**: BMS notes that, in order to address concerns relating to the implausibly low treatment durations for all TKI's, additional scenario analyses were performed by the SHTAC where these values were fixed to either 6.5 or 10 years. BMS would like to draw attention to the fact that 'treatment duration' is a model output and NOT a model input. As such, it cannot be directly altered. By altering treatment durations, it does not make the model more reflective of clinical practice and underlying disease, In order to demonstrate this, we have replicated the analyses using the information provided by the SHTAC group on 18th May 2011. Specifically, the SHTAC informed us that the additional scenario analyses were based on changing lambda values for PFS on the 'treatment duration' worksheet (cells BC12, BC14, BC16). When we used the SHTAC's method, and replicated the PFS and OS, it shows that in all cases PFS is higher than OS for a period of time (Figure 2 [not reproduced here]). BMS believe the method used to overcome the original issue causes more problems than it solves. Intuitively, in any oncology model, one of the key face validity tests is that there can never be more patients in the progression-free health state than there are currently alive (since this would result in a negative number of patients the post-progression health state). When the predicted OS and PFS curves for each intervention are plotted for an assumed treatment duration at 10 years, it is clear that this fundamental principle is violated. BMS would like to emphasise that this is not a minor issue. For patients on high dose imatinib (HDI), the number of individuals predicted to be in PFS is higher than those in OS for over 7 years. The corresponding values for nilotinib and dasatinib are 3.2 years and 1.2 years respectively. Once again, this suggests that the model analyses are fundamentally flawed, and as such it would be perverse of the Committee to use the model as the basis for rational decision making.	The Assessment relies on the available evidence submitted to the Institute and that retrieved from the published literature by the assessment group. 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.

Consultee	Comment	Response
BMS	*Paragraph 4.3.12: 'The Committee acknowledged that, based on the testimony from the clinical specialists, the assumption of similar treatment durations, which are continued for a considerable proportion of the responding person's lifetime, for dasatinib, high-dose imatinib and nilotinib is appropriate. Therefore the Committee considered that the* ***base-case analysis, in which the treatment durations of dasatinib, high-dose imatinib and nilotinib were set to 2.4–3.1 years*** *with overall survival of 12.4–13.4 years (with costs of £162,000–£173,000), was implausible.'* **Comments**: The AC misinterpreted the base-case analysis of the SHTAC model and believed that the treatment durations were not set to 2.4-3.1 years. In face, the treatment durations were derived from the fixed progression free survival in the model (SHTAC AR, page 75, and Table 40). In other words, SHTAC did not set treatment durations, but set the PFS. However, regardless what parameters were set in this model, any outputs will still not be plausible, bearing in mind the above analysis of the PenTAG model and SHTAC revised base-case and additional scenario analysis.	Comment noted. This section has been amended (accordingly, for clarity). See FAD section 4.3.19.
BMS	*Paragraph 4.3.12: 'The Committee did not consider that a most plausible ICER had been presented, but agreed that the least implausible analysis was the second scenario by SHTAC Assessment Group, in which the treatment durations of dasatinib, high-dose imatinib and nilotinib are set to 10 years with overall survivals of 12.4–13.4 years (and costs of £266,000–£300,000). It noted that in this analysis both high-dose imatinib and nilotinib are dominated by dasatinib, and that dasatinib compared with hydroxycarbamide resulted in an ICER of £43,800 per QALY gained.'* **Comments**: BMS would like to emphasise, there cannot be a 'most plausible" or 'least plausible" ICER. As we have demonstrated, any ICER that arises out of the PenTAG/SHTAC model is implausible. It would seem perverse of the Committee to arbitrarily choose one they consider the "best" (or the least worst) among a number of invalid propositions.	The Committee did not consider that a plausible ICER had been presented in any of the economic models, but agreed that the least implausible analysis was the SHTAC scenario in which the treatment durations of dasatinib, high-dose imatinib and nilotinib were set to 10 years with overall survival estimates of 12.4–13.4 years. See FAD section 4.3.19

Consultee	Comment	Response
BMS	*Paragraph 4.3.12: 'The SHTAC Assessment Group's sensitivity analysis showed that for nilotinib compared with hydroxycarbamide,* ***assuming an overall survival estimate of 7 years when compared with a treatment duration of 2 years of nilotinib****, resulted in ICERs higher than £40,000 per QALY gained…The Committee agreed that if it were acknowledged that treatment is continued for most of the person's lifetime, then the (SHTAC) ICERs would increase. The Committee concluded that the ICER of dasatinib compared with hydroxycarbamide would be higher than the SHTAC Assessment Group's figure of £43,800 per QALY gained'.* **Comments**: It is very clear that the Assessment Groups' model does not provide a robust argument. It does not explain how a patient who is being treated for 2 years will have 7 years survival if the treatment is continued until disease progression, death, and intolerance. This is not reflective of clinical practice. It clearly demonstrates that the problem of this model cannot be fixed by merely changing the outputs, such as treatment durations or PFS.	The Assessment relies on the available evidence submitted to the Institute and that retrieved from the published literature by the assessment group. 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.
BMS	*Paragraph 4.3.13: 'It also noted that, of the presented analyses, all suggested ICERs that were higher than those normally considered acceptable for the NHS, and were highly likely to be above the figures (£40,000 per QALY) suggested.'* **Comments**: Not all ICERs versus hydroxycarbamide have been considered (see the additional analysis conducted by BMS with regards to hydroxycarbamide presented above). The "least implausible" ICER chosen by the Committee is from the SHTAC additional scenario analysis, based on the economic model which BMS does not consider to be credible. Indeed, BMS consider that any ICER produced by this PenTAG/SHTAC model should be treated with utmost caution, regardless whether the ICER is above or below the conventional threshold.	Comment noted. The Committee concluded that the ICER from the Bristol-Myers Squibb's additional analysis was not reliable and could not form a suitable basis for a recommendation. See FAD 4.3.15

Consultee	Comment	Response
BMS	*Paragraph 4.3.16: 'However, the Committee agreed that **the available evidence on life extension was too weak and was not considered to be robust**. In addition, no data were presented for the interventions as used in clinical practice. The Committee concluded that dasatinib, high-dose imatinib and nilotinib do not fulfil the end-of-life criteria for people with CML in the accelerated and blast-crisis phases.'* **Comments**: The NICE guidance for 'Appraising life-extending, end-of-life treatments' states that end-of-life treatments must be 'robust and can be shown or reasonably inferred from either progression free survival or overall survival (taking account of trials in which cross-over has occurred and been accounted for in the effectiveness review).' Even in the absence of comparative data for accelerated and blast phase disease, it is difficult to appreciate why the AC considers a clinical trial with 2 year follow-up data is not robust (Apperley et al 2009, Kantarjian et al 2009, Cortes et al 2008). Since achieving and maintaining of response have been proven to be reliable predictors of longer term survival benefits (Marin et al 2008), the data were considered robust enough to form the basis of a decision by the European Commission to approve dasatinib in advanced CML following a positive opinion from the European Medicines Agency. Indeed, on this basis, one must query how many orphan and ultra-orphan medicines are likely to satisfy the AC's (unspecified) standards of robustness. Following the Servier case (Servier Laboratories Limited v National Institute for Health and Clinical Excellence (2010)) it is clear that NICE must place sufficient weight on evidence that is central to a party's case, particularly when such evidence has been held as being robust enough for marketing authorisation purposes. We also query whether the Institute's appraisal procedures are adequate in assessing the clinical and cost-effectiveness of ultra-orphan drugs.	The Committee noted that in the advanced stages of CML, life expectancy is generally less than 24 months. The Committee also agreed that this is a very small population, because fewer than 10% of all people with CML will present at this stage. However, the Committee agreed that the available evidence on life extension was too weak and was not considered to be robust. In addition, no data were presented for the interventions as used in clinical practice. See FAD section 4.3.29

Consultee	Comment	Response
BMS	*Paragraph 4: 'As a result of comments received during consultation,* ***it was agreed to combine an appraisal of the three technologies, dasatinib, high-dose imatinib (600 mg and 800 mg) and nilotinib****, to establish their comparative incremental clinical effectiveness and cost effectiveness. The following actions were implemented'* **Comments:** BMS has serious concerns about the procedures which were followed, and believes these procedures to be unfair, perverse, and outside the scope of NICE's jurisdiction. These concerns can be summarised as follows: In place of HDI as a comparator, the AC chose to use hydroxycarbamide, despite it representing obsolete clinical practice, as made clear by clinical expert submissions during the course of this appraisal. In doing so, the AC has shifted its review from an area where there is robust - albeit limited - evidence (i.e., a randomised trial of dasatinib compared with HDI) to an area for which there is, inevitably, almost no evidence and where evidence is unlikely ever to arise. Any attempt to set up clinical trials in order to generate data comparing dasatinib or nilotinib to hydroxycarbamide would be unethical. This is because the Declaration of Helsinki requires that clinical research involving any 'new intervention' must be conducted against the 'best current proven intervention' and that the use of other interventions, placebo or no therapy is only possible where 'no current proven intervention exists'. The 1996 version of the Declaration, which applies to all pharmaceutical clinical research within the EU, provides that '[i]n any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.' These issues are particularly relevant in the oncology space. By selecting hydroxycarbamide as the most appropriate comparator, the AC is moving from a position where it has meaningful comparative data to a position that is likely to remain evidence free.	The Assessment relies on the available evidence submitted to the Institute and that retrieved from the published literature by the assessment group. The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care, and that for many people hydroxycarbamide or interferon alfa are considered to be little better than best supportive care. It also heard that bone marrow stem cell transplantation could be used, although it carries high risks and is restricted to fit, younger people. See FAD section 4.3.3
BMS	The AC states that 'it was agreed…'. To be clear, BMS did not "agree" to this. In our previous responses to the TAR and the ACD, we have pointed out that HDI should be the comparator, and not be grouped together with dasatinib and nilotinib as interventions. The underlying basis for this decision is unclear and lacks transparency.	This information was included in the ACD, but has been amended following comments from consultees.

Consultee	Comment	Response
BMS	*Paragraph 4.3.3: 'The Committee heard from the clinical specialists that high-dose imatinib followed by dasatinib and nilotinib are in widespread use and are a major advance over the therapies previously available: that is, interferon and hydroxycarbamide.* ***Although stem cell transplantation can be curative, it carries high risks and has restricted applicability (to fit, younger patients)'.*** *Paragraph 4.3.3: 'The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people with CML would most commonly receive treatment with hydroxycarbamide or stem cell transplantation, if possible…'* *Paragraph 4.2.24: 'The cost of stem cell transplantation was taken from the Bristol-Myers Squibb submission and includes the additional cost of £80,000 for the stem cell transplant'.* **Comments**: The Committee is aware that dasatinib (and nilotinib) are highly effective TKIs and have become integrated as standard therapies into the accepted clinical armamentarium for treating CML. Compared with the alternative therapies (high dose imatinib and hydroxycarbamide), dasatinib (and nilotinib) have improved the quality and quantity of life of the CML patient. This position is reinforced by the ELN 2009 Guidelines (Baccarani et al 2009) which are accepted globally. Indeed, the advice received by the Committee from the clinical specialists clearly supports the use of 2nd generation TKIs in patients who are resistant to imatinib.	The Committee concluded that it is clear that dasatinib, high-dose imatinib and nilotinib provide clinical benefit for people with imatinib-resistant CML. However, the Committee agreed that the limited evidence base means that the magnitude of the benefit is uncertain. See FAD section 4.3.9
BMS	When one considers the extent to which CML treatment has improved and progressed since the introduction of TKIs, it seems perverse of the Committee to consider and evaluate agents (as direct comparators to dasatinib and imatinib) that are recognised by the clinical community as being significantly less effective and less well tolerated, and indeed which are not considered viable treatment options.	The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care. The Committee also heard from the clinical specialists that bone marrow stem cell transplantation could be used. The Committee concluded that any one of these treatments could be considered a comparator with high-dose imatinib, nilotinib or dasatinib. See FAD section 4.3.3

Consultee	Comment	Response
BMS	We would like to alert the Committee to the negative clinical and financial consequences of a negative recommendation. It is recognised by the Committee that high dose imatinib, followed by dasatinib and nilotinib are in already widespread use, and are a major advance over the therapies previously available (i.e. interferon and hydroxycarbamide). As a consequence of the preliminary decision the only credible option for patients is that of BMSCT. The Committee also recognise that although BMSCT can be curative, it carries high risks and has restricted applicability (Paragraph 4.3.2) being limited in practice to Caucasian patients, typically under 60 years of age, with no co-morbidities.	Comment noted. The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care. The Committee also heard from the clinical specialists that bone marrow stem cell transplantation could be used. See FAD section 4.3.3
BMS	The preliminary negative decision therefore raises fundamental ethical, discrimination and human right issues in that it prevents doctors from prescribing, and patients from having access to, life-saving treatment. It is discriminatory to make a recommendation that forecloses meaningful treatment to the elderly and patients from ethnic minorities. The outcome also seems disproportionate when one considers the ultra-orphan nature of the disease. It is also worth noting that the more substantial the interference with human rights (e.g., the right not to be discriminated against, the right to life etc.), the more is required by way of justification before the Appraisal Committee should accept that its preliminary decision not to recommend dasatinib is a reasonable rather than a perverse one.	The Committee noted the argument that if dasatinib, high-dose imatinib or nilotinib are not recommended for the treatment of imatinib-resistant CML and that this could raise issues in relation to race, age (the elderly), and comorbidities. However, the Committee concluded that allowing for clinical decisions relating to a range of possible treatments based on individual assessment of risk and benefit does not limit access to the technology for any specific protected group compared with other people. See FAD section 4.3.31
BMS	In addition to the high initial costs (£80,000 to be the lower end of estimate) and the high ongoing costs (estimated to be £2400 per month), there will be a need to upgrade the current NHS infra The Committee noted the argument that if dasatinib, high-dose imatinib or nilotinib are not recommended for the treatment of imatinib-resistant CML and that this could raise issues in relation to race, age (the elderly), and comorbidities. However, the Committee concluded that allowing for clinical decisions relating to a range of possible treatments based on individual assessment of risk and benefit does not limit access to the technology for any specific protected group compared with other people. See FAD section 4.3.31-structure in order to deliver BMSCT to these patients. With growing need for BMSCT as a result of the unavailability of dasatinib and nilotinib, there will be a need for significant investment, which is highly unlikely to offset the costs of dasatinib and nilotinib. On this basis, a negative recommendation seems perverse, discriminatory and inequitable.	The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care. The Committee also heard from the clinical specialists that bone marrow stem cell transplantation could be used. See FAD section 4.3.3.

Consultee	Comment	Response
Novartis	The decision not to recommend nilotinib for resistant chronic myeloid leukaemia (CML) patients is not justified based on the available evidence and we do not consider that all of the relevant evidence has been taken into account. In addition, the summaries of clinical and cost-effectiveness do not represent reasonable interpretations of the evidence. We do not believe that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. Our comments are presented as follows: 1. Summary of main concerns 2. Hydroxycarbamide (HU) is not the appropriate comparator in this setting 3. High dose imatinib is the appropriate comparator in this setting 4. Base case treatment duration of 10 years is inappropriate 5. Inappropriate assumptions in the assessment group model 6. Errors in the ACD 7. The provisional recommendations are not a suitable basis for guidance 8. Conclusion Appendix 1 Additional scenario analyses [not reproduced here] Patient Access Scheme submission template [not reproduced here] Despite the fact that nilotinib is cost-effective versus high-dose imatinib and will be cost-effective versus HU if our concerns are addressed, we want to ensure that imatinib-resistant CML patients will not be condemned to inferior treatment if our concerns are ignored. We have therefore offered a patient access scheme and details of the impact of this scheme are included in the analyses in Appendix 1 and the Patient Access Scheme submission template.	The Committee noted that the manufacturer argued that a number of further changes to the SHTAC analysis should be made. The Committee agreed that some of these adjustments were plausible, but not all. See FAD section 4.3.22. The Committee noted that the manufacturer of nilotinib had agreed a patient access scheme with the Department of Health. The Committee recommended the use of nilotinib for the treatment of adults with chronic and accelerated phase CML that is resistant to standard-dose imatinib or who have imatinib intolerance, if the manufacturer makes nilotinib available with the discount agreed as part of the patient access scheme. See FAD section 4.3.21–4.3.23
Novartis	1. **Summary of main concerns** The decision not to recommend nilotinib for the treatment of imatinib-resistant CML denies patients access to one of the only effective treatments for this condition (other than stem cell transplantation (SCT) which is suitable for only a very small population of patients). If untreated, these patients are likely to have poor prognosis and limited life-expectancy. Nilotinib represents a step-change in the benefits provided by imatinib and this innovative product is an important development in the treatment of CML. As acknowledged in the ACD, nilotinib is clinically effective for imatinib-resistant patients and fulfils an area of unmet need due to the limited treatment options available to patients in this setting. Novartis' main concerns regarding the preliminary recommendations are summarised below.	The Committee considered that the development of dasatinib and nilotinib was not a further major innovation. The Committee did not identify any potential significant and substantial health-related benefits that had not been included in the economic models. See FAD section 4.3.30

Consultee	Comment	Response
Novartis	1.1. The conclusion that hydroxycarbamide (hydroxyurea, HU) is the main comparator is perverse in the light of expert clinical opinion and does not reflect standard clinical practice, past or present. 1.2. All the evidence shows that high-dose (HD) imatinib would be the standard of care in the absence of nilotinib and dasatinib. 1.3. The use of treatment duration of 10 years is not supported by expert clinical opinion. The average treatment duration has been estimated by clinical experts to be approximately 6.6 years. 1.4. The assumptions in the Assessment Group (AG) model do not reflect either clinical opinion or available evidence • Mean dose intensity of xx% from the pivotal nilotinib trial should be taken into account in the analysis, as also recommended by the previous independent AG (PenTAG) • Progression-free survival (PFS) should be linked to major cytogenetic response (MCyR). The AG model instead links overall survival (OS) to MCyR. • The life years gained for nilotinib and dasatinib should be assumed to be the same given that the treatment durations were assumed to be the same. • The utility of HU has been overestimated: it was assumed to be the same as that of nilotinib and even higher than that of SCT, a potentially curative treatment option. • The OS gain on HU treatment has been overestimated as it was based on data from the first line setting. OS on HU in the second-line setting is expected to be worse that in the first line setting.	The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care. The Committee also heard from the clinical specialists that bone marrow stem cell transplantation could be used. See FAD section 4.3.3. The Committee noted its earlier conclusions that more than 50% of people receiving these treatments are likely to do so for more than 10 years, with many people receiving them until death. See FAD section 4.3.19. The Committee noted that the manufacturer argued that a number of further changes to the SHTAC analysis should be made. The Committee agreed that some of these adjustments were plausible, but not all. See FAD section 4.3.22.

Consultee	Comment	Response
Novartis	Novartis conducted additional analyses using the AG model to address these concerns, taking into account the application of a patient access scheme (PAS). The additional analyses comparing nilotinib with HU (an artificial comparator in this setting) resulted in an ICER of £xx,xxx per QALY gained for 6.5 years treatment duration. When the more conservative assumption of 10 years treatment duration is used, the ICER is £xx,xxx per QALY gained. These updated results show that nilotinib is a cost-effective treatment option for imatinib-resistant patients, even when compared with an inappropriate comparator in this setting. Nilotinib is highly cost-effective (i.e. cheaper and more effective) when HU is excluded and is compared with the standard of care (HD imatinib) in all the economic models submitted to NICE. Nilotinib is a necessary treatment with important benefits for patients with chronic phase CML. Nilotinib has been found to be both clinically and cost-effective based on the updated analysis using the independent Assessment Group model. In view of the small number of patients likely to be eligible for treatment, the budget impact of a positive recommendation for nilotinib is likely to be relative low. Our estimates suggest that there will be 21 new chronic phase resistant patients per year in England and Wales, with an associated budget impact of around £500K in year 1 rising to £1.3m in year 5. Furthermore nilotinib is already routinely prescribed and funded in most geographies in England and, under the AWMSG process, dasatinib is also already funded in Wales.	The Committee accepted that with the patient access scheme in place and the use of nilotinib for the treatment of imatinib-resistant CML could be regarded as a cost-effective use of NHS resources. See FAD section 4.3.23 Comment noted.
Novartis	**2. HU is not the appropriate comparator in this setting** **2.1 Introduction** The choice of comparator is of fundamental importance in this and every appraisal. Recommendations based on a comparison with a treatment that does not reflect current use and is associated with no evidence of benefit does not constitute useful guidance to the NHS. As explained in responses to the draft scope, HU is not and has never been used routinely for the treatment of imatinib-resistant CML and therefore is not the treatment that would be displaced should the second-generation TKIs be recommended for use in NHS patients. Accordingly, the assessment of cost effectiveness of nilotinib compared with HU is of limited relevance to the NHS and the clinical community because, in clinical practice, patients who become resistant to imatinib are rarely treated with HU unless there are specific reasons not to receive nilotinib e.g. pregnancy. HU is thus an inappropriate comparator in this setting with no credible evidence on its use nor likely benefit in this setting. A comparison with HU does not provide a proper basis for guidance to the NHS in relation to the use of nilotinib for the treatment of adults with imatinib-resistant chronic phase CML.	The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care. The Committee also heard from the clinical specialists that bone marrow stem cell transplantation could be used. See FAD section 4.3.3.

Consultee	Comment	Response
Novartis	**2.2 Clinical expert evidence** The inclusion of HU as the principal comparator in this appraisal ignores clinical expert opinion and clinical guidelines, all of which show that HU is not routinely used or recommended to treat all patients who are imatinib-resistant. Clinical experts have consistently stated that, in the absence of nilotinib and dasatinib, standard clinical practice would be to dose escalate those patients who become resistant to 400mg imatinib to HD imatinib. For example the Royal College of Physicians stated in their response to the assessment report (AR) that: *"If neither nilotinib nor dasatinib were available, most UK clinicians would opt for high dose imatinib (or stem cell transplantation in the ~20% of patients in whom this is feasible), and it therefore is logical (and clinically relevant) to compare the second generation agents to high dose imatinib."* The evidence shows that HU will only be used in specific patient groups unable to receive TKI treatment, otherwise patients will continue on 400mg imatinib or dose escalate to HD imatinib, depending on the level of loss of response. In these circumstances Novartis believes it is unreasonable for NICE to base guidance for the treatment patients who develop resistance to standard dose imatinib on a comparison with HU because the use of HU in this indication is not supported by evidence and is not reflective of clinical practice and opinion. If, contrary to our view, NICE does have evidence indicating that HU is used in standard practice in this indication (save in patients who are unable to receive TKIs), we would ask that this evidence is identified and disclosed to us at this stage in the appraisal.	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. The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care. The Committee also heard from the clinical specialists that bone marrow stem cell transplantation could be used. See FAD section 4.3.3.

Consultee	Comment	Response
Novartis	**2.3 Appropriate subgroup for HU** Novartis is aware of no evidence for HU providing benefit in patients with imatinib-resistant chronic phase CML. It is therefore viewed as consistent with the provision of best supportive care (BSC) and reserved for a very specific group of patients who are ineligible for TKIs e.g. due to pregnancy, or as a holding dose before their treatment options have been decided. The effect of the current preliminary recommendations in the ACD is therefore to exclude nilotinib, a treatment with demonstrated effectiveness and to restrict patients to use of HU – a treatment that will result in little or no benefit in this setting. The ELN recommendations endorse this position that treatment with HU is appropriate for only a very small subgroup of patients. The guidelines state that HU may still be used only for a short period of time and the only place for HU is "in a patient in whom a TKI is not advised".[1] The same view was expressed by the clinical experts for this appraisal (Professors Apperley and Clark). The decision by the Appraisal Committee to ignore the fact that HU is not a universal comparator in this setting is perverse in light of the evidence available on the use of TKIs in clinical practice. The Committee should consider the comparison of HU and SCT as specific to a very small group of patients with CML who are unable to receive nilotinib or other TKIs. Current practice is that patients would be offered nilotinib, dasatinib or HD imatinib if they are not eligible for stem cell transplant and therefore the analysis should be a comparison of the TKIs excluding HU in this setting.	The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care, and that for many people hydroxycarbamide or interferon alfa are considered to be little better than best supportive care. The Committee also heard from the clinical specialists that bone marrow stem cell transplantation could be used, although it carries high risks and is restricted to fit, younger people. The Committee concluded that any one of these treatments could be considered a comparator with high-dose imatinib, nilotinib or dasatinib. See FAD section 4.3.3.

Consultee	Comment	Response
Novartis	**2.4 Patients are not switched to HU when they become resistant to 400 mg imatinib** The basis of the current assessment suggests that, when patients on 400 mg imatinib become resistant, they should all be switched to HU. However, in the absence of nilotinib, dasatinib and HD imatinib, some patients could still benefit from continuing 400 mg imatinib, depending on the level of resistance. Patients defined as resistant because of loss of complete cytogenetic response could (in the absence of nilotinib, dasatinib and HD imatinib) continue on 400mg imatinib because they might benefit from further imatinib treatment. Clinical experts have stated that when patients lose complete cytogenetic response, in this hypothetical situation of no TKIs, they would continue on 400mg imatinib. It is only when patients lose complete haematological response that clinicians might consider switching them to HU (a treatment option considered to be BSC) because, at that point, there would be no additional benefit from imatinib treatment. The current analysis in the ACD on which the preliminary decision is based implies that when patients become resistant to 400mg imatinib they should all be switched to HU. Novartis believes that this is both inaccurate and does not reflect clinical practice because, depending on the level of resistance, they might continue on 400mg imatinib even when HD imatinib is assumed to be unavailable to patients.	The clinical specialists stated that in approximately 60% of people there is a good response to standard-dose imatinib, and that these people will continue to receive the treatment for life and have a normal life expectancy. The Committee recognised the innovative nature and major change in the treatment of CML that imatinib had provided. However, it heard that 40% of people develop intolerance or resistance to standard-dose imatinib. See FAD section 4.3.2. The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care, and that for many people hydroxycarbamide or interferon alfa are considered to be little better than best supportive care. The Committee also heard from the clinical specialists that bone marrow stem cell transplantation could be used, although it carries high risks and is restricted to fit, younger people. The Committee concluded that any one of these treatments could be considered a comparator with high-dose imatinib, nilotinib or dasatinib. See FAD section 4.3.3

Consultee	Comment	Response
Novartis	**3. HD imatinib is the appropriate comparator in this setting** **3.1 NICE's own guidelines support that HD imatinib should be the reference case comparator** The NICE "Guide to the Methods of Technology Appraisal", dated June 2008 states that, for the reference case, comparators should be "*Therapies routinely used in the NHS, including technologies regarded as current best practice*". There is overwhelming evidence showing that current standard practice is to dose escalate normal dose imatinib or switch to nilotinib or dasatinib and not switch patients to HU. All the evidence we have submitted showing that a standard of care in this setting is HD imatinib has been completely ignored. We therefore emphasise as per our responses to the Assessment Report that the decision of interest to the clinical community is whether nilotinib, dasatinib and HD imatinib are cost-effective when compared head to head with each other. Whether nilotinib and dasatinib are cost-effective compared with HU is of limited relevance to the NHS and the clinical community because, in clinical practice, patients who become resistant to imatinib are rarely treated with HU. Imatinib resistance did not, and could not, exist prior to the availability of imatinib. Once imatinib resistance emerged, dose escalation became standard clinical practice. The consultees, including clinical experts, share the same view that HD imatinib is the comparator in this setting. We note that clinical experts from NCRI, RCP, RCR, ACP and JCCO, whose views were submitted as part of their comments on the draft scope, agreed that HD imatinib, nilotinib or dasatinib are the standards of care in clinical practice. Evidence from written expert personal statements submitted during the original multiple technology appraisal, that considered both imatinib-resistant and imatinib-intolerant patients, also supports this view.	High-dose imatinib is included in this appraisal as an intervention rather than a comparator. See scope The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care, and that for many people hydroxycarbamide or interferon alfa are considered to be little better than best supportive care. The Committee also heard from the clinical specialists that bone marrow stem cell transplantation could be used, although it carries high risks and is restricted to fit, younger people. The Committee concluded that any one of these treatments could be considered a comparator with high-dose imatinib, nilotinib or dasatinib. See FAD section 4.3.3
Novartis	**3.2 Clinical guidelines confirm that HD imatinib would be standard of care for resistant patients in the absence of second generation TKIs** The 2006 European Leukaemia Net Recommendations which were current prior to the availability of dasatinib and nilotinib state "*…the first choice of treatment in patients with imatinib resistance is allogeneic stem cell transplantation. If this is not possible dose escalation of imatinib to 600 or 800mg daily is an option, provided that 400mg daily is tolerated and that resistance to imatinib is not associated with a BCR-ABL mutation with a high level of insensitivity to imatinib.*" These clinical recommendations provide further evidence that, in the absence of the availability of nilotinib and dasatinib, high-dose imatinib would represent the standard of care for resistant patients. The other alternative, allogeneic SCT, is only suitable for a very small population of patients because they need an appropriate donor and also must be healthy enough for the transplant.	High-dose imatinib is included in this appraisal as an intervention rather than a comparator.

Consultee	Comment	Response
Novartis	**3.3 UK practice confirms the use of HD imatinib in the NHS** Results from an analysis of UK patients who participated in an expanded access trial for nilotinib, prior to nilotinib becoming licensed, confirm that high-dose imatinib is used within the NHS for the treatment of resistant chronic phase CML. In this trial, 91% (41/45) of patients with imatinib-resistant chronic phase CML were treated with doses of imatinib at or above 600mg per day prior to entering the trial and receiving nilotinib. Cancer Network guidelines for the treatment of imatinib-resistant CML routinely include the option of using HD imatinib. Once again, this confirms the routine use of HD imatinib in this setting within the NHS. The results from a market research study[2] demonstrate that in the absence of second generation TKIs (i.e. nilotinib and dasatinib), 100% of the 65 responding clinicians would consider high-dose imatinib to be the treatment of choice for chronic phase resistant patients and therefore high-dose imatinib would be used routinely in the NHS. The analysis in this setting should therefore be a comparison of the TKIs excluding HU. In the face of all this evidence, the Appraisal Committee is required to explain why it has rejected HD imatinib as the appropriate comparator for the reference case assessment of nilotinib and why this comparison has not been used as the basis of guidance to the NHS.	High-dose imatinib is included in this appraisal as an intervention rather than a comparator.

Consultee	Comment	Response
Novartis	**4. Base case treatment duration of 10 years is inappropriate** The treatment duration of 10 years relied upon by the Appraisal Committee is neither reflective of clinical expert opinion nor is it a reasonable interpretation of the evidence. Clinical experts (see response dated 22 March 2011 from the RCP to the Assessment Report) have estimated that the average survival for responders and non-responders to be 6.6 years. This estimation is based on the following: • Average age at treatment initiation with nilotinib is 60 years. • 40% of these patients will achieve complete cytogenetic response and survive for about 15 years. Treatment with nilotinib will therefore continue for 15 years. • 60% of patients will be non-responders whose treatment will be withdrawn after 1 year. • Average treatment duration will therefore be 6.6 years (40% of 15 years (6) plus 60% of 1 year (0.6)). The results of a study conducted in Scotland[3] support the view that CML patients will not stay on treatment for as long as 10 years as the Appraisal Committee has concluded. The study collected data on tolerability and clinical outcome of patients treated with second generation TKI following discontinuation of imatinib therapy because of adverse events or failed response. The definition of event free survival in the study included patients discontinuing imatinib because of toxicity or failed response according to ELN recommendations. The results of the study showed that only about 50% of patients resistant to normal dose imatinib were still event free at approximately 18 months. This study therefore partly confirms the clinical expert conclusions that not all patients will respond to a second generation TKIs for a very long time and thus the average survival on second line therapy cannot be as high as 10 years. For the average survival to be as high as 10 years the overall survival of all CML patients from diagnosis (using the same estimates for responders and non-responders) should be at least 25 years. This implies that all CML patients will survive to the age of 85 years at least, an unrealistic assumption given the starting age for treatment of about 60 years, the effects of natural mortality on life expectancy and the impact of the mortality of non-responders on average survival.	The Committee heard from the clinical specialists that in more than 50% of people with imatinib-resistant CML treated with dasatinib or nilotinib, there is a good response to treatment and that this response is usually as good as the initial response to standard-dose imatinib. The clinical specialists expected that these people would receive dasatinib or nilotinib treatment for the rest of their lives, and possibly have a nearly normal life expectancy (that is, at least 10 more years).See FAD section 4.3.6 The Committee agreed that treatment duration could be less than 10 years but the estimate of 6.5 years, which was based on treatment being withdrawn in all people who did not have a complete cytogenetic response, was not plausible. See FAD section 4.3.22

Consultee	Comment	Response
Novartis	It should also be noted that nilotinib is offered as a second line treatment option in this setting after failure of imatinib. It is illogical to expect better survival and therefore a longer treatment duration in the second line setting than the first line setting. Based on data available and our estimations of treatment duration in the first line setting, 10 years as an average estimate of survival and therefore duration of treatment for the second line setting would seem excessive. Given that the average age of CML patients is approximately 60 years, the current assumption implies that survival of CML patients in the first line setting will be shorter than in second line given the life expectancy of 85 years. This is contrary to clinical opinion and the evidence suggesting that patients would benefit more and therefore survive longer in the first line setting compared with the second line setting. It is therefore clear that the 10 years treatment duration is an overestimate of the likely time patients will be treated in the second line setting. Novartis therefore believes that the 6.6 years is a more realistic treatment duration for CML patients in the second line setting and not 10 years. This is consistent with the view expressed by the RCP as referred to above. The decision to consider 10 years as base line treatment duration and conclude that it is conservative does not therefore reflect the available evidence from studies investigating survival of CML patients and expert clinical opinion. We would ask the Appraisal Committee to explain its reliance on the 10 year figure and why it has seemingly rejected the evidence referenced above indicating that a shorter period is more plausible. In Novartis' view, the 10 years treatment duration is less plausible and should be considered as the upper bound of the treatment duration that might be considered in this second line setting. The results from a more realistic treatment duration of 6.5 years should also be considered and taken into account by the Committee as this is closer to the treatment duration estimated by clinical experts.	The Committee agreed that treatment duration could be less than 10 years but the estimate of 6.5 years, which was based on treatment being withdrawn in all people who did not have a complete cytogenetic response, was not plausible. See FAD section 4.3.22.

Consultee	Comment	Response
Novartis	**5. Inappropriate assumptions in the assessment group model** The Committee concluded that the least implausible ICER was £43,800 per QALY gained based on the additional analysis from SHTAC. Novartis maintains that flaws in the structure of the SHTAC model (updated PenTAG model) cause underestimates of the potential benefits of nilotinib resulting in a higher ICER for nilotinib. In addition the SHTAC analysis did not take into account several factors that lead to an improvement in the ICER for nilotinib. These issues are discussed in detail below. When the concerns discussed in this section are taken into account in the AG model and a patient access scheme is considered, the ICER for nilotinib compared with HU for 6.5 years treatment is reduced to £xx,xxx per QALY gained. When the less plausible assumption of 10 years treatment duration is assumed, the ICER is reduced to £xx,xxx per QALY gained. The ICER results with and without the PAS can be summarised as follows: [Table not reproduced here]	The Committee considered the additional analyses submitted by Novartis, see FAD 4.3.21–4.3.23
Novartis	**5.1 Nilotinib dose intensity** The SHTAC analysis did not take into account the impact of dose intensity on the cost effectiveness of nilotinib. In the model that is largely unchanged from the original PenTAG model, the dose intensity of nilotinib is assumed to be 100% when the evidence from the pivotal nilotinib trial showed that the mean dose intensity for imatinib resistant patients was xx%. The original PenTAG analysis acknowledged that dose intensity was an important consideration and suggested that, for the economic model, the mean is required, not the median dose intensity (page 172 of PenTAG AR, 10 August 2009). In the SHTAC analysis, dose intensity for HD imatinib was considered to be 76%, based on the lower bound of the mean in the Jabbour publication. However the dose intensity for nilotinib wa [not reproduced here]s based on the median dose intensity that is far higher than the mean. Novartis concurs with PenTAG's conclusions that the mean should be used instead and the mean dose intensity from the pivotal nilotinib trial has been used in the updated Novartis analysis (see appendix 1).	The Committee considered the additional analyses submitted by Novartis, including the dose intensity adjustment, see FAD 4.3.21–4.3.23 The Committee accepted that with the patient access scheme in place and its earlier conclusion that some of the adjustments to the model were plausible, the use of nilotinib for the treatment of imatinib-resistant CML could be regarded as a cost-effective use of NHS resources.

Consultee	Comment	Response
Novartis	**5.2 No link between PFS and major cytogenetic response (MCyR)** The SHTAC model did not address the fundamental concern that the MCyR rates were not linked to progression-free survival (PFS) in the model. PFS is used to estimate the treatment duration in the model and the evidence shows that a higher response is associated with better PFS which in turn leads to better survival. It seems reasonable to link PFS with MCyR because PFS reflects both the level of response and is also used to estimate the treatment duration. Instead, the current model structure assumes that MCyR is linked to OS and not PFS. This approach by SHTAC leads to an underestimate of the benefits of nilotinib in this setting. Novartis cannot address this limitation because it requires a structural change to the AG model.	The Committee noted that the PenTAG model did not link treatment duration with overall survival and that some of the results were not plausible. In particular, it noted that the estimated overall survival for interferon alfa was implausible and the treatment duration for people receiving nilotinib was lower than would be seen in clinical practice, given the estimated overall survival. See FAD section 4.3.17 The Committee understood that the model updated by SHTAC attempted to correct PenTAG's overestimate of survival on interferon alfa and the discrepancy between the nilotinib and dasatinib treatment durations, but the SHTAC base-case treatment durations still did not reflect the fact that in clinical practice, people will receive treatment until progression or death (this was confirmed by the clinical specialists; see section 4.3.6).See FAD section 4.3.18

Consultee	Comment	Response
Novartis	**5.3 The treatment duration for nilotinib and dasatinib of 10 years is not supported by any data** The initial analysis that was conducted by both PenTAG and SHTAC on treatment duration was based on PFS data and discontinuation rates from the pivotal trials of both nilotinib and dasatinib. These data showed that dasatinib had lower discontinuation rates when compared with nilotinib resulting in higher treatments costs for the former when the discontinuation rates were applied in the model. In the updated SHTAC analysis, the lambda values for PFS have been adjusted to reflect 6.5 years and 10 years treatment durations. However the predicted PFS curves are not extrapolations based on any data as is expected in economic modelling. To illustrate this point Novartis has extracted the PFS curves from the AG model. Figure 1 [not reproduced here]shows the fitted PFS for the original SHTAC base case analysis. Figure 2 shows the PFS curves estimating the most optimistic assumption of 10 year treatment duration compared with trial data. As can be seen in Figure 1 [not reproduced here] above, the original SHTAC base case analysis is based on extrapolations from the data. However the 10 years treatment duration PFS is not based on any fit to the data as can be seen in Figure 2. This is a limitation in the analysis because the type of curve fitted is determined by the type of data available. In the absence of data as in Figure 2 [not reproduced here], it is hard to justify such a PFS fit in the model. This issue is compounded further by the fact that the model does not link the PFS to OS as discussed earlier. All this adds to the uncertainty in the model and it is likely that the model is underestimating the benefits of nilotinib by not linking PFS to OS.	The Committee heard from the clinical specialists that in more than 50% of people with imatinib-resistant CML treated with dasatinib or nilotinib, there is a good response to treatment and that this response is usually as good as the initial response to standard-dose imatinib. The clinical specialists expected that these people would receive dasatinib or nilotinib treatment for the rest of their lives, and possibly have a nearly normal life expectancy (that is, at least 10 more years).See FAD section 4.3.6. The Committee did not consider that a plausible ICER had been presented in any of the economic models, but agreed that the least implausible analysis was the SHTAC scenario in which the treatment durations of dasatinib, high-dose imatinib and nilotinib were set to 10 years with overall survival estimates of 12.4–13.4 years. See FAD section 4.3.19. The Committee agreed that treatment duration could be less than 10 years but the estimate of 6.5 years, which was based on treatment being withdrawn in all people who did not have a complete cytogenetic response, was not plausible. See FAD section 4.3.22

Consultee	Comment	Response
Novartis	**5.4 The survival benefit for nilotinib assumed in the model should be the same as that of dasatinib** Although the Committee accepts clinical opinion that nilotinib and dasatinib are broadly the same with respect to their benefits, they have assumed a longer overall survival and hence a higher QALY gain for dasatinib based on the dasatinib MCyR. If the treatment duration is assumed to be the same (an unsubstantiated assumption) then it is logical to also assume the same survival benefit for the two drugs. In the base case SHTAC analysis, dasatinib's treatment duration was based on data from the pivotal dasatinib trial and this also translated into a higher benefit through the MCyR. In the additional scenario analysis, the Committee has assumed equal treatment durations based on no data, suggesting that the survival benefit should also be assumed to be the same (in the absence of data). Novartis views the approach by the Committee to be unfair and suggests that the same survival gain for nilotinib and dasatinib is assumed. However the above not withstanding, if survival for nilotinib is to be based on observed MCyR rates from the pivotal trials, then the most up to date data should be used i.e. a MCyR of 56% for nilotinib. This estimate was noted in the SHTAC AR but was not applied in either the SHTAC's base case or updated scenario analyses. When this rate is applied in the model, the life years gained are 13.25 compared to life years gained of 13.40 for dasatinib. This confirms our view (consistent with that of clinical experts and the Appraisal Committee) that the efficacy of the two drugs should be treated as the same. To ensure fairness, Novartis suggests that the same life years, and hence same QALYs gained, for the two drugs be used in their considerations. With this in mind, the conclusion in paragraph 4.3.12 of the ACD that dasatinib dominates nilotinib is incorrect. Novartis has conducted updated analysis assuming the same survival gain as dasatinib (see appendix 1 [not reproduced here]).	The Committee considered the additional analyses submitted by Novartis, including the the assumption of survival benefit equal to that of dasatinib, see FAD 4.3.22 The Committee also agreed that there was no good evidence to distinguish between dasatinib and nilotinib; a conclusion also supported by the clinical specialists. See FAD section 4.3.9.

Consultee	Comment	Response
Novartis	**5.5 Utility of HU overestimated** The utility of HU in the chronic phase (CP) has been assumed to be the same as that of the second generation TKIs - that is 0.85. Clinical opinion (as discussed earlier) suggested that HU does not lead to any improvement in either PFS or OS. For HU to have the same utility as nilotinib which was specifically designed to delay disease progression and therefore lead to better survival is perverse and overestimates the benefit of HU in this setting. It is significant that Professor Clark has suggested that patients with chronic phase CML treated with nilotinib have a near normal quality of life. Patients who receive SCT, a potentially curative treatment option, have a utility of 0.71 in the model, implying that a patient on HU will do better than a patient who has undergone a successful transplant. This is both counterintuitive and inaccurate and is a clear indication that the utility benefits of HU have been exaggerated. There are no published utility values for HU in this setting but given the limited benefits HU confers on patients based on clinical expert opinion, it could be argued that the utility of HU in CP could be between the utility of SCT and that of nilotinib. Novartis has therefore decided to consider the average of utility of SCT and nilotinib. This gives an average utility of 0.78 and this value is applied in the updated analysis (see appendix 1 [not reproduced here]).	The Committee did not agree with Novartis that the utility value for people treated with hydroxycarbamide should be lower for the same health states achieved by other treatments. It accepted that health state durations were shorter with hydroxycarbamide but thought that this should not be compounded by utility value adjustments. See FAD section 4.3.22.

Consultee	Comment	Response
Novartis	**5.6 OS benefit for HU overestimated** The SHTAC analysis that informs the Committee's decision utilises the survival estimates of HU from the Novartis model. The survival estimates of HU are very likely to be overestimated as in the absence of any other HU data, Novartis resorted to using first line HU efficacy data.. Again this reflects the fact that HU is not used and therefore there is no evidence on its efficacy in this setting. Novartis convened an advisory board meeting to gather clinical opinion on the efficacy of the artificial comparators such as HU. The clinical experts at the advisory board suggested that in the absence of any data on the use of HU in the second line setting, the only evidence (albeit with many limitations) will be the first line HU data from the various published trials of patients with a high Sokal risk score. The clinical experts explained that 5 year OS for HU in the second line will be expected to be less than 10% given that HU does not induce CCyR, a marker for improved survival. Novartis calculated a 5 year survival on HU of 16% based on first line data. It should be noted that this survival is an overestimate because this is from the first line setting for patients who are not resistant to imatinib. Given that clinical experts suggested that the 5 year OS of patients on HU will be less than 10%, the use of the 16% survival in the Novartis model was an overestimate of the OS of patients on in the CP. Although this survival estimate for HU was used in the model, Novartis noted that the results were to be treated with caution because of the limitations discussed earlier. Novartis therefore believes that the survival of patients on HU has been overestimated in the SHTAC model resulting in a reduced incremental survival benefit for nilotinib. Novartis has therefore conducted updated scenario analyses in the AG model to address this concern by assuming that the OS for HU was 3 years (See appendix 1 [not reproduced here]).	The Committee considered the additional analyses submitted by Novartis including the lower estimate of survival with hydroxycarbamide. See FAD sections 4.3.22.and 4.3.23 The Committee accepted that health state durations were shorter with hydroxycarbamide but thought that this should not be compounded by utility value adjustments. See FAD section 4.3.22.

Consultee	Comment	Response
Novartis	**6. Comments on errors in the ACD** **Page 5, Section 2.6** This section states, after its mention that the treatment option of imatinib dose escalation is recommended in TA70 only in the context of clinical trials, that: *"Other treatment options for people with imatinib-resistant CML include interferon alfa, hydroxycarbamide, allogeneic stem cell transplantation, dasatinib and nilotinib"*. It should be noted that TA70 was issued in 2003 and that treatment has advanced during the eight year period since that date. Today, interferon alfa (IFN) and hydroxyurea (HU) are not standard treatment options. Clinical experts have indicated that IFN and HU are, in fact, only prescribed in rare situations as a fall-back where a second line TKI cannot be used e.g. during pregnancy, or as a holding treatment until long term treatment has been decided. Results from a market research study (2010)[2] confirm that high-dose imatinib should be the principal comparator for patients with resistance. 100% of the 65 clinicians responding stated that they would consider high-dose imatinib in the absence of second line TKIs.	See updated sections 2.8 and 2.10 in FAD The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care, and that for many people hydroxycarbamide or interferon alfa are considered to be little better than best supportive care. The Committee also heard from the clinical specialists that bone marrow stem cell transplantation could be used, although it carries high risks and is restricted to fit, younger people. The Committee concluded that any one of these treatments could be considered a comparator with high-dose imatinib, nilotinib or dasatinib. See FAD section 4.3.3
Novartis	**Page 8, Section 3.7** This section, which does not accurately reflect nilotinib's mode of action, states: "*Nilotinib does not inhibit the Scr family of tyrosine kinases."* This statement implies that the Committee consider that the inhibition of the Src pathway as instrumental in the development of CML and by not inhibiting this pathway, nilotinib is not best placed to combat CML. On the contrary, it should be noted that the known cause of CML is in fact Bcr-Abl. The role of Src in CML is not recognised and is therefore irrelevant in the context of this appraisal. It should also be noted that, in contrast to the multi-targeted action of dasatinib, nilotinib was rationally designed to build on the considerable success of the imatinib molecule, and target Bcr-Abl more specifically than imatinib. It is 20-30 times more potent *in-vitro and* studies performed *in-vitro* show that nilotinib inhibits 32/33 known imatinib resistant Bcr-Abl mutations.	The statement is not factually incorrect and remains in the FAD.

Consultee	Comment	Response
Novartis	**Page 9, Section 4** This section states *"In November 2009, NICE issued preliminary recommendations for a multiple technology appraisal (MTA) appraising the use of dasatinib and nilotinib for chronic myeloid leukaemia (CML) inpatients whose treatment with imatinib has failed because of resistance and/or intolerance. As a result of comments received during consultation, it was agreed to combine an appraisal of the three technologies, dasatinib, high-dose imatinib (600 mg and 800 mg) and nilotinib, to establish their comparative incremental clinical effectiveness and cost effectiveness."* This section is misleading since there was agreement from all the professional bodies (Royal College of Physicians, Royal College of Pathologists/British Committee for Standards in Haematology, Royal College of Nursing) and a clinical expert that high-dose imatinib should be the appropriate comparator, not one of the interventions. All agreed that HU is an inappropriate comparator. This opinion continued to be expressed as evidenced by the comments on the draft scope from the Royal College of Physicians, which stated that "..in chronic phase the only appropriate comparator is escalation of imatinib to 600 or 800 mg daily, from standard dose of 400 mg daily."	This text does not appear in the FAD

Consultee	Comment	Response
Novartis	**Page 10, Section 4.1.2** This section states that: *"The SHTAC Assessment Group did not identify any new or updated studies of nilotinib for imatinib-resistant CML."* There have been several references to paucity of data and the fact that nilotinib data are immature. The Committee has not considered recent data up to a minimum follow-up of 24 months, despite clear reference to this in the Novartis submission. In the chronic phase, 6 month follow up of nilotinib was published in Blood in 2007 by Kantarjian. This was followed by abstracts showing minimum follow up of 24 months by Kantarjian in both Haematologica 2009 and Blood 2009 and since then a full publication has been released, again authored by Kantarjian in Blood, February 2011.[4] The Assessment Group was therefore aware of the existence of the data as a result of the abstracts published in 2009 and the full reports were published at around the same time as the Assessment Report in February 2011. While supplementary reports were subsequently prepared by the Assessment Group and issued on 25 March and 4 April, there was no attempt to review and analyse the important long-term data in relation to nilotinib, before the meeting of the Appraisal Committee on 12 April 2011. The failure to take into account the 24 month data was unfair as was the criticism of the data for milotinib by the Committee in this context. This is particularly important in the context of the economic analysis where benefit is directly derived from the MCyR rate. It is noted that the most up to date and published 24 month results have not been utilised in the SHTAC economic model. These 24 month data include the following overall results: [Table not reproduced here] The Committee also state that there were data only 'from some patients' in the accelerated phase from a single-arm cohort study. It fails to take into consideration the data published by Le Coutre in Blood in February 2008 which showed 6 month follow up of 137 patients, or the subsequent abstract citing minimum follow up of 24 months.	Section 4.1.13 of the FAD states that: No new trials of nilotinib in imatinib-resistant chronic-phase CML were identified by the SHTAC Assessment Group. This statement is not factually inaccurate 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.
Novartis	In addition to the abstracts and publications from the registration trial highlighted above, there is further evidence to support both chronic and accelerated phase nilotinib treatment in the ENACT expanded access study authored by Nicolini (Haematologica 2009). This study reports results on 1,422 chronic phase patients and 181 accelerated phase patients and again, the Committee fails to take into consideration these data. It is particularly surprising that these data have not been taken into account in the context of the Appraisal Committee's criticism of the evidence base relating to nilotinib (paragraph 4.3.6 of the ACD), a concern which Novartis does not believe is valid.	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.

Consultee	Comment	Response
Novartis	**Page 11, Section 4.1.3** The ACD states that results from the Start R study treatment arms should be considered separately due to methodological limitations and the high level of cross over from imatinib to dasatinib at 12 weeks. Novartis agrees that this is a fair approach.	Comment noted.
Novartis	**Page 14, Section 4.1.12** This section refers to only immature CML-CP data being available for nilotinib with lengthier follow-up being available only in abstract form. Novartis would like to clarify that the abstract form of the data which was publically available at the time of submission of this appraisal in October 2010, confirms results up to a minimum follow-up of 24 months and these figures have since been published in Blood (Kantarjian et al, Blood 2011 117: 1141-1145) in full. Novartis would request that the full publication is recognised as substantiating the data in the abstracts and that the 24 month data is used. Our comments in relation to section 4.1.2 are repeated here.	Section 4.1.12 of the ACD was not factually inaccurate, however section 4.1.13 of the FAD has been amended, for clarity.
Novartis	**Page 14, Section 4.1.13** This section states that the nilotinib data for chronic phase was pooled. Novartis would like to highlight that these pooled data reflect not only the responses achieved on the licensed dose of 400mg nilotinib but also on the range of doses that were analysed in the phase I trial. The results therefore appear lower than when referring to the trial data for the licensed dose. Additionally, only 6 month cut-off is considered. However, as already stated, minimum follow-up of 24 months was available at the time in abstract form and fully published in Blood in February 2011 (Kantarjian et al, Blood 2011 117: 1141-1145). Novartis requests that the full publication is used which substantiates the data in the abstracts of a minimum follow-up 24 month data which shows: CCyR rates of 44% overall, MCyR of 56% overall[3] and CHR of 85% overall (72% CHR in resistant only patients)[4].	Section 4.1.13 of the ACD was not factually inaccurate, however section 4.1.14 of the FAD has been amended, for clarity.

Consultee	Comment	Response
Novartis	**Page 15, Section 4.1.14** This section states: *"Limited data on progression free survival were available and no published studies were identified. No data were available that provided results separately for participants with imatinib resistance and those with imatinib-intolerance".* Whilst it is true, as stated, that progression free survival is not available in the public domain for resistant only patients, the combined data for resistant and intolerant patients at a minimum of 24 month follow-up is clearly shown in the abstract presented as a poster at ASH 2009. Progression free survival was 64% at 24 months and the figures have since been published in Blood in February this year. In particular it should be noted that a new analysis of the data was carried out for the submission specifically on imatinib resistant patients and this data was fully described in our submission. It is therefore incorrect to say that no data were available that provided results separately for patients with imatinib resistance.	Comment noted. The statement that "no data were available that provided results separately for participants with imatinib resistance and those with imatinib-intolerance" does not appear in the FAD. See FAD section 4.1.16
Novartis	**Page 15, Section 4.1.15** This section states: *"No studies of nilotinib provided rates of haematological adverse events separately for people with imatinib resistance."* Once again, we would like to point out that, while such data is not published, it was provided to support our submission. Our comments in relation to section 4.1.14 are repeated here.	Comment noted. The statement that "no studies of nilotinib provided rates of haematological adverse events separately for people with imatinib resistance" does not appear in the FAD. See FAD 4.1.17.
Novartis	**Page 17, Section 4.1.21** This section refers to a single arm cohort study with "*some participants with accelerated phase CML. This was a dose-ranging phase one study, and as such the results of this study were viewed with caution by the Assessment Groups".* Novartis would like to highlight that the 6 month follow up of 137 patients in the accelerated phase arm of the 2101 trial was published in Blood in 2008, authored by Le Coutre. This was subsequently updated with minimum follow up of 24 months in an abstract by Hochhaus in Haematologica 2009. There are also data from the ENACT expanded access study authored by Nicolini (Haematologica 2009) which provide updates on 1,422 chronic phase patients and 181 accelerated phase patients, all of which the Committee fails to take into consideration. Our comments in relation to section 4.1.14 are repeated here.	Comment noted. No factual correction required see FAD 4.1.21.

Consultee	Comment	Response
Novartis	**Page 21, Section 4.2.11** This section, under the heading of Manufacturers' Submissions, states: *"Novartis presented cost-effectiveness analyses of nilotinib and high dose imatinib compared with stem cell transplantation and hydroxycarbamide in people with chronic-phase imatinib-resistant CML."* We would like to point out that this was merely an exploratory analysis presented in accordance with the Scope, despite our disagreement with HU as a comparator in this appraisal; our base case analysis presented the cost-effectiveness of nilotinib compared with high-dose imatinib. In the case of imatinib-resistant CML, clinical practice and recent European recommendations indicate that second-generation TKIs, nilotinib and dasatinib, and stem cell transplantation (SCT) should be used. Despite this body of opinion, the scope for this appraisal determined that the interventions, including nilotinib, should be compared with hydroxycarbamide (HU) and interferon alfa (IFN-α). These comparators are not used in clinical practice as second-line therapies and very few data exist in any second-line setting. Indeed, the introduction of imatinib rendered the use of HU and IFN-α largely obsolete. Once imatinib was available, clinical practice evolved to dose-escalate imatinib to either 600 mg/day or 800 mg/day as the emergence of imatinib resistance came to light. For patients not able to access nilotinib and dasatinib, accepted clinical practice is to use HD imatinib and not HU or IFN-α. This means that, according to NICE's guiding principles, HD imatinib should be the comparator in this appraisal because it is the treatment that will be displaced should nilotinib and dasatinib be accepted for use in the NHS. Accordingly, we have presented an analysis in which HD imatinib is treated as a comparator.	See FAD 4.2.14
Novartis	**Page 29, Section 4.2.15** This section states: "In the first scenario (treatment duration set to 10 years..." This should read "In the second scenario..."	Comment appears to relate to 4.2.28 in the ACD, see FAD 4.2.43 and 4.2.44
Novartis	**Page 29, Section 4.2.29** This section states: *"The SHTAC Assessment Group noted that the economic models provided by PenTAG, Bristol-Myers Squibb and Novartis resulted in ICERs greater than £30,000 per QALY gained for all treatments."* This is not correct since, in the Novartis base case analysis of nilotinib vs high-dose imatinib, nilotinib dominated high-dose imatinib.	See FAD 4.2.45 Clarifies that ICERs are versus the base case treatment (interferon alfa)

Consultee	Comment	Response
Novartis	**Page 30, Section 4.3.2** This section states: *"...high-dose imatinib followed by dasatinib and nilotinib are in widespread use and are a major advantage over the therapies previously available: that is interferon and hydroxycarbamide*." This statement is misleading and suggests that dasatinib and nilotinib are a third line treatment after high-dose imatinib; however this is not the case. We assume the text is intended to refer to "high-dose imatinib and more recently-introduced products dasatinib and nilotinib..." and would suggest that the wording is amended to avoid misinterpretation and confusion. For the avoidance of doubt, as per the licences for nilotinib and dasatinib, and as is clear from the ELN recommendations 2009, nilotinib, dasatinib and high-dose imatinib are all options as a second line treatment and, in current clinical practice, one of these options would be selected by the clinician upon a patient failing on imatinib.	This section has been amended (accordingly, for clarity). See FAD section 4.3.4
Novartis	**Page 32, Section 4.3.4** **This section comments on the use of MCyR as a surrogate for OS and states:** **"** ...and heard from the clinical specialists that the strongest link was between major molecular response and overall survival." Novartis questions the interpretation of this discussion between the Committee and the clinicians and is unaware of the evidence relied upon. The Committee seem to imply that CCyR is not important and does not link to OS. However, our own discussions with clinicians indicate that CCyR is the first main goal of treatment and that, as highlighted in a publication by Hughes from the IRIS trial, there is a clear correlation between achievement of CCyR, overall survival and PFS. MMR is effectively the next step in treatment goals and it is widely understood that achievement of MMR protects the CCyR response (patients with an MMR maintain a CCyR for longer than those who don't achieve an MMR). There is also increasing evidence that MMR itself correlates with overall survival and progression free survival. In these circumstances, Novartis would ask NICE to clarify the evidence from clinical specialists relied upon by the Committee and identify any data in support of their position.	This information was included in the ACD, but has been amended following comments from consultees.
Novartis	**Page 33, Section 4.3.5** This section states: *"The Committee also agreed that there was no good evidence to distinguish between dasatinib and nilotinib, a conclusion also supported by the clinical experts."* If this conclusion is accepted, then the economic evaluation should also use same QALY for nilotinib and dasatinib in the calculation of the ICER (refer to our discussion in point 5.4 of this document).	The Committee considered the additional analyses submitted by Novartis, including the assumption of survival benefit equal to that of dasatinib, see FAD 4.3.22.and 4.3.25

Consultee	Comment	Response
Novartis	**Page 35, Section 4.3.8** This section states: *"The Committee first noted that the acquisition costs of all three interventions are in excess of £30,000 per person per year and that the cost of imatinib has recently increased;"* Novartis would like to point out that the imatinib price increase was introduced in accordance with the 2009 Pharmaceutical Price Regulation Scheme (PPRS) whereby scheme members can modulate the pricing of pharmaceuticals, but must still deliver price adjustment savings required under the PPRS agreement. It should also be noted that the annual costs of imatinib were higher than annual costs of nilotinib before the imatinib price increase, meaning that the pivotal decision that nilotinib is cheaper and more effective remains even with the previous imatinib price.	This information was included in the ACD, but has been amended following comments from consultees.
Novartis	**Page 35, Section 4.3.8** This section further states that: *"The Committee also considered that if each year of life were adjusted by quality of life the resulting costs per QALY would be likely to be higher than the annual costs of the drugs."* Although the above statement is correct on a theoretical basis it assumes that the new technology is compared to nothing i.e. no costs to the comparative arm of the analysis. In this particular instance the current routine treatment option for CML patients who are resistant to 400mg imatinib is HD imatinib and the annual costs of HD imatinib are higher than those of nilotinib. Thus although the annual cost of nilotinib is in excess of £30,000 per year, it is still cheaper but more beneficial than the current treatment option in the NHS (HD imatinib). This will be the treatment option that will be displaced if nilotinib were to be recommended. We therefore request NICE to consider removing section 4.3.8 or at worst reword the section to ensure that facts are represented correctly.	This information was included in the ACD, but has been amended following comments from consultees.

Consultee	Comment	Response
Novartis	**Page 41, Section 4.3.17** This section states: *"The Committee considered that the development of dasatinib and nilotinib, in terms of pharmacological progress beyond imatinib was not innovative."* We believe that this view regarding nilotinib is incorrect and does not reflect the innovative approach to the development of the molecule. As imatinib data matured, it was noted that not all imatinib patients achieved an optimal response on therapy and it is known that many have to discontinue due to adverse events. The unmet clinical need was recognised and nilotinib was specifically designed to address these issues. Tasigna was rationally designed based on the imatinib molecule but to be more specific in its binding to the Bcr-Abl kinase domain, the single known cause of CML. This targeted design resulted in improved responses and an improved safety profile in the second line setting. Nilotinib represents a step-change in the benefits provided by imatinib, the first TKI in class and an important development in the treatment of CML. These factors do not appear to have been taken into account by the Committee in preparation section 4.3.17 of the ACD. This innovative approach was recognised when nilotinib was commended by judges, including Sir Michael Rawlins, of the Prix Galien award in 2008 for innovation in research and development in the orphan drug category for rare conditions. It was recognised that nilotinib targets the definitive cause of CML, has improved and more flexible binding to Bcr-Abl, thereby overcoming drug resistance to imatinib, and preferentially targets Bcr-Abl, reducing the risk of unwanted off-target side effects.	The Committee recognised the innovative nature and major change in the treatment of CML that imatinib has provided since it has been introduced and recommended for use by NICE (technology appraisal guidance 70, October 2003), and discussed whether dasatinib and nilotinib should be considered to be innovative treatments. The Committee considered that the development of dasatinib and nilotinib was not a further major innovation. The Committee did not identify any potential significant and substantial health-related benefits that had not been included in the economic models. See FAD section 4.3.30

Consultee	Comment	Response
Novartis	**7. The provisional recommendations are not a suitable basis for guidance** Novartis does not agree that the provisional recommendations are sound or a suitable basis for guidance to the NHS. As was stated by the clinical experts and reported in the ACD section 4.3.3 *"For people receiving hydroxycarbamide, the prognosis is poor with a median life expectancy of around 5 years".* Notwithstanding this view, the preliminary decision is based on the comparison of nilotinib with HU – a treatment option that is neither relevant in this setting nor reflective of clinical practice in England and Wales. It is simply not credible to issue guidance which has the effect of excluding what are now standard therapies for CML resistant to standard-dose imatinib, based on a comparison with a treatment which is not used in current NHS practice. Indeed, the Committee has accepted these as considerably superior interventions to HU as stated in Section 4.3.2: *"high-dose imatinib followed by dasatinib and nilotinib are in widespread use and are a major advantage over the therapies previously available: that is interferon and hydroxycarbamide"*. The draft recommendations, if passed into final guidance, will condemn patients who have limited treatment options to an ineffective treatment (HU) that has never been used routinely for treating patients in this setting. They also represent a retrograde step in the treatment in resistant CML patients, a position which is not consistent with NICE's stated aim to promote the longer term interest of the NHS in the development of innovative treatments for the future. The Committee stated that *"they understand that the side-effect profile of treatment is an important factor when considering the treatment options for people with CML that is resistant to standard-dose imatinib" (section 4.3.7).* However, if a negative ACD is allowed to develop into a subsequent negative FAD, the Committee are removing the clinicians' option to individualise treatment based on side effect profiles because the ACD does not recommend either nilotinib, dasatinib or high-dose imatinib. As a result, only palliative treatment options with considerably poorer side effect profiles will be the forced drugs of choice.	The Committee accepted that with the patient access scheme in place the use of nilotinib for the treatment of imatinib-resistant CML could be regarded as a cost-effective use of NHS resources. See FAD section 4.3.23

Consultee	Comment	Response
Novartis	It is highly unlikely that any formal clinical trial comparing the TKIs to HU – the comparator selected by the Committee in this appraisal. It will be unethical to expect patients to recruit to a trial where one of the treatment options (HU) is clearly not beneficial because it does not induce any form of response that leads to better survival outcomes. Clinical experts have stated to NICE, as part of the consultation process, that because the efficacy and tolerability of nilotinib and dasatinib might be similar, the sample size required to show meaningful and statistically significant differences of the two drugs will be large and yet the eligible patient population is very small. Due to the ethical issues and the potential practical difficulties in conducting such a trial, no new evidence will be available in the future on the comparisons of the TKIs with HU. This view is supported by CML patient groups who stated that: *"The ethical as well as practical dimensions involved in recruiting patients to such trials from an extremely small patient population, who are already subject to recruitment to existing trials, must lead us to the conclusion that this is likely to remain an aspiration of regulators rather than a reality."* The current preliminary recommendation if passed into final guidance will therefore not change in the future when the guidance is reviewed. It is therefore unlikely that any new head to head data will be available to inform a guidance review in this respect. This will effectively mean that CML patients in England and Wales will not have access to life saving treatment when they fail on imatinib, thereby reducing the life expectancy of these patients. This is counter to NICE's core values of ensuring that patients have access to cost effective treatment options. In the opinion of leading clinicians[3] this will potentially leave patients with imatinib-resistant CML in England and Wales in a disadvantaged position compared to those in Europe. The provisional recommendations are therefore not sound and suitable basis for guidance to the NHS.	The Committee accepted that with the patient access scheme in place the use of nilotinib for the treatment of imatinib-resistant CML could be regarded as a cost-effective use of NHS resources. See FAD section 4.3.23

Consultee	Comment	Response
Novartis	**8. Conclusion** In conclusion, the ACD does not reflect the available evidence and, accordingly, the preliminary recommendations do not constitute a reasonable or scientifically sound or suitable basis on which to base guidance to the NHS. In particular the inclusion of HU as the principal comparator for resistant patients is inconsistent with NICE's procedures and current clinical practice within the NHS and elsewhere. The comparison of nilotinib with HU relied upon by the Committee does not represent a valid basis for excluding nilotinib from NHS use. We also submit that consideration of a 10 year treatment duration is not based on any evidence and clinical opinion suggests that this is an overestimate of the treatment duration in the second line setting. Clinical experts suggested that the average treatment duration is approximately 6.6 years when various factors discussed earlier were taken into account. The survival benefit of nilotinib and dasatinib should have been assumed to be the same and nilotinib mean dose intensity should have been taken into account. We also believe that the overall survival and utility gain for HU in the CP has been overestimated. We have conducted additional analysis based on the AG model addressing these concerns and comparing nilotinib with HU (a comparator we strongly object to). Despite the fact that nilotinib is cost-effective versus high-dose imatinib and will be cost-effective versus HU if our concerns are addressed, we want to ensure that imatinib-resistant CML patients will not be condemned to inferior treatment if our concerns are ignored. We have therefore offered a patient access scheme and the impact of this scheme is included in the analyses presented. The analysis, taking our proposed PAS into account, resulted in a reduced ICER of £xx,xxx per QALY gained for 6.5 years treatment. When the more optimistic assumption of 10 years treatment duration is assumed, the ICER is reduced to £xx,xxx per QALY gained. Nilotinib is highly cost effective (i.e. cheaper and more effective) when compared with the standard of care in the NHS (HD imatinib). The results of all the economic models submitted to NICE showed that nilotinib dominates HD imatinib. Nilotinib therefore represents a cost effective treatment option for imatinib-resistant patients as it is cheaper and more effective than the current standard of care in the NHS. Our updated analysis has shown that nilotinib is also cost effective when compared with HU, an inappropriate comparator.	The Committee accepted that with the patient access scheme in place the use of nilotinib for the treatment of imatinib-resistant CML could be regarded as a cost-effective use of NHS resources. See FAD section 4.3.23

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
NCRI/RCP/RCR/ACP.JCCO	The preliminary decision not to recommend dasatinib, nilotinib and high dose imatinib for the treatment of chronic myeloid leukaemia (CML) resistant to standard doses of imatinib is most regrettable and disappointing,. 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 Panel prioritisation exercise, applications for exceptionality to relevant PCT or most recently from the Cancer Drug Fund. Several hundreds of patients in the UK have benefited from their prescription and now lead productive lives of good quality having been restored to a near normal life expectancy The removal of these drugs from the UK's armamentarium against CML is a retrograde step and in complete contrast to the practice in the rest of the European Union, the USA, Australia and New Zealand, amongst others. Yet again the decision is based not on efficacy, which was broadly accepted by the Committee, but on a putative cost produced by only certain analyses within the economic model.	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. Recommendations are based on evidence of both clinical and cost effectiveness.
NCRI/RCP/RCR/ACP.JCCO	The decision making process is based on the results of complicated statistical models, understood in their entirety by few of the medical and pharmacological experts. These models are exactly that, models. The results can be altered quite dramatically by introducing changes in any number of variables and they can only be as accurate as the information that is used for the original assumptions. In this particular case the statisticians responsible for the modelling freely acknowledge that the relatively short follow-up of these drugs that was reported in the publications, has been inadequate to guarantee their accuracy. In addition there are no data available for the outcome of the use of the various comparators in situations of imatinib resistance for the simple reason that they are ineffective and no patient or physician would accept their use when potentially effective drugs are available. The following statement was made on page 74 of the Technology Assessment Report (TAR) produced by the Southampton Health Technology Assessments Centre (SHTAC), 'However, it must be stressed that because of the concerns relating to data for the comparators, results should be treated with due caution.'	The Committee heard that high-dose imatinib, dasatinib and nilotinib are a major advance over earlier therapies, that is, interferon alfa and hydroxycarbamide. See FAD section 4.3.3 The Committee concluded that it is clear that dasatinib, high-dose imatinib and nilotinib provide clinical benefit for people with imatinib-resistant CML. However, the Committee agreed that the limited evidence base means that the magnitude of the benefit is uncertain. See FAD section 4.3.9

Nominating organisation	Comment	Response
NCRI/RCP/RCR/ACP.JCCO	As a consequence SHTAC produced a number of results regarding the cost effectiveness of these drugs, altered considerably by altering the duration of treatment and the duration of survival. For many of these, the QALY of the technologies was within the range deemed acceptable. By altering these parameters and by choosing an effective but exceptionally inexpensive comparator, hydroxycarbamide, the QALY became unacceptably large and it was on this basis that the decision was reached. In contrast the following statements were made in the summary of the findings of the SHTAC model (page 86 of the TAR) • Results suggest that the three interventions, dasatinib, nilotinib and high dose imatinib, have similar costs and effectiveness. • Nilotinib, dasatinib and high dose imatinib are all cost-effective when compared with hydroxycarbamide, for a willingness to pay of about £30,000 per QALY.	The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care. The Committee also heard from the clinical specialists that bone marrow stem cell transplantation could be used. The Committee concluded that any one of these treatments could be considered a comparator with high-dose imatinib, nilotinib or dasatinib. See FAD section 4.3.3. The clinical specialists expected that these people would receive dasatinib or nilotinib treatment for the rest of their lives, possibly with a nearly normal life expectancy (that is, at least 10 more years. See FAD section 4.3.6.
NCRI/RCP/RCR/ACP.JCCO	Hydroxycarbamide is not a realistic choice as a comparator as it does not confer any survival benefit in CML, it merely controls symptoms. It will not be used in CML in chronic phase (CP) resistant to imatinib unless effective agents such as the second generation tyrosine kinase inhibitors (2G-TKI) are completely removed from the market and there is complete loss of control of the blood counts. Either a 2G-TKI will be used, or in their absence, standard dose imatinib will be used. To insist in the use of hydroxycarbamide as the comparator is simply not to recognise modern leukaemic management.	The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care. The Committee also heard from the clinical specialists that bone marrow stem cell transplantation could be used. The Committee concluded that any one of these treatments could be considered a comparator with high-dose imatinib, nilotinib or dasatinib. See FAD section 4.3.3.

Nominating organisation	Comment	Response
NCRI/RCP/RCR/ACP.JCCO	In section 4.1.2 of the ACD there is the following statement: 'The SHTAC Assessment Group did not identify any new or updated studies of nilotinib for imatinib-resistant CML' The phase II study of nilotinib for imatinib resistant CML was published online in November 2010 and in hard copy in January 2011 (Kantarjian HM et al. Blood. 2011 Jan 27;117(4):1141-5. Epub 2010 Nov 22). It provides the 24 month follow-up of this study and has not been considered. In addition the clinical experts repeatedly stated that hydroxycarbamide, a palliative therapy, is not considered an appropriate treatment for patients who have demonstrated resistance to imatinib but still have a 50% chance of excellent responses and long overall survivals with high quality of life. Their written and verbal evidence was not taken into account. With respect to the use of the technologies in accelerated phase and blast crisis, the 'end of life' criteria are clearly met, as without treatment these two conditions have a median life expectancy of considerably less than 24 months	The section has been amended (accordingly, for clarity).
NCRI/RCP/RCR/ACP.JCCO	Comments regarding the interpretation of the cost-effectiveness have been made in the introduction to this document. In addition it is important to note that the final economic model was tabled at the meeting of the Appraisal Committee without providing members and clinical experts any time to seek critical review of the methodology. The individual presenting the data was one of very few people in the room who would have appreciated the complexity (and accuracy or inaccuracy) of the model so the chance of critical interpretation was low. In addition he moved through complex slides at a rapid rate, precluding rational discussion and challenge. There are undoubtedly some mistakes in the ACD, of variable importance. For completeness these are acknowledged below. Unfortunately these mistakes reflect the fact that the ACD has been put together by researchers unfamiliar with the disease, its management and expected outcomes. Although in general they have interpreted data correctly there are sufficient numbers of errors to cast doubt on the final decision being based on accurate information.	Comment noted.

Nominating organisation	Comment	Response
NCRI/RCP/RCR/ACP.JCCO	**2.5** 'After the introduction of imatinib into routine clinical practice, 5-year relative survival increased from 27.1% in 1990–92 to 48.7% in 2002–4 for all age groups combined ($p < 0.0001$ for the trend).' Since imatinib became frontline treatment in the UK only after the initial results of the phase III study (IRIS) became available and the drug had been approved by NICE (TA 70 issued October 2003), 5 year survival rates could not have been available in 2002-2004. The figure of 48.7% underestimates considerably the impact of this drug on the outcome of this disease. The real value is of the order of that quoted for the IRIS study of 85% at 8 years.	This information was included in the ACD, but has been amended following comments from consultees.
NCRI/RCP/RCR/ACP.JCCO	**3.1** 'Dasatinib ... It is an orally active inhibitor of SRC and the Src-family of kinases.' This is true but the action of dasatinib in CML is because of its inhibition of BCR-ABL in a very similar manner to imatinib and nilotinib.	Comment noted. Section 3.1 of the FAD states: 'Dasatinib has been shown to directly inhibit 21 out of 22 mutant forms of BCR-ABL that are resistant to imatinib.'
NCRI/RCP/RCR/ACP.JCCO	**4.1.3** 'The Assessment Groups expressed concerns that none of the RCTs reported methods of allocation concealment, all were of an open-label design and none presented power calculations.' When imatinib is ineffective and the patient is not eligible for an allogeneic stem cell transplant, their disease will be fatal. Dasatinib and nilotinib were drugs that were rationally designed to act in cases of imatinib failure. It is always easy to produce criticisms of studies when not personally responsible for a better design but these criticisms seem banal. How could they be anything other than open label? There is no alternative chemotherapeutic agent that can induce major or complete cytogenetic responses in patients with imatinib failure so any power calculations would be worthless. Many patients were included in these studies so it is very easy to perform a power calculation retrospectively and see that the numbers recruited would have exceeded any requirement. These are therefore petty criticisms, which when written down and unchallenged, serve to undermine the efficacy of these agents.	The Committee noted that the clinical trials available were non-comparative, of short duration and had used surrogate outcomes to predict overall survival. See FAD section 4.3.9 However, the Committee concluded that it is clear that dasatinib, high-dose imatinib and nilotinib provide clinical benefit for people with imatinib-resistant CML. However, the Committee agreed that the limited evidence base means that the magnitude of the benefit is uncertain. See FAD section 4.3.9
NCRI/RCP/RCR/ACP.JCCO	**4.1.4** 'All other studies used higher dosages of nilotinib' This statement should read 'All other studies used higher dosages of dasatinib'	This section has been amended (accordingly, for clarity). See FAD section 4.1.4

Nominating organisation	Comment	Response
NCRI/RCP/RCR/ACP.JCCO	**4.1.8** 'Three single-arm cohort studies that assessed high-dose imatinib and an update to the comparative RCT of dasatinib and high-dose imatinib were identified. As previously noted, this RCT was considered to be of limited use because of the extent of crossover and the study design, and the treatment arms were considered separately.' The dismissal of the RCT of high dose imatinib versus dasatinib because of early cross-over is unfortunate since useful information can be obtained from this study. There are a number of aspects of study design which include an ethical element alongside the statistical considerations. Patients failing standard dose imatinib are aware that they once more have a fatal disease. It is unethical to ask them to consider entry to a trial in which they could be randomised to an ineffective agent and expect them to remain on this arm indefinitely to satisfy the statisticians. At some point the treatment must be considered to have failed so that they can be offered alternatives, including stem cell transplantation. Three months was not an unreasonable period of time to expect some degree of cytogenetic response. Irrespective of the early cross-over this study showed that high dose imatinib could not achieve complete cytogenetic responses in patients who had failed to show any degree of cytogenetic response on standard dose imatinib. These data have since been confirmed in other studies and suggest the futility of his approach in certain patient sub-populations.	The Committee was aware of only one comparative trial, which compared dasatinib with high-dose imatinib, but noted the restricted comparison (only with high-dose imatinib) and the comments from the Assessment Groups on the interpretation problems with this trial. See FAD section 4.3.7 The Committee heard from the clinical specialists that high-dose imatinib is being used in clinical practice for people whose CML has previously had a good response to treatment with standard-dose imatinib. The Committee acknowledged the clinical specialists' view that for CML that is resistant to standard-dose imatinib, high-dose imatinib was unlikely to be as beneficial as dasatinib and nilotinib. See FAD 4.3.4
NCRI/RCP/RCR/ACP.JCCO	**4.2.1** 'The SHTAC Assessment Group considered that although the results of this study were credible, there were some methodological limitations and it was unclear how generalisable the model parameters and the results are to the UK' Rather than simply stating that the results might not be generalisable to the UK and thereby undermining the value of the study, could SHTAC explain why results obtained in a Northern European population, with whom the UK share considerable ancestry and genotypes, might not be valuable.	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. The clinical specialists argued that participants in clinical trials do not reflect the population seen in clinical practice because the trials included participants who had worse disease prognoses than would be seen in current clinical practice. See FAD section 4.3.8

Nominating organisation	Comment	Response
NCRI/RCP/RCR/ACP.JCCO	**4.2.27** 'The SHTAC Assessment Group explored the case in which dasatinib has a longer treatment duration than high-dose imatinib and nilotinib by varying the progression-free survival for dasatinib between 3.1 years (as in the SHTAC base case) and 6.5 years (as in the PenTAG base case), while keeping progression-free survival for high-dose imatinib and nilotinib constant. Extending the progression-free survival and treatment duration of dasatinib results in higher costs for dasatinib with no change in QALYs. Therefore the longer the treatment duration the less favourable the results compared with the other interventions. The SHTAC Assessment Group explored the case in which dasatinib has a longer treatment duration than high-dose imatinib and nilotinib by varying the progression-free survival for dasatinib between 3.1 years (as in the SHTAC base case) and 6.5 years (as in the PenTAG base case), while keeping progression-free survival for high-dose imatinib and nilotinib constant. Extending the progression-free survival and treatment duration of dasatinib results in higher costs for dasatinib with no change in QALYs. Therefore the longer the treatment duration the less favourable the results compared with the other interventions. Why was this analysis done? As the evidence suggests that dasatinib and nilotinib are equally efficacious (a statement accepted by SHTAC) what is the value of trying to model a situation in which dasatinib is given for a longer duration than nilotinib or high dose imatinib?	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.
NCRI/RCP/RCR/ACP.JCCO	**4.3.2** 'The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people with CML would most commonly receive treatment with hydroxycarbamide or stem cell transplantation, if possible, and that these were the appropriate comparators for dasatinib, high-dose imatinib and nilotinib.' The clinical specialists stated on many occasions that if a patient was resistant to imatinib but remained in chronic phase that the most likely scenario would be that they remained in imatinib 400mg or where possible were given an increased dose.	The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care. The Committee also heard from the clinical specialists that bone marrow stem cell transplantation could be used. The Committee concluded that any one of these treatments could be considered a comparator with high-dose imatinib, nilotinib or dasatinib. See FAD section 4.3.3

Nominating organisation	Comment	Response
NCRI/RCP/RCR/ACP.JCCO	**4.3.3** 'It heard from the clinical specialists that high-dose imatinib is being used in clinical practice but only in people whose CML has previously shown a good response to initial treatment with standard-dose imatinib; that is, good blood count response, complete cytogenetic response and complete molecular response.' The clinical experts did not state this. They said without any qualifications that high dose imatinib was being widely used in patients who had failed standard dose imatinib. They did say that it was most likely to be effective in inducing a cytogenetic response if the patient had previously had such a response but had subsequently lost this response. 'The Committee heard from the clinical specialists that people whose CML does not respond to dasatinib or nilotinib within 12 months would receive treatment with hydroxycarbamide or, if suitable, stem cell transplantation.' This statement is misleading because the clinical experts qualified their answer by saying that if there was good haematological control then the patient would probably stay on the current drug but some might be give the alternative second generation TKI. 'For people receiving hydroxycarbamide, the prognosis is poor, with a median life expectancy of around 5 years' This is true for patients receiving hydroxycarbamide form diagnosis, not after failing both first and second generation TKI	The Committee heard from the clinical specialists that high-dose imatinib is being used in clinical practice for people whose CML has previously had a good response to treatment with standard-dose imatinib. The Committee acknowledged the clinical specialists' view that for CML that is resistant to standard-dose imatinib, high-dose imatinib was unlikely to be as beneficial as dasatinib and nilotinib. See FAD section 4.3.4 The Committee heard from the clinical specialists that for people with imatinib resistant CML receiving interferon alfa or hydroxycarbamide, the prognosis is poor, with a median life expectancy of around 5 years. See FAD section 4.3.6
NCRI/RCP/RCR/ACP.JCCO	**4.3.4** 'The Committee noted the poor evidence base for all interventions for people whose CML is resistant to standard-dose imatinib. It was aware of only one comparative trial, which compared dasatinib with high-dose imatinib, but noted the comments from the Assessment Groups on the poor study design and the interpretation problems with this trial.' Although this might be the Committee's statement it is evidently untrue. There is excellent evidence that dasatinib and nilotinib are able to induce a complete cytogenetic response in approximately 50% of patients who fail to achieve or who lose CCyR on imatinib. There is not a single CML expert in the world who would argue that these drugs are ineffective. The criticism is of the trial design not of the drugs.	The Committee concluded that it is clear that dasatinib, high-dose imatinib and nilotinib provide clinical benefit for people with imatinib-resistant CML. See FAD section 4.3.9.

Nominating organisation	Comment	Response
NCRI/RCP/RCR/ACP.JCCO	The provisional recommendations are not sound (if only because the economic model is based on shaky foundations) and are certainly not a suitable basis for guidance in the NHS. CML is a rare disease but has an influence far beyond its incidence. It provides a story of remarkable success by using the molecular understanding of the basis of the disease to design successful targeted agents, the mechanism and unwanted side effects of which are radically different from conventional chemotherapy. The outcome of cancer treatment in the UK has been the subject of much criticism in future years and enormous effort is being expended in trying to correct this. Limiting the use of highly effective drugs in an eminently treatable condition will perpetuate the contrast between the UK and the rest of the developed world.	Comment noted.
NCRI/RCP/RCR/ACP.JCCO	The proposed recommendation of the Committee has a number of ramifications for inequality. First, if these drugs are denied to those who are resistant to standard dose imatinib , then more patients will be referred for allogeneic stem cell transplantation (allo-SCT). The success of allo-SCT is dependent on the degree of tissue match between recipient and donor. Any patient of non-Caucasian origin is less likely to find a compatible unrelated donor and therefore less likely to benefit from this treatment and more likely to die of their disease. Furthermore, as has been stated above there will be inequality of access to effective therapy in the European Union.	The Committee noted the argument that if dasatinib, high-dose imatinib or nilotinib are not recommended for the treatment of imatinib-resistant CML and that this could raise issues in relation to race, age (the elderly), and comorbidities. However, the Committee concluded that allowing for clinical decisions relating to a range of possible treatments based on individual assessment of risk and benefit does not limit access to the technology for any specific protected group compared with other people. See FAD section 4.3.31

Nominating organisation	Comment	Response
CML Support Group UK	We have strong objections to the above ACD as detailed below. We join with leading expert CML clinicians (letter to The Daily Telegraph 23rd May) in considering the reasoning that resulted in the preliminary negative recommendation to be *"inconsistent"* and *"perverse"*. In addition we think that the methodology implicitly advocated to provide the *"strong"* evidence base that the Committee concluded is absent here, is impossible to mobilise and that it is disingenuous of the Committee to suggest it could be. We also think that, more fundamentally, NICE should think very seriously about reforming its procedures and processes for the appraisal (and assessment) of TKIs, or more generally pharmacogenomic therapies, for rare diseases with correspondingly small patient populations. Finally we also feel that NICE has not clearly articulated their policy concerning pharmaceutical innovation; there is no set of transparent criteria to establish its status in any particular case or measure of innovation once established. Granting of innovation status appears to proceed on an ad hoc basis with the Committee supporting its award with, in this case, over generalized assertions based on dubious scientific judgement.	The Assessment relies on the available evidence submitted to the Institute and that retrieved from the published literature by the assessment group. 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.

Nominating organisation	Comment	Response
CML Support Group UK	**<u>Inconsistency in assigning value to clinicians life expectancy evidence</u>** The Committee accepts that all three drugs do *"provide clinical benefit"* when prescribed for this group of patients. This concurs with the review commissioned by the Committee from the Health Technology Assessment (HTA) provider (SHTAC) as it does with the evidence presented by leading specialist haematologists. The Committee also say: *".... the paucity of the evidence base means that the magnitude of the benefit is uncertain."* (ACD: 4.3.6.) The SHTAC notes that *"Limitations in the data exist ..."* (SHTAC: Assessment Report p.5) However, the Committee notes, and later resorts to, evidence presented by the same expert haematologists that shows that in imatinib resistant CML: *"...over 50% of people with CML treated with dasatinib or nilotinib, but not with high-dose imatinib, there is a good response to treatment and that this response is usually as good as the initial response to standard-dose imatinib. The clinical specialists expected that these people would receive dasatinib or nilotinib for the rest of their lives, possibly with a near normal life expectancy (that is, at least 10 more years) "* (ACD 4.3.3) The Committee rely on the *"near normal life expectancy"* observation, referred to above (ACD: 4.3.3.), on two occasions to express reservations about the economic evaluation evidence presented to them. These are: In their examination of the economic model developed by Novartis (ACD: 4.3.10) and, secondly, in the assessment of the SHTAC model (ACD: 4.3.12). They were critical of the *"much lower than would be expected"* treatment durations in the former and that the *"base-case treatments durations"* do not reflect likely treatment durations in the case of the latter. In summary, the Committee seems to have no issue with the adequacy of this evidence to critique aspects of the economic modeling evidence presented. but also regards the same evidence as contributing to *"paucity"* status when commenting on the clinical effectiveness of the drugs subject to this appraisal. It is inconsistent to rely on evidence that is later disregarded as weak.	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. The reliability of the available evidence is considered by the Committee when formulating its recommendations.

Nominating organisation	Comment	Response
CML Support Group UK	A) <u>QUALY values for imatinib, dasatinib and nilotinb compared to HU (hydroxycarbamide)</u> Noting that there was no evidence to distinguish between nilotinib and dasatinib the Committee concluded that: *"...the ICERs for these treatments compared with hydroxycarbamide would both be higher than £43,800 per QALY gained and could be considerably more"* (ACD 4.3.12) And that "*...dasatinib or nilotinib could not be recommended as a cost-effective use of NHS resources"* for this patient population. TA 70 noted a similar conclusion with regard to imatinib: *"The results from the independent model suggested, however, that the cost effectiveness of imatinib when compared with HU was not acceptable, with an ICER of around £87,000 per QALY."* (TA 70: 4.3.7.) But, because of known limitations concerning the clinical effectiveness data, the Committee, TA 70 notes, asked the assessment team to undertake an additional analysis which resulted in: ".... slightly improved ICERs for imatinib, to around £60,000 when compared with HU" (TA 70:4.3.8) Nevertheless the Committee proceeded to give a positive recommendation to imatinib. In the 2006 paper entitled "Appraising Orphan Drugs" NICE notes (4.1.2.) : *"No particular scientific or technical problems have arisen during the Institute's appraisals of those orphan drugs that have been referred to it. Many, however, have had incremental cost effectiveness ratios (ICERs) at the "high" end of what NICE and its appraisal consider to be cost effective within the NHS."* Both imatinib, dasatinib and nilotinib are at the 'high' end yet one, at standard dose, is recommended and the others not. This is inconsistent.	The NICE methods guide states that "Above a most plausible ICER of £20,000/QALY, judgements about the acceptability of the technology as an effective use of NHS resources are more likely to make reference to explicit factors including: the degree of uncertainty surrounding the ICERs, the innovative nature of the technology, the particular features of the condition and population receiving the technology, where appropriate, the wider societal costs and benefits, Above an ICER of £30,000/QALY, the case for supporting the technology on these factors has to be increasingly strong."

Nominating organisation	Comment	Response
CML Support Group UK	B) Limitation of comparators to current first line treatment therapies. Even though it had been established that IFN-a (interferon alpha) was not to be *"considered a cost-effective treatment compared to HU"* (TA 70: 4.3.9) since its ICER was *"in excess of £1 million per QUALY"* (TA 70: 4.3.7), the Committee nevertheless decided that, since IFN-a was, at that time, a standard first line treatment for CML it was therefore appropriate to compare it to imatinib in terms of its ICER. Having taken this decision the Committee proceeded to conclude that imatinib, as a first line treatment for CML *"may result in a better use of NHS resources for CML"* (TA 70: 4.3.10) On this logic the current ACD should have insisted on using only standard dose imatinib as a comparator in its appraisal since this is the current first line treatment.	The reference case stipulates that the appropriate comparators are therapies routinely used in the NHS, including technologies regarded as current best practice. See Guide to the Methods of Technology Appraisal section 5.2.5 and 5.2.6. The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care. The Committee also heard from the clinical specialists that bone marrow stem cell transplantation could be used. The Committee concluded that any one of these treatments could be considered a comparator with high-dose imatinib, nilotinib or dasatinib. See FAD section 4.3.3
CML Support Group UK	C) Actual comparators used in this ACD If an argument is put forward that standard dose imatinib has no benefit and thus should not be a comparator then why did the committee not decide to abandon HU as a comparator on the grounds that HU offers no possibility of enabling patients to survive the 10 years set out in the second scenario (see below ACD: 4.3.2) selected as being the *"least implausible"* Obviously there can be no HU ICER values entered in the second scenario table (Table 3) since all patients prescribed it would have died before the 10 year time-line set yet the Committee still insists on using it as comparator (SHTAC *"Additional scenarios analysis"* p. 2)	The reference case stipulates that the appropriate comparators are therapies routinely used in the NHS, including technologies regarded as current best practice. See Guide to the Methods of Technology Appraisal section 5.2.5 and 5.2.6. The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people would receive treatment with interferon alfa, hydroxycarbamide or best supportive care. The Committee also heard from the clinical specialists that bone marrow stem cell transplantation could be used. The Committee concluded that any one of these treatments could be considered a comparator with high-dose imatinib, nilotinib or dasatinib. See FAD section 4.3.3

Nominating organisation	Comment	Response
CML Support Group UK	D) Non TKI comparators We would argue that it is perverse to reason HU still qualifies for the status first line treatment. To do so would logically require other therapies like busulphan to also be included. The current use of HU or busulphan is not as first line treatment but is rather either a 'conditioning treatment' prior to some other therapeutic intervention or, where no first line intervention is appropriate, as Best Supportive Care.	This appraisal is for the treatment of imatinib-resistant chronic myeloid leukaemia (CML), and for people with CML for whom treatment with imatinib has failed because of intolerance. It does not appraise the use of the technologies for the first-line treatment of CML.
CML Support Group UK	E) Stem cell transplantation Stem Cell/Bone Marrow Transplantation is also absent from consideration in the *"least implausible"* scenario analysis yet it is surely more qualified for first line status than HU or bulsulphan in that it offers the possibility of long term survival for those for whom it can be considered and who manage to avoid the risks associated with its implementation.	This appraisal is for the treatment of imatinib-resistant chronic myeloid leukaemia (CML), and for people with CML for whom treatment with imatinib has failed because of intolerance. It does not appraise the use of the technologies for the first-line treatment of CML.

Nominating organisation	Comment	Response
CML Support Group UK	**<u>The impossibility of mobilising a traditional evidence based methodology</u>** The ACD Committee was also critical of the use of interferon-alpha as a comparator (in both the Bristol Myers Squibb and PenTAG models) making clear that it preferred the comparators recommended by the clinical specialists, after discounting the possibility of resort to any of the TKIs, which were HU and stem cell transplantation (SCT). Since the Committee notes (ACD: 4.3.2.) the majority of this patient group will be likely to be unsuitable for SCT, the more so given the median age of 60 cited in the ACD, the comparator defaults to HU. Yet the committee accepts that for HU *"...the prognosis is poor, with a median life expectancy of around 5 years"* (ACD: 4.3.3) whilst also accepting the evidence of these same clinicians that more than 50% of patients could possibly expect *"a near normal life expectancy"* if prescribed nilotinib or dasatinib with responses being *"as good as the initial response to standard-dose imatinib"* (ACD 4.3.3.) The Committee expressed dissatisfaction with all the clinical studies reviewed by the HTA provider (SHTAC) and noted the considerable reservations expressed by the provider regarding the design, interpretation and execution of the trials/studies reviewed. It is reasonable to assume, because of its position at the top of the hierarchy of an evidence based approach to medicine, that an acceptable trial would be a double blind randomized clinical trial (RCT). However it is self evident that attempting to recruit patients from an already very small patient population, rendered even smaller by the availability of the drugs in question in comparable countries, presents very formidable problems.	The Assessment relies on the available evidence submitted to the Institute and that retrieved from the published literature by the assessment group. 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.
CML Support Group UK	All three TKI drugs are prescribed and reimbursed all over Western Europe, the USA, Canada, Australia and New Zealand, in some 90 nations in total.	Comment noted.

Nominating organisation	Comment	Response
CML Support Group UK	Since the trial would use HU as the stated preferred comparator it is inevitable that there would be very considerable crossovers from the HU arm given its established lack of efficacy relative to the drugs in question. Indeed it is highly likely that, in such circumstances, the trial would be abandoned so that even a default from the preferred intention-to-treat to a per-protocol analysis, as the Committee requested of the HTA team with regard to imatinib (TA 70: 4.3.8.), would not be possible. Given the particular circumstances involved, and the ethical issues raised as a consequence, it is not implausible to speculate that it would prove impossible to even propose a trial which would of course act as a major deterrent to those that might fund it at the initial planning stage. This is best described as a Catch 22 situation where a NICE ACD proposes a negative recommendation due to what the CEO, Andrew Dillon, calls *" very weak"* evidence (NICE Press Release 5th May 2011) which carries with it an implicit assumption that it would be possible to generate '*very strong'* evidence that was acceptable to the Committee. Yet all concerned know that such evidence will never be forthcoming since the means of establishing it can and will never be operational. It is not as if NICE is unaware of the problem.	The Assessment relies on the available evidence submitted to the Institute and that retrieved from the published literature by the assessment group. 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.

Nominating organisation	Comment	Response
CML Support Group UK	TA 70 observes that the European Agency for the Evaluation of Medicinal Products (EMEA- now EMA) marketing authorization of imatinib in November 2001 was granted on the basis of surrogate measures which included haematological (HR) and cytogenetic response (CR) rates, and progression free survival rather than Randomized Clinical Trial (RCT) data. The EMEA (EMA) argued this was because: *" the indications for which the medicinal product in question (imatinib) is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence/data on the quality, safety and efficacy of the medicinal product."* (TA 70: 3.2.) TA 70 noted that the previous Guidance TA 50, for the current licensed indications was "based on evidence primarily from case series" (TA 70: 4.3.2.) TA 70 is based on a reliance on a single open label, non randomized RCT (IRIS) and three case studies but: *" .. the published supportive evidence from the RCT relied principally on surrogate measures of efficacy such as the achievement of an HR and/or a CR"* (TA 70: 4.3.2.) because of the absence of long term survival data. However the Committee considered that: *" ..based on current evidence of the significance of CR and HR in CML, and knowledge of the effect of imatinib – that the relationship between CR and survival is sufficiently strong to support the use of CR, in particular, as a surrogate measure of survival in people with chronic-phase CML."* (TA 70: 4.3.3.) but: *"the Committee did not believe it was possible, based on the current evidence, to determine precisely the absolute survival gain that would result from switching from IFN-α to imatinib as first-line treatment."* (TA 70: 4.3.4.) - in part because the Committee was aware of *"high crossover rates in the IRIS trial"* (the RCT referred to) (TA 70: 4.3.5.) Nevertheless the Committee recommended that, even with such a "paucity" of data, *"Imatinib is recommended as first-line treatment for people with Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) in the chronic phase."* (TA 70:1.1.) Yet the committee came to the opposite conclusion, with its negative recommendation, in this ACD even though the evidence was also, similarly not comprehensive.	The Assessment relies on the available evidence submitted to the Institute and that retrieved from the published literature by the assessment group. 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.

Nominating organisation	Comment	Response
CML Support Group UK	There is a more general criticism applicable here concerning the particular genetic mutations for which a TKI is active against. The principle underlining a TKI is that it is effective only against those mutations for which it was designed and that it is counter intuitive and counter productive to deploy it when they are not present. We argue that, with likely recipient minute patient populations for what are already rare diseases, RCTs, as currently designed, should be abandoned altogether and substituted with a more appropriate design based on a Bayesian approach. Bayesian approaches imply updating prior probability distributions of efficacy through new data in order to give rise to posterior probability distributions. There is a requirement for sufficient information to be available to empower the statistics required which would be sourced from clinical practice and biological evidence, other clinical studies, the natural history of the disease, analogies with more frequently occurring diseases etc. The ongoing development of digitalized e-health records with common design matrixes accumulated in instantly accessible data warehouses offer tantalizing possibilities in terms of the contribution they could make to such an approach.	Comment noted.

Nominating organisation	Comment	Response
CML Support Group UK	**Innovation status: criteria for qualification** The Committee does not find nilotinib and dasatinib to be innovative *"in terms of pharmacological progress beyond imatinib"* Imatinib is, however, a drug that does attract their innovation classification. They give no substance to this decision. There are, as far as we are aware, no publicly available NICE criteria deployed to grade the degree of innovation displayed in any particular case and it seems such classificatory work proceeds on an ad hoc basis. Of course we accept that imatinib represented a 'step change' in cancer therapy in much the same way as penicillin represented a 'step change', as in a first of its kind, but would think it either perverse or demonstrative of a misunderstanding of the science not to regard successor generations as representing an innovation. Pharmacogenomics, the tailoring of products to particular genetic configurations characteristic of small sub sets of patient populations for diseases like CML, sits at the leading edge of advanced manufacturing industries like pharmaceuticals. Scientists working in research institutions and those engaged in similar work in academic institutions, would be surprised, to say the least, that their work in developing successor generations of inhibitors is not considered to represent *"pharmacological progress beyond imatinib"* and would no doubt wish the committee, or indeed NICE, to articulate their innovation policy in rather more detail than hitherto has been the case, in order to demonstrate that they had not made any *"pharmacological progress beyond imatinib"*.	The Committee considered that the development of dasatinib and nilotinib was not a further major innovation. The Committee did not identify any potential significant and substantial health-related benefits that had not been included in the economic models. See FAD section 4.3.30
CML Support Group UK	Elsewhere in the appraisal the committee accepts, and indeed use as a resource in their appraisal work, evidence supplied by expert clinicians that confirms that, in more than 50% of the patients involved, a *"good response"* to nilotinib and dasatinib was achieved with patients able to anticipate living *"possibly with a near to normal life expectancy (that is, more than 10 years)"*. They also note responses were *"usually as good"* as the response to the first line drug they accept to be innovative, standard dose imatinib. It is axiomatic that the *"more than 50%"* of patients referred to above would certainly regard dasatinib or nilotinb as representing *"pharmacological progress beyond imatinib"* especially since the alternative would be HU.	Comment noted.

Nominating organisation	Comment	Response
CML Support Group UK	**Equalities** There are issues to be considered that fall under this heading. We feel NICE need to recognise in a more policy driven manner that there are two populations that are under represented in terms of stem cell transplants. One are ethnic minorities, especially the African Caribbean community, and their gross under-representation in donor registries and the other is the population on the upper side of the current median age for stem cell transplantation. We would like it noted that in the former case greater encouragement ought to be offered to organisations like the African Carribbean Leukaemia Trust to assist them in building ethnically diverse donor registry and secondly, that additional resources should be devoted to the research of new technologies that involve the use of inhibitors in stem cell transplants with the objective of making them safer and more easily tolerated than is the case at present.	The Committee noted the argument that if dasatinib, high-dose imatinib or nilotinib are not recommended for the treatment of imatinib-resistant CML and that this could raise issues in relation to race, age (the elderly), and comorbidities. However, the Committee concluded that allowing for clinical decisions relating to a range of possible treatments based on individual assessment of risk and benefit does not limit access to the technology for any specific protected group compared with other people. See FAD section 4.3.31

Comments received from commentators

Commentator	Comment	Response
Commissioning Support, Appraisals Service (CSAS)	On behalf of the Commissioning Support, Appraisals Service (CSAS), I would like to submit our comments on the appraisal consultation document for the Multiple Technology Appraisal on dasatinib, high-dose imatinib or nilotinib for imatinib-resistant chronic myeloid leukaemia (CML) in the NHS in England and Wales. CSAS is in agreement with the appraisal committee's decision that this technology does not represent a cost effective use of scarce NHS resources.	Comment noted
CSAS	Unit costs: Dasatinib costs £83.50 per 100mg tablet (excluding VAT; 'British national formulary' [BNF] edition 61). Assuming a treatment regimen of 100mg once daily the per person cost of dasatinib treatment is £30,477 per year. Imatinib costs £53.47 per 400mg tablet (excluding VAT; BNF edition 61) and at a maximum dose of 400mg twice daily this would result in an annual per person cost of £39,032.61. However, the cost of imatinib increased in December 2010 to £57.48 per 400mg tablet (excluding VAT; 'Monthly Index of Medical Specialties' [MIMS] April 2011), which would now make the annual cost at the 400mg twice daily dose, £41,960. The cost of nilotinib is £21.72 per 200mg tablet (excluding VAT; BNF edition 61), and assuming a dose of 400mg twice daily this makes an annual cost £31,711. Costs of all drugs may vary in different settings because of negotiated procurement discounts.	Comment noted

Commentator	Comment	Response
CSAS	Affordability: An estimated 560 people are diagnosed with CML in the UK each year, an age standardised rate of 1.2 per 100,000 men and 0.7 per 100,000. The CSAS rapid evidence review estimated that 80% of people with CML receive standard dose imatinib, and 12% of these will be resistant. As such with a CML population prevalence of 0.001% it was estimated that in a PCT of average size 300,000 was one person every three years would be eligible for these treatments.	Comment noted
CSAS	Efficacy: The Assessment Group conducted a systematic review of evidence on the clinical efficacy of dasatinib, nilotinib and high-dose imatinib compared with each other, and with other treatment options, in people with CML resistant to standard-dose imatinib, and identified only one RCT directly comparing dasatinib and high-dose imatinib. All other trials were single arm. The comparative RCT had methodological limitations and a high level of crossover (80% switched from imatinib to dasatinib after 13 weeks). In this trial the outcome of complete cytogenetic response (considered a surrogate outcome for overall survival) was reached by 26 months in 43.6% of those receiving dasatanib, 63.4% of whom had a major molecular response. It was reported that 74% of those receiving high-dose imatinib achieved complete cytogenetic response at 18 months, 55.6% of whom had a major molecular response. Median survival was not reached in the trial. Due to the study design and high crossover the Assessment Group considered that the treatment arms could not be compared.	Comment noted
CSAS	Appraisal of the evidence: The Appraisal Committee noted the short trial duration in terms of expected survival, and the overall poor evidence base for all interventions in people whose CML is resistant to standard-dose imatinib. The Committee also aware noted that no evidence was presented on the use of dasatinib, high-dose imatinib and nilotinib adjuvant to intensive chemotherapy for people with advanced disease, as would be used in practice. Also, specialists considered that the people included in clinical trials had worse disease prognoses than would be seen for treatment in current clinical practice. It was agreed that dasatinib, high-dose imatinib and nilotinib would provide clinical benefit for people with imatinib-resistant CML, and the Committee agreed with specialists that in practice, dasatinib and nilotinib would be preferred over high-dose imatinib for people with imatinib-resistant CML. However, there was agreement that there was no good evidence to distinguish between dasatinib and nilotinib, and that the poor evidence base means that the magnitude of the benefit is uncertain.	Comment noted
CSAS	Safety: The Committee heard from specialists that dasatinib and nilotinib are better tolerated than imatinib, and it was also considered that older treatments such as interferon alfa are poorly tolerated.	Comment noted

Commentator	Comment	Response
CSAS	Cost effectiveness: The Appraisal Committee considered two Markov models submitted by the manufacturers of dasatanib (Bristol-Myers Squibb) and nilotinib (Novartis), and a model developed by PenTAG in the original appraisal of imatinib-resistant and imatinib-intolerant CML. Bristol-Myers Squibb assessed the cost effectiveness of dasatinib, high-dose imatinib and nilotinib compared with standard-dose imatinib, allogeneic stem cell transplantation and interferon alfa in people with imatinib-resistant CML. Data on progression came from a dose-ranging RCT of dasatinib, other clinical studies and opinion. Data from the RCT were limited to 48 months of follow-up and the manufacturer extrapolated longer-term progression-free survival by assuming that the monthly rate of progression after 48 months was equal to that observed during the final year of the published data. Drug acquisition costs came from BNF60. High-dose imatinib and nilotinib were dominated by dasatinib, and the base-case ICER of dasatinib compared with interferon alfa was £38,883 per QALY gained. Novartis assessed nilotinib and high-dose imatinib compared with SCT and hydroxycarbamide in people with chronic-phase imatinib-resistant CML. Drug acquisition costs came from BNF60. Base-case results showed that high-dose imatinib was dominated by nilotinib, and the ICER of nilotinib compared with hydroxycarbamide and stem cell transplantation was £44,028 per QALY. PenTAG estimated the cost effectiveness of dasatinib, high-dose imatinib and nilotinib in people with imatinib-resistant chronic-phase CML, but the Assessment Group was unable to identify suitable effectiveness data for comparator treatments in people with advanced CML with which to populate the model. Drug acquisition costs came from BNF58. In the base-case high-dose imatinib was dominated by nilotinib. The ICER of nilotinib compared with interferon alfa was £44,600 per QALY gained, and dasatinib compared with interferon alfa resulted in an ICER of £75,800 per QALY gained. Dasatinib compared with nilotinib resulted in an ICER of £277,700 per QALY gained.	Comment noted

Commentator	Comment	Response
CSAS	Appraisal of the economic evaluation: The Appraisal Committee noted the use of complete cytogenetic response as a surrogate outcome for overall survival and heard from the clinical specialists that the strongest link was between major molecular response and overall survival. The Committee also noted that the acquisition costs of all three interventions are in excess of £30,000 per person per year, and that the recently increased cost of imatinib is included in only one of the economic models (Novartis). In the Bristol-Myers Squibb the Committee noted the cost of interferon alfa was almost double that in other models and that there was no comparison to hydroxycarbamide. They also did not consider the extrapolation of longer-term progression-free survival to be appropriate. The Novartis model was notable in having no comparison with dasatanib and no separate comparisons for interferon and hydroxycarbamide. The economic models provided by PenTAG, Bristol-Myers Squibb and Novartis resulted in ICERs greater than £30,000 per QALY gained for all treatments. In all of the models, nilotinib had the lowest ICERs. The Committee did not consider that a plausible ICER had been presented. All models were considered to have treatment durations different from what would be seen in current practice where people would be treated until death. They concluded that there is no evidence to distinguish between dasatinib and nilotinib and that the ICERs for these treatments compared with hydroxycarbamide would both be higher than £43,800 per QALY gained and could be considerably more if treatment were continued for the person's lifetime. The Committee also noted that high-dose imatinib was dominated in all models and therefore could not be recommended as a cost-effective use of NHS resources for the treatment of chronic-phase CML that is resistant to standard-dose imatinib.	Comment noted
CSAS	Additional factors: The Committee was aware that end-of-life criteria may be met by people with accelerated or blast phase CML who are resistant to imatinib. However, though life expectancy at this stage is less than 24 months and less than 10% of all people with CML would present at this stage, the Committee agreed that the available evidence on life extension was too weak and not robust, and that no data were presented for the interventions as used in clinical practice. The Committee concluded that high-dose imatinib, dasatinib and nilotinib do not fulfil end-of-life criteria for people with advanced CML.	CSAS

Commentator	Comment	Response
Healthcare Improvement Scotland (HCIS) Commentator 1	We have conducted a West of Scotland and Lothian audit for all patients treated initially with imatinib 400mg per day from diagnosis. Restricted access to second generation tyrosine kinase inhibitors in the UK could result in suboptimal treatment for almost half of chronic myeloid leukaemia patients: results from a West of Scotland and Lothian population study.Gallipoli P, Shepherd P, Irvine D, Drummond M, Holyoake T. Br J Haematol. 2011 Apr 22. doi: 10.1111/j.1365-2141.2011.08653.x This audit demonstrates that in the real world approximately 50% of patients who are started on imatinib at diagnosis will remain on imatinib and in good response 5 years later. However 50% of patients will have discontinued imatinib therapy. These patients include a tiny number who proceed to stem cell transplant, some who have intolerance to imatinib (nearly 20%) and switch to one of the second generation agents, either dasatinib or nilotinib, some who fail imatinib and switch to dasatinib or nilotinib and some who are deemed to have a sub-optimal response to imatinib and are switched to dasatinib or nilotinib. The study included 122 patients diagnosed between 2002 and 2010. 44 patients of 122 stopped imatinib because of intolerance or failed response of whom 39 went onto second generation drugs dasatinib or nilotinib. For these 39 patients the median time on imatinib was 13.2 months but 19.2 months on second generation strongly suggesting the the second generation drugs were both tolerated and effective. Indeed 25 of 39 patients were deemed to have had a satisfactory response, 10 were intolerant and 4 failed to respond. The EFS on second generation drugs was 58% which was better than for imatinib first line at 53%. Both the intolerant to imatinib and the failed imatinib groups did equally well on second generation drugs going against the idea of reviewing intolerance separately to resistance. In other words 60% of patients who do not do well with imatinib will be rescued by dasatinib or nilotinib.	Comment noted

Commentator	Comment	Response
HCIS Commentator 1	My take on this is that both nilotinib and dasatinib are exceptionally good drugs when used for those who fail imatinib either for INTOLERANCE or for RESISTANCE. In the worst case scenario (hypothetical) if a patient became imatinib resistant and imatinib was discontinued the person might die the following day, whilst in the very best case scenario they would go on to dasatinib or nilotinib and live a normal life (eg more than 10 years). If in this setting the drug price is too high then the threshold for QALY set at £30,000 is likely to be bridged simply because dying immediately is cheaper than living on drug for 10 years. In reality if we stop imatinib in these cases they will not die the following day but their life expectancy would be limited to months/few years as they are already a high risk group as they are imatinib resistant and given palliative therapy with hydroxyurea they would all enter blast crisis and die with a median somewhere around 24 months. If these same patients were given dasatinib or nilotinib we know from the audit above, performed in Scotland on real Scottish CML patients, that their EFS would be 57.9% at 3 years and overall survival 91% (only 4 deaths 2 of which were CML unrelated caused, 1 post-transplant and 1 from CML).	Comment noted
HCIS Commentator 1	The recommendations are completely out of line with our clinical experience of using these drugs. These drugs work in 60% of patients who become resistant to imatinib. These drugs are very well tolerated and given on an out patient basis. Only today I have been in a clinic full of patients on second generation TKI dasatinib and nilotinib who would have died from disease progression had they not been given these drugs. The doctors all know that this is FACT. The decision by NICE is only made on the basis of cost – this being the case the only way out of this situation is to try to force the drug companies to lower their price.	Recommendations are based on evidence of both clinical and cost effectiveness.
HCIS Commentator 1	What happens in Scotland currently is that every patient diagnosed with CML is commenced on imatinib 400mg or entered into SPIRIT 2 trial which offers a 50:50 randomisation between dasatinib and imatinib. The patients are monitored every 3 months. We apply the ELN recommendations (JCO 2009, Baccarani M et al,). If the patients fail imatinib they either go onto dasatinib or nilotinib (95%) or are considered for a stem cell transplant (no one recently in Glasgow). Similarly if patients show a suboptimal response according to ELN they go onto dasatinib or nilotinib. Similarly if intolerant they switch to one of these agents. In a tiny number of patients we find they develop haematological toxicity with all 3 available TKI and if not fit for stem cell transplant (the vast majority) we use hydroxycarbamide. NO patient is on interferon for treatment of CML in WOSCC.	The Committee heard from the clinical specialists that, in clinical practice, treatment with dasatinib, high-dose imatinib and nilotinib is given in accordance with European guidelines, which specify time-dependent targets. If the CML is responding to treatment, the treatment will be continued until progression or until the person dies (from non-CML causes). If CML does not respond to dasatinib or nilotinib within 12 months, treatment may be discontinued, occasionally changing to hydroxycarbamide and/or, if suitable, stem cell transplantation. See FAD section 4.3.5

Commentator	Comment	Response
HCIS Commentator 1	Absolutely. If we cannot give the 50% of patients who become intolerant or resistant to imatinib either nilotinib or dasatinib then we would use stem cell transplant with mortality of 10-40% depending on age and with +++ long term complications (only applicable in a small minority of cases <15%) or hydroxycarbamide a palliative agent thus condeming these patients to disease related death within a short time window when we know there are good drugs out there for these patients. I hope that by applying for each case individually we would still be able to prescribe nilotinib or dasatinib for all those cases who develop imatinib resistance as there is really no other choice that makes any sense.	Comment noted.
HCIS Commentator 1	I would hope our extensive experience with these drugs in Scotland and our careful audit and analysis of outcome would be taken into account. I have led these studies from the beginning (PI Scotland for all imatinib, nilotinib and dasatinib trials to date) with huge input from Dr Mark Drummond. It has been our privilege to be able to secure amazingly good drugs for patients with CML all over the country – Arran, the Borders, Fife, Wick etc (even one case by sleeper from Kent and another from London). Please ensure we can continue to serve our patients as we have been doing until now.	Comment noted.

Commentator	Comment	Response
HCIS Commentator 2	I would suggest reading the following article: Restricted access to second generation tyrosine kinase inhibitors in the UK could result in suboptimal treatment for almost half of chronic myeloid leukaemia patients: results from a West of Scotland and Lothian population study.Gallipoli P, Shepherd P, Irvine D, Drummond M, Holyoake T. Br J Haematol. 2011 Apr 22. doi: 10.1111/j.1365-2141.2011.08653.x As with the use of all TKIs since they became available in 2002 we have audited their use extensively in Scotland. This clearly illustrates that we would be doing almost 50% of our CML population a disservice by removing their availability. These patients MAY have recourse to transplant (approximately a 30% mortality rate depending on source data used and pt factors) a procedure which costs £70,000 with approx £2,400 ongoing monthly cost thereafter (which includes a £21,000 per readmission sum). In the NICE economic model this probably looks fairly attractive; killing patients with the treatment certainly does reduce ongoing drug costs. How out of step this decision is can be easily gleaned from the literature on the subject (see ELN Guideleines, JCO 2009 Baccarini et al). This is a Europe-wide consensus guideline produced with UK representation. Our audit results show that 60% of patients who go onto these drugs achieve an excellent response. Without them this group would now comprise patients on high dose imatinib (600-800mg daily, expensive, toxic & less effective than nil or das, dead as a result of transplant, some cured and well as a result of transplant with a significant cohort alive but with serious transplant induced co-morbidities including downstream secondary cancers, heart disease etc, patients on palliation with hydroxycarbamide, a useless- but cheap-treatment but keeps white cell count down, and perhaps a few individuals on interferon. The latter remains expensive (approx £1000 per month) and produces acceptable responses in only 10-20%, with considerable toxicity. In short treatment would return to a hodge-podge of unsatisfactory treatments from the useless to reasonably effective (HD IM) to the downright lethal.	Comment noted.

Commentator	Comment	Response
HCIS Commentator 2	Any drug that prevents death, but demands ongoing administration, is going to be unattractive to our current economic modelling systems. It is my understanding that the economic model used by NICE (& produced by PENTAG) was hugely flawed, specifically with regard to the comparator drugs in which Hydroxycarbamide (which costs pennies) featured highly. This comparator is laughably inappropriate, as all doctors asked to comment on the model (including myself) pointed out. The correct comparator should have been high dose imatinib. This is even more expensive (approx £40,000 pa) and significantly more toxic than either dasatinib or nilotinib. I appreciate that cost-modelling does not take into account the 'social' costs of therapy however I would appeal to the SMC / QIS to give some thought to this: CML patients may now have a near normal life expectancy thanks to these drugs. This is entirely down to scientific and pharmaceutical advances and is a triumph of modern medicine. Furthermore, these patients also function normally and importantly RETURN TO WORK. If we didn't have 2nd line TKIs many patients would be held on imatinib either at standard or high dose; this would still cost a significant amount (in the case of high dose IM considerably more than das or nil). Uncomfortable imatinib side effects would have to be tolerated (after all the alternative is not there) and QoL would suffer. Many patients would stop functioning and many would stop work. I cannot think of a single working patient in our large CML practice (60-80 patients) who has stopped work for disease or treatment related reasons.	Comment noted. The reference case stipulates that the perspective on outcomes should be all direct health effects whether for patients or, where relevant, other individuals (principally carers). The perspective adopted on cost should be that of the NHS and PSS. If the inclusion of a wider set of costs or outcomes is expected to influence the results significantly, such analysis should be presented in addition to the reference case analysis; see section 5.3.3.1. of the Guide to the Methods of Technology Appraisal
HCIS Commentator 2	Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? *If not, why do you consider that the recommendations are not sound?* No. For all the reasons above.	Comment noted
HCIS Commentator 2	"What happens in Scotland currently is that every patient diagnosed with CML is commenced on imatinib 400mg or entered into SPIRIT 2 trial which offers a 50:50 randomisation between dasatinib and imatinib. The patients are monitored every 3 months. We apply the ELN recommendations (JCO 2009, Baccarani M et al,). If the patients fail imatinib they either go onto dasatinib or nilotinib (95%) or are considered for a stem cell transplant (no one recently in Glasgow). Similarly if patients show a suboptimal response according to ELN they go onto dasatinib or nilotinib. Similarly if intolerant they switch to one of these agents. In a tiny number of patients we find they develop haematological toxicity with all 3 available TKI and if not fit for stem cell transplant (the vast majority) we use hydroxycarbamide. NO patient is on interferon for treatment of CML in WOSCC".	Comment noted

Commentator	Comment	Response
HCIS Commentator 2	Yes. We would do more transplants, have more transplant related deaths and have more patients remaining on imatinib (including high dose) with chronic toxicity. We would use interferon in some circumstances (again at considerable expense & toxicity) in the knowledge it would only benefit a minority (10-20% at most). For those denied 2nd Gen TKIs a proportion would still get them; we would make a good case on a non-formulary / exceptionality basis. Please note; while I am no health economist I rather suspect that by the time you add all these cases up (HD IM, Transplant, 2GTKIs granted on a NF application) and factor in the chronically ill who are unable to work we are not going to be saving very much money after 'unapproving' these drugs.	Comment noted. The reference case stipulates that the perspective adopted on cost should be that of the NHS and PSS. If the inclusion of a wider set of costs or outcomes is expected to influence the results significantly, such analysis should be presented in addition to the reference case analysis; see section 5.3.3.1. of the Guide to the Methods of Technology Appraisal
HCIS Commentator 2	We have a strong CML background in this country with a Scotland-wide network of interested expert clinicians and a nationwide Treatment Guideline in preparation. This will incorporate the role of nilotinib as first line therapy if approved (see below). These drugs are used within tight local guidelines and are audited regularly (as we have demonstrated). The same cannot be said for England outwith the larger interested centres.	Comment noted.

Commentator	Comment	Response
HCIS Commentator 2	A final and important comment is with regards the availability of Nilotinib as a first line treatment. I understand that this is currently going through the SMC and will involve a price reduction to that of Imatinib when used first line. The implications of this for the use of the second line agents are two-fold: 1. Less patients will fail first line therapy. Nilotinib is more effective than imatinib. My estimates from the literature are that 10-20% of patients will require a 2nd line agent with nil as compared to 30-40% in our IM audit / literature. Furthermore, for patients intolerant of nil, imatinib will be used (cost neutral) as a second line therapy (a major shift in Scottish practice). Therefore we are looking at only 10% or so of patients escalating to dasatinib, a marked reduction from before. I would therefore expect the treatment of CML to become gradually more cost effective with less use of these agents in the second line. **2.** Nilotinib cost reduction. This is available for patients treated with nilotinib as first line. This immediately produces a grey 'first line area'. What if a patient is rapidly intolerant of imatinib, say within days or even 4-6 weeks, who has not yet achieved a remission (and this does happen)? I would still consider use of nilotinib here as 'first-line' as far as long-term disease control is concerned. Thus a proportion of what we would have considered 2nd line (and paid for accordingly) might, quite legitimately, be accepted for first line discounted therapy. I should point out that I have discussed this issue with Novartis (in my view the fairest and most ethical company involved in treating blood cancers) and they agree that the line is a blurred in this regard but that they would honour the agreement (indeed they do not ask for evidence re line of therapy). These two important issues need to be taken into account when making the decision on 2G TKIs in a Scottish context.	Comment noted.
HCIS Commentator 2	I would reiterate Professor Holyoake's plea to reverse this NICE MTA. As I have illustrated above it is based on a flawed economic model with unrealistic cost comparators. First line Nilotinib will alter the picture in the coming years. If these drugs are refused we can safely predict that many patients will die unnecessarily from inappropriate and ineffective treatments in the years to come. I think it would be a grave error to align ourselves with this decision while the rest of Europe looks on in disbelief.	Comment noted.

Summary of comments received from members of the public

In total, 657 members of the public responded to the consultation. Of these 451 people contributed by individually written email or letter and 206 people commented via the NICE website. This table summarises those 657 public comments received as emails, letters and web comments in line with NICE's processes. The responses are categorised according to key themes and examples are quoted.

Theme	Response
Clinical effectiveness of high dose imatinib, dasatinib and nilotinib and comparator drugs/ bone marrow transplant Many respondents commented on the clinical effectiveness of the drugs being appraised (high dose imatinib, dasatinib and nilotinib): • *Please could you explain me how anyone can suggest that higher doses of Imatinib treatment are not recommended or are not working? As far as I am concern and I am one of these patients as long I am alive and feeling fantastic with full haematological response to treatment it is in my opinion as effective as any cancer treatment can possibly be…* • *She originally took the drug imatinib but suffered serious and disabling side effects which she tolerated for two years. After this time the level of the defective gene which causes CML to develop started to rise and her consultant advised changing the drug to nilotonib which she has been taking since December 2010. This drug has so far proved very effective with few troubling side effects and her levels have dropped and she is nearly in remission…* • *…was diagnosed with CML (in chronic phase PCR 80.135) in May 07 and was initially prescribed Imatinib at 100mg/day. However, by Apr08 it was clear that the initial gradual improvement from the treatment (Nov 07 PCR 7.743) was not being sustained and things were deteriorating (Mar 08 PCR 63.476). Treatment with Dasatinib 100 mg/day started in May 08 and immediately showed significant improvement (Sep 08 PCR 0.027) representing Major Molecular Response.* Some respondents also reported negative personal experiences of bone marrow transplants and of comparator drugs: • ***…****Her bone marrow transplant failed and she was put on a drug trial for imatinib (glivec). The drug has been very effective for her – without it she would have died ten years ago…* • *There is no viable alternative, Hydroxia Urea [sic] and Interferon, are very temporary medicines, and only hold back the disease for months.*	Recommendations are based on evidence of both clinical and cost effectiveness. 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.

Theme	Response
Costs/cost effectiveness Respondents made a number of different observations about costs: • *These drugs have been providing most CML patients a quality and longevity of life they would not have enjoyed some 12 years ago, with a prognosis of 3 to 5 years expected then. I cannot say what these drugs have cost to the NHS in monetary terms, but balanced against their quality of life there can be no comparison… The alternative cost to the NHS of providing care to CML patients I am sure would be far greater than providing tablets to treat the problem, with periodic visits to haematology departments for health checks to monitor the individual.* • *Many Nations around the world risk and spend millions to save lives and here your 'financial cut-backs' are going to put many lives at risk!* • *This is not a matter of cost, this is life and death and I'm shocked a change is even being considered. Even if a handful of people benefit from the next generation of treatment it HAS to be worth it.* Some respondents noted patients' own contributions to the NHS, as tax payers or as NHS or public sector employees: • *The majority of CML patients have worked for the most part of their life and have paid there [sic] dues. Now they are being told that you can't have the medication that keeps you going and gives you a hope of a normal life.*	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 NICE process Comments about the NICE process focussed on two perceived problems: Some respondents criticised NICE for not having a CML specialist as part of the committee membership: • *It is noted that on the appraisals committee there is not one cancer specialist let alone a CML specialist.* Some people also said that the NICE process doesn't take patient choice sufficiently into account: • *I feel let down and disappointed – and not a little afraid. I'm doing well on Imatinib 400mg but if that stops working, where does that leave me? Quite honestly, living with leukaemia is bad enough, without having the added worry of people trying to withdraw our safety net.*	The Appraisal Committee is an independent advisory body. Members include people who work in the NHS, patient and carer organisations, relevant academic disciplines, and pharmaceutical and medical devices industries. The invited clinical specialists and patient experts are present for the discussions of the Committee at its first meeting and are encouraged to interact fully in the debate with the Committee, including both responding to and posing questions. (see Guide to the Methods of Technology Appraisal, Chapter 6)

Theme	Response
Equity, equality and human rights A number of respondents raised issues relating to equity or challenged the NICE decision within the context of human rights legislation: • *In the Appraisal consultation document, it is concluded [ref 4.3.18] that the preliminary recommendations do not discriminate. While this may appear so on the surface, it could be argued that its implementation would in practice be age-discriminatory. While transplant treatment is a relevant treatment for younger people, it is not considered an option for those aged over 65 (like myself - but I still play squash). Removing the option of treatment with second-generation TKIs, currently available to everyone, will result in discrimination against the over 65?s and be, in effect, age-discriminatory in my view. Perhaps this would need to be tested in court to prove otherwise* Many respondents challenged the fact that NICE was restricting use of dasatinib, high-dose imatinib and nilotinib when such restrictions did not apply to patients in other countries in Europe: • *What we can't understand is that withdrawing alternative drugs for Imatinib resistant patients essentially leaves them with two options;1-Move to Scotland or elsewhere in the EU to get these drugs, 2-A bone marrow transplant which obviously isn't available to everybody and in itself can bring even more problems than it solves.* • *The available annual UK patient population that would qualify is around a 120 but this would include patients in Scotland where these drugs are already available. As they are in countries in Western Europe.* • *The draft recommendation also goes against the direction of travel we see prevailing in Scotland and other Western European countries where these drugs will continue to be available.*	The Committee noted the argument that if dasatinib, high-dose imatinib or nilotinib are not recommended for the treatment of imatinib-resistant CML and that this could raise issues in relation to race, age (the elderly), and comorbidities. However, the Committee concluded that allowing for clinical decisions relating to a range of possible treatments based on individual assessment of risk and benefit does not limit access to the technology for any specific protected group compared with other people. See FAD section 4.3.31

Theme	Response
Other Some respondents commented that they agreed with the conclusion of the Southampton Health Technology Assessment Centre report commissioned by NICE and therefore did not understand the preliminary no recommendation. Most respondents also argued that the drugs are effective and thus did not agree with the decision • *…the results of single arms studies suggest that the interventions dasatinib, nilotinib and high dose imatinib can lead to improvements in haematological and cytogenetic responses in people with imatinib resistant CML.* • *Being a patient with cml for the past 4years and on high dose imatibib (800mg) this treatment has been a life saver, as a result cml has had almost no impact on my life, I continue to work in a demanding full time occupation and lead a normal social calendar. Without the availability of this treatment the results would probably be very different.* • *This is a devastating blow for CML patients who are showing early signs of resistance to Imatinib (like our son in law). They are at most immediate risk, facing a bleak future and very short life expectancy on previous treatments that are known to be virtually useless, but all patients currently with a good response to standard dose Imatinib will be extremely worried that they may develop resistance.* Some respondents also commented that the decision made did not conform to Andrew Lansley's promise of a reformed NHS that would give patients "real choice for the first time."	Recommendations are based on evidence of both clinical and cost effectiveness. 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.

Theme	Response
Comments raised by health professionals Health professionals raised several issues on the themes of clinical effectiveness, cost effectiveness, comparator effectiveness and patient choice: • *Up to 30% of CML patients will not respond adequately to standard dose imatinib. Evidence shows that many of these patients will respond to either a higher dose of imatinib or a second generation tyrosine kinase inhibitor. Untreated CML patients are at risk of transformation to blast crisis and death. The only other treatment option is allogeneic transplantation which carries a considerable morbidity and mortality and is not available to all patients due to lack of donor availability / patient age. Thus refusing to fund these drugs discriminates against those of ethnic minority background (where donors may not be available) and older patients in whom transplants may not be possible. These drugs clearly save lives and are associated with minimal toxicity.* • *on the evidence evaluation this would seem a reasonable conclusion, but there will be arguements [sic] in favour of continued treatment following progression/ resistance to standard dose imatinib.* • *Commissioners were unaware that many centres were dose escalating imatinib prior to the launch of Dasatinib and Nilotinib, to the extent that it has been reported as common practice. This clarification of cost-effectiveness is therefore valuable to commissioners.* • *5 patients (out of approx 20 with CML) in our hospital failed to respond to Imatinib (less than Major Cytogenetic response or worse). 4 have gained complete cytogenetic responses (or better) to Dasatinib which has been durable for years. All are very well with no significant side effects, fit and able to work (PS 0), all 4 are in their 40s or early 50s, several with young children. To deny them this drug and therefore the option of long term survival with good health (as opposed to bone marrow transplantation) is not acceptable. I cannot defend this decision to my patients. The other 1 patient on Dasatinib (who did not respond) has gone on to have a bone marrow transplant and is fairly well but has some Graft versus host disease and it is early days.* • *If a good response to TKI is achieved this is akin to a cure but without the very significant toxicity and mortality risk of a transplant. The 2 are not comparable.*	Comments noted The Committee noted the argument that if dasatinib, high-dose imatinib or nilotinib are not recommended for the treatment of imatinib-resistant CML and that this could raise issues in relation to race, age (the elderly), and comorbidities. However, the Committee concluded that allowing for clinical decisions relating to a range of possible treatments based on individual assessment of risk and benefit does not limit access to the technology for any specific protected group compared with other people. See FAD section 4.3.31
General comments All respondents disagreed with the recommendations in whole or in part.	Comments noted

Response to:

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Appraisal consultation document Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (part review of NICE technology appraisal guidance 70)

Prepared by:

Bristol-Myers Squibb Pharmaceuticals Limited

27th May 2011

Executive Summary

Bristol-Myers Squibb (BMS) has reviewed the Appraisal Consultation Document (ACD) relating to dasatinib for the treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance to standard dose imatinib. BMS is disappointed with the preliminary recommendation of the ACD that does not recommend dasatinib for use on the NHS in this setting.

BMS has concerns about the Appraisal Committee's (AC) conclusions relating to dasatinib due to what are agreed difficulties in producing a robust economic model on which to make informed conclusions. We have noted before that we are aware of the difficulties in undertaking modelling with any certainty in this setting, because of the lack of comparative data. BMS is obviously keen that an informed decision point is reached based on the best information possible. There are two possible ways to achieve this, namely:

1) the Institute commissions an independent re-modelling exercise to develop an economic model that all parties feel is credible or
2) the appraisal should be referred to the Decision Support Unit (DSU).

There is no question that, for patients who are imatinib-resistant, both dasatinib and nilotinib are transformational treatments. They may offer a real chance of full life expectancy for a significant group of patients who would otherwise have reached the end of the road with regard to their treatment options, other than a bone marrow transplant. This last point appears to be accepted by all.

The AC acknowledges also that, even in the advanced stages of the disease, there is likely to be real clinical benefit and that there is merit in the view of clinicians that patients in a real-life setting are likely to perform better than those in trials. This is because they will access treatment earlier and are likely to be in better overall physical state than trial patients. Whilst accepting that this benefit cannot be accurately quantified, and given the impossibility of generating new comparative data (what we have is realistically all that can ever - ethically - be generated), this is surely a situation where the potential benefits of the improved real-life performance and the clinical support for these benefits should be given greater weight than the uncertainty. This is doubly the case, given that any effective alternative for patients at this stage is likely to be associated with a substantially sub-optimal side-effect profile.

We have noted below the areas where we feel that the model has significant shortcomings, which have the effect of increasing of the ICER. Correction of these

would offset many of the increases in the ICERs that the AC believes result from assuming a longer duration of treatment, and would provide more overall certainty. Our modelling leads us to believe that it should be possible to end up with ICER values that, with greater certainty, are in the normal range considered acceptable under the end of life criteria.

Our main points of contention with the ACD are as follows:

- The original (and revised) Assessment Group (AG) economic model contains fundamental shortcomings and cannot be reliably used for decision-making. These relate both to the assumptions on which the model is built and the methods used in its construction. The model allows for individuals to spend longer in one health state than they do alive, and uses inconsistent approaches to modelling key parameters for different drugs. The approach also allows for individuals on the older, less effective interventions to have a lower rate of disease progression than those on newer and more effective drugs.
- The interpretation of 'continuation of treatment until death' is flawed. Whilst we accept that treatments are given until death for patients who continue to respond to treatment, however, importantly, they are also given until disease progression, or until the development of intolerance. It is incorrect to assume that the same treatment is always given until death.
- The AC's interpretation of methods and outputs of BMS modelling is incorrect, as discussed in detail in section 2.3. This results in conclusions that are unfair and unrepresentative of the true value of these technologies.
- Additional evidence does, in fact, exist beyond that considered by the AC. For example, in order to make an informed decision around the comparative cost effectiveness of hydroxycarbamide (on the assumption that the AC insists it is "...probably the most appropriate comparator", a position with which BMS and clinical experts disagree), an in-depth analysis of the efficacy and cost of this treatment, should surely be required from the AG and manufacturers. The current conclusion about hydroxycarbamide is based on the contested AG model.
- The 'face validity' check of model outputs represents an over-simplification of the real-life clinical situation. The AC has disregarded the overall treatment costs that should include much more expensive and more complicated post-failure treatments such as Bone Marrow Stem Cell Transplantation (BMSCT), (predominately a 3rd line therapy). If, as implied by the ACD, dasatinib and nilotinib were not available more patients would need to receive these high cost

3rd line treatments at increased cost to the NHS. Such an outcome seems counter-intuitive. The practical reality of this is, that in the absence of TKIs in the 2nd line setting at a rough estimate a minimum of 300 patients each year will be left with a BMSCT as their only realistic treatment option. This is likely to stretch the bone marrow transplant infrastructure in England and Wales to breaking point and to impose significant extra costs onto the NHS.

- Where BMSCT is the only credible treatment option it is likely to exclude many patients who are not Caucasian, young and healthy. This is due to the lack of suitable donors, so that the effect of this guidance is to discriminate against anyone who is of an ethnic minority, old and with multiple co-morbidities.

This preliminary recommendation, if carried forward into the Final Appraisal Determination, would therefore have serious negative consequences for patients. Dasatinib and nilotinib have become standard treatments for patients with CML, in the 4 years they have been available, improving the quality and quantity-of-life of CML patients over alternative treatments. Dasatinib is currently used in the majority of cancer networks in the UK, with an estimated 450 patients currently benefiting from treatment with it. Virtually all Primary Care Trusts in the NHS who have received funding applications have agreed to fund it.

Patients in England will receive care that is poor by EU standards, given that European recommendations embrace the use of dasatinib. There is also the making of a new UK postcode lottery, since dasatinib has been approved by HTA agencies in Scotland and Wales and the London Cancer New Drugs Group (LCNDG). The preliminary negative decision also raises fundamental ethical and human right issues in that it prevents doctors from prescribing, and patients from having access to, potentially life-saving treatment. This outcome seems disproportionate when one considers the ultra-orphan nature of the disease.

We are keen to collaborate fully with NICE and its Appraisal Committee to develop a credible independent economic model and to seek to generate robust outcomes that are understood and ratified by all stakeholders at NICE, BMS and the wider community. We believe the best way to move forward on this is by utilising one of the two approaches set out above and we look forward to hearing the Institute's views on this suggestion. Given the meaningful and high quality extra years of life that these treatments offer, it must be right to explore all avenues to find an acceptable solution and ensure that patients are able to access these treatments.

Summary box of key points:

Issues		Answer	Evidence/Argumentation
1	Has all of the relevant evidence been taken into account?	No	- Updated pivotal data for dasatinib in chronic phases CML (BMS -034 study) has not been included - Previously, BMS did not choose hydroxycarbamide as a comparator in the analysis as we do not believe this is an appropriate comparator. However, in this ACD response, in order to address the AC's concerns about such a comparison, BMS provides an exploratory analysis of hydroxycarbamide
2	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	No	- The Committee's interpretation of evidence is based upon 'face value' checks and 'simplistic' modification of a fundamental flawed economic model - The interpretation of the BMS economic model is incorrect, and the conclusions are misleading - The clinical evidence and clinical experts' opinions have been misinterpreted. All the extensive, senior clinical advice that BMS has received insists that patients who do not respond to dasatinib or nilotinib within 12 months, would **NOT** receive hydroxycarbamide (considered obsolete in this indication). Instead, they would receive another 2nd generation TKI, and then proceed to BMSCT - The interpretation of 'continuation of treatment until death' is flawed. Whilst we accept that treatments are given until death for patients who continue to respond to treatment, however, importantly, they are also given until disease progression, or until the development of intolerance. It is incorrect to assume that the same treatment is always given until death.
3	Are the provisional recommendations sound and a suitable basis for guidance to the NHS?	No	- NHS guidance based on these recommendations would lead to a unique situation in the developed world, whereby new CML patients would be consigned to ineffective care and reduced life expectancy.

Section 1. Has all of the relevant evidence been taken into account?

1.1. No, not all relevant evidence has been taken into account

Paragraph 4.1.4: *'Four studies provided data on dasatinib for imatinib-resistant chronic-phase CML. All of these studies had been identified by PenTAG and* ***one was updated with the SHTAC Assessment Group review'****.*

Comments: The SHTAC did not include an update of a pivotal study of dasatinib (i.e. the dose-ranging study BMS-034). The PenTAG and the SHTAC assessment reports only included the 6-month follow-up data of this study (Shah et al 2008), whilst the 2-year follow up data was presented in the American Society of Haematology in 2008 (Shah et al 2008a) and then published early 2010 (Shah et al 2010), and the 4-year follow-up data has been presented in the American Society of Clinical Oncology (Shah et al 2010a). These data (BMS-034 2 year follow-up along with the BMS-017 data) formed the basis of EMA approval of dasatinib.

Paragraph 4.1.5: *'PenTAG provided pooled summary results for three outcomes. A complete cytogenetic response was reported in 37.4% of participants (95% confidence interval [CI] 34.2 to 40.5), 50.9% had a major cytogenetic response (95% CI 47.6 to 54.1) and 89.2% had a complete haematological response (95% CI 87.2 to 91.3)'.*

Comments: Pooled complete cytogenic response (CCyR) (37.4%) is reported in PenTAG report (Table 15) that includes 6-month follow-up data from BMS-034 (33.9%). The 24-month follow-up data of this study shows a much higher CCyR (50%) (Shah et al 2010), and this has not been taken account. There are similar discrepancies regarding the pooled major cytogenetic response (MCyR) and complete haematological response (CHR) (see PenTAG report: Table 16 and Table 25).

Paragraph 4.1.16: *'One dose-ranging RCT and one single-arm cohort study were identified that reported results for dasatinib in participants with accelerated-phase CML. The Assessment Groups considered that the RCT was of low methodological quality as it* ***did not report allocation concealment*** *and had an open-label design.'*

Comments: The highlighted statement has not taken into account the evidence of the allocation concealment reported in the clinical study report (CSR). The allocation concealment is reported as: Each site enrolled subjects into the study at the time of eligibility screening by accessing a call-in interactive voice response system (IVRS)

after informed consent had been obtained. A subject number was assigned at this time. After completion of all screening evaluations, all eligible subjects were then randomly assigned to one of two treatment arms (dasatinib or imatinib) in a 2:1 ratio. To enrol a subject, a phone call was made by the site to the central randomization centre using a 24-hour toll-free number. The randomisation procedure dynamically minimized the imbalance between treatment arms within each of the following stratification factors: 1) site and 2) cytogenetic response on imatinib (cytogenetic response (minimal, minor, partial or complete) vs no cytogenetic response). Upon completion of randomisation, the first dose of study therapy was administered within three days.

Paragraph 4.3.3: *'The Committee heard from the clinical specialists that people whose CML does not respond to dasatinib or nilotinib within 12 months* ***would receive treatment with hydroxycarbamide*** *or, if suitable, stem cell transplantation. For people receiving hydroxycarbamide, the prognosis is poor,* ***with a median life expectancy of around 5 years'.***

Comments: The clinical evidence, and clinical experts' opinions, have clearly been misinterpreted. All the extensive, senior clinical advice that BMS has received and that NICE has received as part of this appraisal (e.g. see comments from Dr Patrick Cadigan, RCP Registrar on behalf of: NCRI/RCP/RCR/ACP/JCCO) clearly show that patients who do not respond to dasatinib or nilotinib within 12 months, would **NOT** receive hydroxycarbamide (considered obsolete in this indication). Instead they would receive another 2nd generation TKI, and then proceed to BMSCT.

Historically, hydroxycarbamide has only been used in the 1st line setting. The evidence relating to hydroxycarbamide in the 2nd line setting is minimal. It is safe to assume however that patients resistant to 2nd generation TKIs are unlikely to respond to hydroxycarbamide and the median survival is likely to be significantly less than the 5 years cited above (in the 1st line setting). In this respect, the Chronic Myeloid Leukemia Trialists' Collaborative Group (1997) state that, in newly diagnosed patients, the survival rate is only 44% at 5-years.

Paragraph 4.3.4: ***'****The Committee noted that the economic models available to them had used major cytogenetic response as a surrogate for overall survival and heard from the clinical specialists that* ***the strongest link was between major molecular response and overall survival****.'*

Comments: The highlighted statement is not a reflection of current clinical knowledge. As noted in the ELN guideline (Baccarani et al 2009) and Marin et al

(2008), complete cytogenetic response is the most important response-related prognostic factor since Marin's et al (2008) concluded that 'At 12 months, the only independent predictors for PFS were: (1) being in CCyR (complete cytogenetic response)..... and (2) prior loss of CCyR ……; At 18 months, the only independent predictor for PFS was being in CCyR'. Furthermore, Marin et al (2008) stated that 'the achievement of MMR (major molecular response) at 12 or 18 months **failed to** confer any benefit in 5-year PFS or OS'.

The ELN guideline stated that: 'In these patients (treated with dasatinib and nilotinib), the response-related prognostic factors that have been identified for imatinib may apply as well to dasatinib and nilotinib, but it should not be overlooked that the response to these drugs is more rapid' (Baccarani et al 2009).

Section 2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, the summaries of clinical and cost effectiveness are not reasonable interpretations of the evidence.

2.1. Interpretation of quality and quantity of evidence:

Paragraph 4.3.4: *'The Committee noted the **poor evidence base for all interventions** for people whose CML is resistant to standard-dose imatinib'*

Comments: This statement is not a reasonable interpretation of the evidence. There is sufficient evidence demonstrating the safety and efficacy of dasatinib from 7 phase 2 and phase 3 clinical trials that include over 2,000 patients. Whilst we appreciate the issue regarding the paucity of comparative data, the majority of the available evidence supports dasatinib as an effective intervention. Such trials were considered sufficiently robust for the European Medicines Agency to grant a marketing authorisation and therefore we fail to see how the AC can consider the evidence base poor.

Paragraph 4.3.5: *'The Committee was aware that no evidence was presented on the use of dasatinib, high-dose imatinib and nilotinib (accelerated phase only) in this way (i.e. **as adjuvant treatment with intensive chemotherapy for acute leukaemia**) and that the evidence base in this advanced stage of the disease was very limited'.*

Comments: This statement is not a reasonable interpretation of the evidence. In advanced phase CML there is evidence regarding the clinical efficacy of dasatinib monotherapy ((Apperley et al 2009, Kantarjian et al 2009, Cortes et al 2008). It should be remembered that this appraisal is to assess the clinical and cost-effectiveness of dasatinib used in CML patients as monotherapy (as defined in the final scope). It is not to assess dasatinib used in the neo-adjuvant/adjuvant setting (TKI initiated before and/or after BMSCT) and any such discussions or opinions in this ACD are procedurally unfair.

2.2. Interpretation of 'intuitive' evidence:

Paragraph 4.3.8: *'The Committee was aware that,* ***for people who respond, these treatments (dasatinib and nilotinib) are given daily, very often until death****, and that this results in high treatment costs for every year of life lived with CML'*

Comments: This statement is not a reasonable interpretation of the evidence and oversimplifies the clinical situation. The interpretation of 'continuation of treatment until death' is flawed. Whilst we accept that treatments are given until death for patients who continue to respond to treatment, however, importantly, they are also given until disease progression, or until the development of intolerance. It is incorrect to assume that the same treatment is always given until death.

In clinical practice, for those people with CML, and who cannot be treated with dasatinib and nilotinib, the treatment options are other TKIs, various combination of treatments, and finally (only if they are suitable), BMSCT.

These post-failure treatments are likely to attract high costs (such as treating Graft versus Host Disease; managing co-morbidities and serious adverse effects; hospitalisation; blood tests; weekly visits to the GP; blood transfusion; hospital based out-patient visits etc). All these costs, not only the initial drug or transplantation costs, should be taken into account. It is too simplistic to conclude that only treatments such as dasatinib and nilotinib will result in high treatment costs for every year of life lived with CML. Should dasatinib and nilotinib be unavailable, the alternative treatments will result in even higher treatment costs.

Paragraph 4.3.8: *'The Committee also considered that if each year of life were adjusted by quality of life the resulting costs per QALY would be likely to be higher than the annual costs of the drugs. The Committee agreed that these considerations would be important in checking the face validity of each of the economic models and outputs……'*

Comments: The argument above is intuitive and does seem to have 'face value'
If an intervention costs £1, and gives a year of life, the ICER would be £1 per life year gained. If that year was given a utility weight (i.e. QALY weight - quality adjusted life years) of 0.5 the ICER becomes £2 per QALY gained. However, BMS requests clarification of the Committee's logic on this point, since a drug's acquisition costs are only one component of the total treatment costs. It is important to recognise that any 3rd line intervention for CML includes a combination of drugs, chemotherapeutic agents and BMSCT.

Thus, if a patient 'fails' treatment more quickly, or has a poorer prognosis, on treatment A compared with treatment B, it can be expected that treatment A will incur far greater third line costs than treatment B. Consider the following case study. If most patients on hydroxycarbamide will be classified as failures at 1 year, then a large proportion of them will receive BMSCT. However, if a much smaller proportion of patients fail dasatinib at 1 year, then much fewer patients will receive BMSCT. Therefore, the difference in front line acquisition costs is offset.
In summary, in the presence of significant cost offsets, the TOTAL incremental lifetime cost per patient can be a lot lower than the incremental lifetime acquisition costs.

2.3. Interpretation of BMS model:

Paragraph 4.2.4: *'The published data from the dasatinib trial were limited to 48 months of follow-up and the manufacturer extrapolated longer-term progression-free survival* ***by assuming that the monthly rate of progression after 48 months was equal to that observed during the final year of the published data****.'*

Paragraph 4.3.9: *'the Committee noted that the transition probabilities were extrapolated* ***by taking the rate of progression from months 36 to 48 forward****; the Committee was concerned that* ***this implied no one would progress from the (healthy) complete cytogenetic response state after 3 years****. It considered that this is not plausible, given that it had heard from the clinical experts that a proportion of people with CML will experience disease progression'.*

Comments: The highlighted parts of the above sentences are not a reasonable interpretation of the evidence.

Firstly, in our economic model (Excel format), we actually extrapolated longer-term progression-free survival based on the progression rate observed from months 6 and

48, not the final year of the trial data (i.e. not by taking the rate of progression from month 36 and 48 forward).

Secondly, the AC suggests that BMS model extrapolation implies no one ever progressed from the CCyR state after 4 years, this is incorrect.

Firstly, during the trial period, there is not progression observed in the trial from month 23 to month 47 for patients who achieved CCyR (Table 1).

Table 1 PFS estimates at different time points (taken from model worksheet "Prognosis (CP)"

	NR	CHR	PCyR	CCyR	MR
23 month	30.0%	63.6%	83.3%	94.2%	94.2%
24 month	30.0%	62.2%	83.3%	94.2%	94.2%
25 month	30.0%	60.9%	83.3%	94.2%	94.2%
…	30.0%	59.6%	83.3%	94.2%	94.2%
33 month	30.0%	58.4%	83.3%	94.2%	94.2%
34 month	30.0%	57.1%	83.3%	94.2%	94.2%
…	30.0%	55.9%	83.3%	94.2%	94.2%
46 month	30.0%	52.6%	82.4%	94.2%	94.2%
47 month	30.0%	49.5%	81.4%	94.2%	94.2%

Secondly, while there is no progression at the last year in the trial (see Table 1), we have not used this information to inform the extrapolation process. Instead, earlier data was used to derive the progression rates (i.e. data from months 6 and 48) and hence there is increasing progression at 48 months onwards, especially with CCyR patients. Sample proportions from the model are reproduced below to support this statement (Table 2).

Table 2: PFS estimates at different time points (taken from model worksheet "Prognosis (CP)"

	NR	CHR	PCyR	CCyR	MR
47 months	25.8%	25.80%	59.40%	94.20%	94.20%
48 months	24.1%	24.11%	58.54%	93.92%	93.92%
49 months	22.5%	22.54%	57.70%	93.63%	93.63%
50 months	21.1%	21.07%	56.86%	93.35%	93.35%
	…	…	…	…	…
70 months	12.3%	12.27%	35.13%	88.74%	88.74%
	…	…	…	…	…
100 months	4.8%	4.76%	17.61%	87.14%	87.14%
	…	…	…	…	…
200 months	0.2%	0.23%	1.72%	74.17%	74.17%

Paragraph 4.2.4: *'The rates of progression with the other treatments were taken from other clinical studies and assumptions'*

Comments: The above sentence is not a reasonable interpretation of the evidence. The rates of progression were based on the initial best response levels. For example, patients with CCyR would have a certain rate of progression, whilst patients do not respond to treatment would have another rate of progression. In this case, the relationship between progression and response levels are the same for all treatments. This relationship (rates of progression) is based on dasatinib 4-year follow up trial data. Therefore, the rates of progression with the other treatments were the same as those of dasatinib. However, since the initial best response levels vary of different treatments, the progression free survival become different.

Paragraph 4.3.9: *'First, the (BMS) model estimated that the cost for people receiving interferon alfa was higher (in some cases double) than that of all of the other economic models……'*

Comments: As noted in the summary of product characteristics for Interferon alfa-2a (Roferon A): *"Roferon-A should be administered under the supervision of a qualified physician experienced in the* ***management of the respective indication****"*

As such, the total monthly cost must include not only the cost of treatment, but also all outpatient/ administration costs relating to treatment administration. Assuming that treatment is needed three times per week, this would result in 13 outpatient visits per month (3 per week * 4.33 weeks per month). Thus, administration costs would range from £325 per month (if all were performed via a GP nurse at the practice) to £1,400 per month (if all were performed via a hospital based oncology outpatient visit).

In terms of drug costs, assuming a body surface area of $1.7m^2$, and a dose of 6 MIU, the monthly cost of treatment (including inevitable wastage due to lack of vial sharing) is £550 if 1ml vials are used, and £1,376 if 2.5ml vials are used (vial dose 10MU/ml).

Therefore BMS would argue that the cost of interferon used in our model is likely to be at the lower end of the costs range, and as a result all ICERs represent values close to or on the upper threshold for this comparison.

Paragraph 4.3.9: *'(the BMS model) did not include a comparison with hydroxycarbamide. The Committee noted the testimony of the clinical specialists that hydroxycarbamide was probably the most appropriate comparator (along with stem cell transplantation if possible) '.*

Comments: BMS does not consider hydroxycarbamide as a valid comparator because clinical evidence suggests that this would be obsolete clinical practice (see comments above). Therefore, data on hydroxycarbamide, and in particular best initial response to treatment, were not included in the original BMS model. Nevertheless, we have conducted the following exploratory exercise by estimating:

1) Efficacy of dasatinib: based on clinical trial data (Shah et al 2008a), at 12 months, 8.1% patients were non-responders
2) Discontinuation of dasatinib: 10.2% (quoting PenTAG report)
3) Efficacy of hydroxycarbamide: since hydroxycarbamide is given largely to modify white blood cell counts, the efficacy of this product as a treatment for CML was assumed to be the same as observed for interferon. For example, 100% patients were non-responders.
4) Discontinuation rates of hydroxycarbamide: it is assumed that the premature discontinuation rate is the same as the IFN (55.5% as reported in IRIS, quoting PenTAG report).

5) The cost of hydroxycarbamide: it was calculated on the basis of information in the product SPC and includes all tests, doctor visits etc. The following statements are notes in the Summary of Product Characteristics for Hydrea 500 mg Hard Capsules

(http://www.medicines.org.uk/EMC/printfriendlydocument.aspx?documentid=19081&companyid=43, accessed 6th may 2010).

"The complete status of the blood, including bone marrow examination, if indicated, as well as kidney function and liver function should be determined prior to, and repeatedly during, treatment. The determination of haemoglobin level, total leukocyte counts, and platelet counts should be performed at least once a week throughout the course of hydroxycarbamide therapy"

"Severe anaemia must be corrected with whole blood replacement before initiating therapy with hydroxycarbamide. If, during treatment, anaemia occurs, correct without interrupting Hydrea therapy"

"The possibility of an increase in serum uric acid, resulting in the development of gout or, at worst, uric acid nephropathy, should be borne in mind in patients treated with hydroxycarbamide , especially when used with other cytotoxic agents. It is therefore important to monitor uric acid levels regularly and maintain a high fluid intake during treatment."

Hence, given that hydroxycarbamide is an oral medication, the following need to be included into the calculation of treatment costs:

- Weekly blood tests
- Weekly visits to the GP of the purposes of provision of a blood sample
- A proportion of individuals requiring a blood transfusion
- This proportion also requiring a hospital based out-patient visit

For the purposes of calculation, the following values have been used to calculate the cost of hydroxycarbamide treatment (Table 3).

Table 3: Calculation of mostly treatment costs of hydroxycarbamide

	Value	Source	Comment
Cost of a blood test	£2.97	NHS SRC	
Cost of a GP nurse contact session	£25.00	Curtis	
Percentage of patients requiring blood transfusion per month	10%	Assumption	
Cost of blood transfusion	£57.07	NHS SRC	
Cost of hospital outpatient session	£108.00	Curtis	Corresponds to haematologist/ oncologist based contact

When the additional costs are included, the **total** monthly cost for hydroxycarbamide is £150.62.

We also note that for patients who fail 2nd line treatment (non-responders and early discontinuation), 31% patients are eligible for BMSCT (Oxford Outcomes 2009). The costs of BMSCT in 3rd line use were calculated as below:

- The one-off cost of BMSCT is £80,000 (the lower-end estimated from clinical experts)
- The ongoing cost of post BMSCT (31% * £2,400) = £744 per month, according to clinical experts' estimates
- % patients treated with BMSCT and alive at one year = % eligible * (% non-responders + % early discontinuation). Thus, for patients treated with dasatinib, the calculation is as follows: % BMSCT's = 30.8%* (8.1%+ 10.2%) = 5.7%.

The results generated using these assumptions are presented in Table 4.

Table 4: Results using alternative approach to treatment costs (vs. hydroxycarbamide)

	Total costs	Total QALYs	Δ Costs	ΔQALYs	ICER
Base case					
Dasatinib	£301,384	6.659			
Hydroxycarbamide	£162,593	1.690	£138,791	4.969	£27,932

Thus, the cost-effectiveness ratio generated for dasatinib compared to hydroxycarbamide is at the upper end of the costs range used by NICE in their decision making process. In this regard, we would argue that the additional benefits

of treatment (in particular the additional 8.6 years in the progression free state) should be taken into account when making a reimbursement decision.

Paragraph 4.3.9: *'The Committee concluded that the base-case ICER resulting from the Bristol-Myers Squibb model of £38,900 per QALY gained is an underestimate and would be substantially higher* ***if the relevant comparator (hydroxycarbamide) and more plausible assumptions about progression were used****'.*

Comments: As noted above, the AC misinterprets the progression assumptions used in the BMS model, therefore BMS disagrees with the hypothesis that any alternative approach would result in an increase in the ICER. This statement is not evidence based and is misleading.

2.4. Interpretation of Assessment Groups' model:

Paragraph 4.3.11: *'The Committee noted that the (PenTAG) model* ***does not link treatment duration and overall survival*** *and that some of the results are not plausible. In particular, it noted the overall survival for interferon alfa is implausible and the treatment duration for people receiving nilotinib is lower than would be seen given the estimated overall survival. The Committee therefore concluded that PenTAG's model underestimated the most optimistic ICER; that of £44,600 for nilotinib compared with interferon alfa.'*

Paragraph 4.3.12: *'The Committee understood that the (SHTAC) model attempted to correct PenTAG's overestimate of survival on interferon alfa and the discrepancy between the nilotinib and dasatinib treatment durations. However, the Committee noted that* ***the SHTAC Assessment Group's model also had the major limitation of PenTAG's model of assessing treatment duration and overall survival by unrelated methods****'.*

Comments: As BMS have noted consistently throughout all the appraisals of 2nd line CML interventions, the simple, fundamental rule of any health economic model is that it is an accurate representation of the underlying disease process. We are pleased that some of the inaccuracies in the model have been acknowledged by the AC. However, the 'PenTAG model does not link treatment duration and overall survival' is the consequence of a fundamental flaw in the model structure, that is, the response rate is not used as a common surrogate outcome measure for OS and PFS. It is important to note that by changing the 'treatment duration' alone will not improve or correct the model.

Indeed, BMS are deeply concerned that no effort has been made to change the flawed modelling approach. As noted by the AC, the base-case of SHTAC analysis is based a revised version of the PenTAG model, and it did not fix the fundamental

problem, but merely altered some data outputs (for example, PFS). It would therefore seem perverse of NICE to make a reimbursement decision for a whole class of interventions based on a flawed economic model.

The model initially developed by PenTAG, and slightly modified by SHTAC, have not addressed this fundamental issue. Serious and fundamental flaws exist in both the assumptions on which the model is built and the methods used in the construction. In particular, the model allows for individuals to spend longer in one health state than they do alive, and uses inconsistent approaches to modelling key parameters for different drugs (implicitly stating that they act in a biologically different manner). The approach also allows for individuals on the older, less effective, interventions to have a lower rate of disease progression than those on newer and more effective drugs.

Implications of not using a common surrogate outcome measure for OS and PFS

The lack of link between response rates and PFS means that altering the value for the chosen surrogate marker (Major Cytogenetic response – MCyR) has no impact on time in Progression Free Survival (PFS). In other words, regardless of whether the MCyR response rate is set to 0% or 100%, the amount of time spent on therapy in chronic phase ('CP on-treatment') remains constant (Table 5).

Table 5: Impact of different MCyR rates on the treatment durations in the chronic phase

MCyR rates	Life years (CP on treatment)	Life years (CP off treatment)
0%	3.15	6.07
25%	3.15	7.91
50%	3.15	9.74
75%	3.15	11.25
100%	3.15	13.42

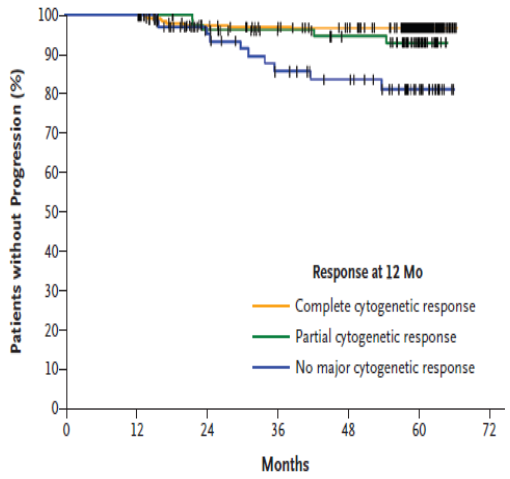
In the model, individuals are also assumed to spend time in chronic phase without any treatments ('CP off-treatment'), and the time spent in 'CP off-treatment' is set as the difference between Overall Survival (OS) and the amount of time spent in 'CP on-treatment'. As a result of this approach, even when a patient does not respond to the treatment (response rate is set to 0%), he/she can still remain in chronic phase

without receiving any treatment – for as long as 6 years! This is not supported by clinical data and fundamentally undermines the clinical credibility of the model.

As noted by PenTAG in their original report, there is a body of evidence supporting the hypothesis that a complete cytogenic response (CCyR) (defined as no Ph+ chromosomes in the bone marrow) is a predictor of both OS and PFS (Figure 1).

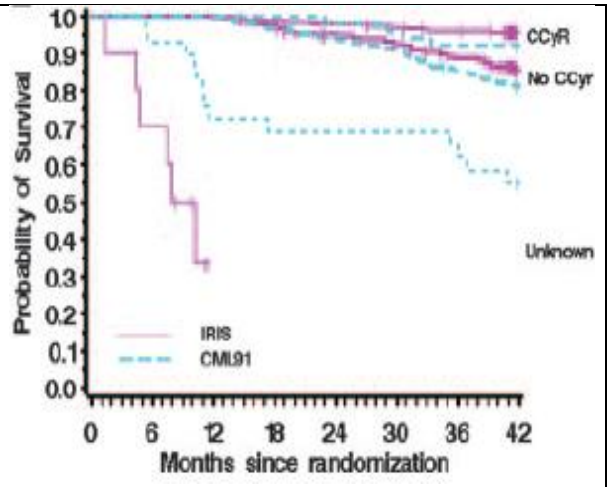
It is important to note that (a) both plots were derived from individuals in the same clinical trial (IRIS) and (b) other authors have identified the same relationship (Druker et al 2006, Roy et al 2006).

Figure 1: Use of CCyR as a predictor of PFS and OS in patients with CML)



PFS

(Reproduced from Druker et al. (2006)



OS

(Reproduced from Roy et al. (2006)

BMS consider it extremely unlikely, given the proven causal link between CCyR and PFS, that no such link exists between MCyR (defined as ≤35% Ph+ chromosomes in the bone marrow). The PenTAG/SHTAC model is therefore fundamentally flawed in the way it represents the underlying disease, and as such the model cannot form the basis of rational decision making.

In addition to the problem of 'no link between response rates and PFS', another issue with PenTAG/SHTAC model is the counter-intuitive and inconsistent methods used to model OS and PFS of different treatments. Given the Committee's desire to include face validity checks into the decision making process it is worthwhile reflecting, in abstract terms, on the nature of CML. In general, for people who do not have CML, the rate of death will increase over time by virtue of the natural aging process. For people with CML, because of natural disease progression, loss of response, intolerance to treatment, time, etc, the rate of death would also be expected to

increase over time. This leads to the conclusion that an increasing rate of death should be observed in any parametric function used to model OS and PFS.

The PenTAG approach used to model OS is based on a Weibull model with a gamma value (the parameter controlling the rate of change) being set to less than one. This means that the rate of death decreases over time.

In terms of PFS, with the exception of high dose imatinib (HDI) where a Weibull function is used (and the fitted progression rate increases over time), all interventions are modelled using exponential distributions. This approach is flawed on three levels:

1) It assumes a constant rate of disease progression over time. That is, if a patient has had CML for 20 years, the rate of progression is the same as if the patient has had it for one day.
2) By using a different method to model high dose imatinib (HDI) and IFN, the result is that after a short period of time (from model cycle 10 onwards), patients on HDI have a higher rate of progression than those on interferon (IFN).
3) As a direct consequence of this mixed modelling approach, individuals in the IFN arm can expect to spend longer in the PFS state than alive (predicted undiscounted PFS state occupancy: 3.47 years, predicted overall survival: 3.41 years), see Table 6.

Table 6: Predicted state occupancy estimates (years)*

	Dasatinib 100mg	**Nilotinib 800mg**	**Imatinib 800mg**	**Hydroxycarbamide**
Overall survival	13.19	13.07	12.45	3.50
Progression free survival	3.62	3.62	3.45	3.56

* Values derived by dividing the totals in cells D2 and F2 on the relevant worksheets by 1000 to get per-person cycle estimates and this value by six to get per-person annual estimates

In summary, the numerous flaws in the methods used to model these key parameters suggest that the results from the model cannot be interpreted with any confidence.

Paragraph 4.3.12: *'the SHTAC Assessment Group's base-case treatment durations did not reflect what the Committee had heard from the clinical specialists that in clinical practice, people will receive treatment until progression or death (see section 4.3.3). It noted, however, that two main scenario analyses as well as a sensitivity analysis of survival versus treatment duration had been developed to reflect this problem.'*

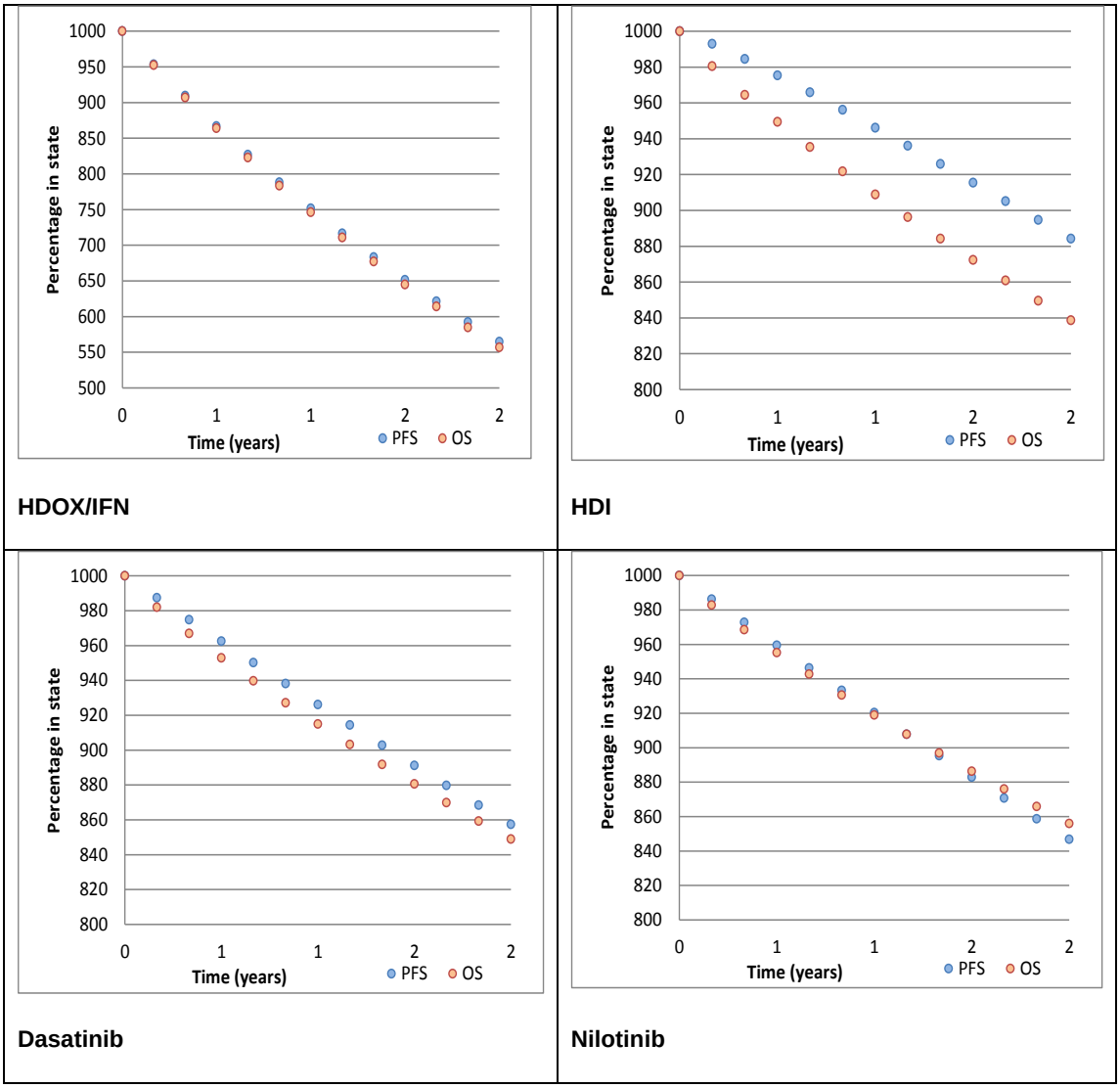
Comments: BMS notes that, in order to address concerns relating to the implausibly low treatment durations for all TKI's, additional scenario analyses were performed by the SHTAC where these values were fixed to either 6.5 or 10 years.

BMS would like to draw attention to the fact that 'treatment duration' is **a model output** and **NOT a model input.** As such, it cannot be directly altered. By altering treatment durations, it does not make the model more reflective of clinical practice and underlying disease, In order to demonstrate this, we have replicated the analyses using the information provided by the SHTAC group on 18th May 2011. Specifically, the SHTAC informed us that the additional scenario analyses were based on changing lambda values for PFS on the 'treatment duration' worksheet (cells BC12, BC14, BC16). When we used the SHTAC's method, and replicated the PFS and OS, it shows that in all cases PFS is higher than OS for a period of time (Figure 2). BMS believe the method used to overcome the original issue causes more problems than it solves. Intuitively, in any oncology model, one of the key face validity tests is that there can never be more patients in the progression-free health state than there are currently alive (since this would result in a negative number of patients the post-progression health state). When the predicted OS and PFS curves for each intervention are plotted for an assumed treatment duration at 10 years, it is clear that this fundamental principle is violated.

BMS would like to emphasise that this is not a minor issue. For patients on high dose imatinib (HDI), the number of individuals predicted to be in PFS is higher than those in OS for over 7 years. The corresponding values for nilotinib and dasatinib are 3.2 years and 1.2 years respectively.

Once again, this suggests that the model analyses are fundamentally flawed, and as such it would be perverse of the Committee to use the model as the basis for rational decision making.

Figure 2: predicted overall and progression free survival arising from replication of SHTAC analyses



Paragraph 4.3.12: *'The Committee acknowledged that, based on the testimony from the clinical specialists, the assumption of similar treatment durations, which are continued for a considerable proportion of the responding person's lifetime, for dasatinib, high-dose imatinib and nilotinib is appropriate. Therefore the Committee considered that* ***the base-case analysis, in which the treatment durations of dasatinib, high-dose imatinib and nilotinib were set to 2.4–3.1 years*** *with overall survival of 12.4–13.4 years (with costs of £162,000–£173,000), was implausible.'*

Comments: The AC misinterpreted the base-case analysis of the SHTAC model and believed that the treatment durations were not set to 2.4-3.1 years. In face, the treatment durations were derived from the fixed progression free survival in the model (SHTAC AR, page 75, and Table 40). In other words, SHTAC did not set

treatment durations, but set the PFS. However, regardless what parameters were set in this model, any outputs will still not be plausible, bearing in mind the above analysis of the PenTAG model and SHTAC revised base-case and additional scenario analysis.

Paragraph 4.3.12: *'The Committee did not consider that a most plausible ICER had been presented, but* ***agreed that the least implausible analysis was the second scenario by SHTAC Assessment Group, in which the treatment durations of dasatinib, high-dose imatinib and nilotinib are set to 10 years*** *with overall survivals of 12.4–13.4 years (and costs of £266,000–£300,000). It noted that in this analysis both high-dose imatinib and nilotinib are dominated by dasatinib, and that dasatinib compared with hydroxycarbamide resulted in an ICER of £43,800 per QALY gained.'*

Comments: BMS would like to emphasise, **there cannot be a 'most plausible" or 'least plausible" ICER**. As we have demonstrated, any ICER that arises out of the PenTAG/SHTAC model is implausible. It would seem perverse of the Committee to arbitrarily choose one they consider the "best" (or the least worst) among a number of invalid propositions.

Paragraph 4.3.12: *'The SHTAC Assessment Group's sensitivity analysis showed that for nilotinib compared with hydroxycarbamide,* ***assuming an overall survival estimate of 7 years when compared with a treatment duration of 2 years of nilotinib,*** *resulted in ICERs higher than £40,000 per QALY gained…The Committee agreed that if it were acknowledged that treatment is continued for most of the person's lifetime, then the (SHTAC) ICERs would increase. The Committee concluded that the ICER of dasatinib compared with hydroxycarbamide would be higher than the SHTAC Assessment Group's figure of £43,800 per QALY gained'*.

Comments: It is very clear that the Assessment Groups' model does not provide a robust argument. It does not explain how a patient who is being treated for 2 years will have 7 years survival if the treatment is continued until disease progression, death, and intolerance. This is not reflective of clinical practice. It clearly demonstrates that the problem of this model cannot be fixed by merely changing the outputs, such as treatment durations or PFS.

2.5. Critique of Committee's conclusions

Paragraph 4.3.13: *'It also noted that, of the presented analyses, all suggested ICERs that were higher than those normally considered acceptable for the NHS, and were highly likely to be above the figures (£40,000 per QALY) suggested.'*

Comments: Not all ICERs versus hydroxycarbamide have been considered (see the additional analysis conducted by BMS with regards to hydroxycarbamide presented above). The "least implausible" ICER chosen by the Committee is from the SHTAC additional scenario analysis, based on the economic model which BMS does not consider to be credible. Indeed, BMS consider that any ICER produced by this PenTAG/SHTAC model should be treated with utmost caution, regardless whether the ICER is above or below the conventional threshold.

Paragraph 4.3.16: *'However, the Committee agreed that* ***the available evidence on life extension was too weak and was not considered to be robust****. In addition, no data were presented for the interventions as used in clinical practice. The Committee concluded that dasatinib, high-dose imatinib and nilotinib do not fulfil the end-of-life criteria for people with CML in the accelerated and blast-crisis phases.'*

Comments: The NICE guidance for 'Appraising life-extending, end-of-life treatments' states that end-of-life treatments must be *'robust and can be shown or reasonably inferred from either progression free survival or overall survival (taking account of trials in which cross-over has occurred and been accounted for in the effectiveness review).'* Even in the absence of comparative data for accelerated and blast phase disease, it is difficult to appreciate why the AC considers a clinical trial with 2 year follow-up data is not robust (Apperley et al 2009, Kantarjian et al 2009, Cortes et al 2008). Since achieving and maintaining of response have been proven to be reliable predictors of longer term survival benefits (Marin et al 2008), the data were considered robust enough to form the basis of a decision by the European Commission to approve dasatinib in advanced CML following a positive opinion from the European Medicines Agency.

Indeed, on this basis, one must query how many orphan and ultra-orphan medicines are likely to satisfy the AC's (unspecified) standards of robustness. Following the Servier case *(Servier Laboratories Limited v National Institute for Health and Clinical Excellence (2010))* it is clear that NICE must place sufficient weight on evidence that is central to a party's case, particularly when such evidence has been held as being robust enough for marketing authorisation purposes. We also query whether the Institute's appraisal procedures are adequate in assessing the clinical and cost-effectiveness of ultra-orphan drugs.

Section 3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

No, the provisional recommendations are not sound and not a suitable basis for guidance to the NHS.

Paragraph 4: *'As a result of comments received during consultation,* ***it was agreed to combine an appraisal of the three technologies, dasatinib, high-dose imatinib (600 mg and 800 mg) and nilotinib****, to establish their comparative incremental clinical effectiveness and cost effectiveness. The following actions were implemented'*

Comments: BMS has serious concerns about the procedures which were followed, and believes these procedures to be unfair, perverse, and outside the scope of NICE's jurisdiction. These concerns can be summarised as follows:

- In place of HDI as a comparator, the AC chose to use hydroxycarbamide, despite it representing obsolete clinical practice, as made clear by clinical expert submissions during the course of this appraisal. In doing so, the AC has shifted its review from an area where there is robust - albeit limited - evidence (i.e., a randomised trial of dasatinib compared with HDI) to an area for which there is, inevitably, almost no evidence and where evidence is unlikely ever to arise. Any attempt to set up clinical trials in order to generate data comparing dasatinib or nilotinib to hydroxycarbamide would be unethical. This is because the Declaration of Helsinki requires that clinical research involving any 'new intervention' must be conducted against the 'best current proven intervention' and that the use of other interventions, placebo or no therapy is only possible where 'no current proven intervention exists'. The 1996 version of the Declaration, which applies to all pharmaceutical clinical research within the EU, provides that '[i]n any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.' These issues are particularly relevant in the oncology space. By selecting hydroxycarbamide as the most appropriate comparator, the AC is moving from a position where it has meaningful comparative data to a position that is likely to remain evidence free.

- The AC states that *'it was agreed…'*. To be clear, BMS did not "agree" to this. In our previous responses to the TAR and the ACD, we have pointed out that HDI should be the comparator, and not be grouped together with dasatinib and nilotinib as interventions. The underlying basis for this decision is unclear and lacks transparency.

Paragraph 4.3.*3:* *'The Committee heard from the clinical specialists that high-dose imatinib followed by dasatinib and nilotinib are in widespread use and are a major advance over the therapies previously available: that is, interferon and hydroxycarbamide. Although* ***stem cell transplantation can be curative, it carries high risks and has restricted applicability (to fit, younger patients)****'*.

Paragraph 4.3.3: *'The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people with CML would most commonly receive treatment with hydroxycarbamide or stem cell transplantation, if possible…'*

Paragraph 4.2.24: *'The cost of stem cell transplantation was taken from the Bristol-Myers Squibb submission and includes the additional cost of £80,000 for the stem cell transplant'*.

Comments: The Committee is aware that dasatinib (and nilotinib) a*re highly effecti*ve TKIs and have become integrated as standard therapies into the accepted clinical armamentarium for treating CML. Compared with the alternative therapies (high dose imatinib and hydroxycarbamide), dasatinib (and nilotinib) have improved the quality and quantity of life of the CML patient. This position is reinforced by the ELN 2009 Guidelines (Baccarani et al 2009) which are accepted globally. Indeed, the advice received by the Committee from the clinical specialists clearly supports the use of 2nd generation TKIs in patients who are resistant to imatinib.

Table 7. Treatment Recommendations

Type of Disease	Recommendation
Chronic phase	
First line	
All patients	Imatinib 400 mg daily
Second line	
Imatinib intolerant	Dasatinib or nilotinib
Imatinib suboptimal response	Continue imatinib same dose; or test high dose imatinib, dasatinib, or nilotinib
Imatinib failure	Dasatinib or nilotinib; alloHSCT in the patients who have experienced progression to AP/BP and in patients who carry the T315I mutation
Third line	
Dasatinib or nilotinib suboptimal response	Continue dasatinib or nilotinib, with an option for alloHSCT in patients with warning features (ie, prior hematologic resistance to imatinib, mutations) and in patients with an EBMT risk score ≤ 2
Dasatinib or nilotinib failure	AlloHSCT
Accelerated and blast	
First line	
Patients who are TKI naïve	AlloHSCT, preceded by imatinib 600 or 800 mg, dasatinib, or nilotinib, in case of mutations poorly sensitive to imatinib
Second line	
Patients with prior treatment of imatinib	AlloHSCT, preceded by dasatinib or nilotinib

Abbreviations: AlloHSCT, allogeneic hematopoietic stem-cell transplantation; AP, accelerated phase; BP, blast phase; EBMT, European Group for Blood and Marrow Transplantation; TKI, tyrosine kinase inhibitor.

(From Baccarani et al 2009)

When one considers the extent to which CML treatment has improved and progressed since the introduction of TKIs, it seems perverse of the Committee to consider and evaluate agents (as direct comparators to dasatinib and imatinib) that are recognised by the clinical community as being significantly less effective and less well tolerated, and indeed which are not considered viable treatment options.

We would like to alert the Committee to the negative clinical and financial consequences of a negative recommendation**.** It is recognised by the Committee that high dose imatinib, followed by dasatinib and nilotinib are in already widespread use, and are a major advance over the therapies previously available (i.e. interferon and hydroxycarbamide). As a consequence of the preliminary decision the only credible option for patients is that of BMSCT. The Committee also recognise that although BMSCT can be curative, it carries high risks and has restricted applicability (Paragraph 4.3.2) being limited in practice to Caucasian patients, typically under 60 years of age, with no co-morbidities.

The preliminary negative decision therefore raises fundamental ethical, discrimination and human right issues in that it prevents doctors from prescribing, and patients from having access to, life-saving treatment. It is discriminatory to make a recommendation that forecloses meaningful treatment to the elderly and patients from ethnic minorities. The outcome also seems disproportionate when one considers the ultra-orphan nature of the disease. It is also worth noting that the more substantial the interference with human rights (e.g., the right not to be discriminated against, the right to life etc.), the more is required by way of justification before the Appraisal Committee should accept that its preliminary decision not to recommend dasatinib is a reasonable rather than a perverse one.

In addition to the high initial costs (£80,000 to be the lower end of estimate) and the high ongoing costs (estimated to be £2400 per month), there will be a need to upgrade the current NHS infra-structure in order to deliver BMSCT to these patients. With growing need for BMSCT as a result of the unavailability of dasatinib and nilotinib, there will be a need for significant investment, which is highly unlikely to offset the costs of dasatinib and nilotinib.

On this basis, a negative recommendation seems perverse, discriminatory and inequitable.

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Appendix 1 Factual comments

Page/ Paragraph	**ACD Text**	**BMS Comment**
Page 11/ Para. 4.1.4	'The dose-ranging RCT was the only study of dasatinib that used the UK dosage in the marketing authorisation, that is, 100 mg once daily for chronic-phase CML. All other studies used higher dosages of **nilotinib**'	Last word 'nilotinib' should be 'dasatinib'
Page 13/ Para. 4.1.7	'Discontinuation due to **intolerable events** was reported separately for participants with imatinib resistance only in the comparative RCT…'	Please change the 'intolerable events' into 'adverse events' in order to avoid confusion. The original sentence on page9 is: 'Discontinuations because of AEs occurred in 23 patients (23%) receiving dasatinib…' (Kantarjian et al (2009)
Page 29/ Para. 4.2.28	'In the **first scenario** (treatment duration set to 10 years)…'	'first scenario' should be changed into 'second scenario'

Comments from Novartis Pharmaceuticals UK Limited on the Appraisal Consultation Document (ACD) for the Health Technology Appraisal of Nilotinib for the Treatment of Adults with imatinib resistant Chronic Myeloid Leukaemia

Thank you for your invitation to comment on the above Appraisal Consultation Document (ACD) and accompanying documents, which were released on 27 April 2011.

The decision not to recommend nilotinib for resistant chronic myeloid leukaemia (CML) patients is not justified based on the available evidence and we do not consider that all of the relevant evidence has been taken into account. In addition, the summaries of clinical and cost-effectiveness do not represent reasonable interpretations of the evidence.

We do not believe that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.

Our comments are presented as follows:

1. Summary of main concerns
2. Hydroxycarbamide (HU) is not the appropriate comparator in this setting
3. High dose imatinib is the appropriate comparator in this setting
4. Base case treatment duration of 10 years is inappropriate
5. Inappropriate assumptions in the assessment group model
6. Errors in the ACD
7. The provisional recommendations are not a suitable basis for guidance
8. Conclusion

Appendix 1 Additional scenario analyses

Patient Access Scheme submission template

Despite the fact that nilotinib is cost-effective versus high-dose imatinib and will be cost-effective versus HU if our concerns are addressed, we want to ensure that imatinib-resistant CML patients will not be condemned to inferior treatment if our concerns are ignored. We have therefore offered a patient access scheme and details of the impact of this scheme are included in the analyses in Appendix 1 and the Patient Access Scheme submission template.

1. **Summary of main concerns**

The decision not to recommend nilotinib for the treatment of imatinib-resistant CML denies patients access to one of the only effective treatments for this condition (other than stem cell transplantation (SCT) which is suitable for only a very small population of patients). If untreated, these patients are likely to have poor prognosis and limited life-expectancy. Nilotinib represents a step-change in the benefits provided by imatinib and this innovative product is an important development in the treatment of CML. As acknowledged in the ACD, nilotinib is clinically effective for imatinib-resistant patients and fulfils an area of unmet need due to the limited treatment options available to patients in this setting.

Novartis' main concerns regarding the preliminary recommendations are summarised below.

1.1. The conclusion that hydroxycarbamide (hydroxyurea, HU) is the main comparator is perverse in the light of expert clinical opinion and does not reflect standard clinical practice, past or present.
1.2. All the evidence shows that high-dose (HD) imatinib would be the standard of care in the absence of nilotinib and dasatinib.
1.3. The use of treatment duration of 10 years is not supported by expert clinical opinion. The average treatment duration has been estimated by clinical experts to be approximately 6.6 years.
1.4. The assumptions in the Assessment Group (AG) model do not reflect either clinical opinion or available evidence

- Mean dose intensity of [redacted] from the pivotal nilotinib trial should be taken into account in the analysis, as also recommended by the previous independent AG (PenTAG)
- Progression-free survival (PFS) should be linked to major cytogenetic response (MCyR). The AG model instead links overall survival (OS) to MCyR.
- The life years gained for nilotinib and dasatinib should be assumed to be the same given that the treatment durations were assumed to be the same.
- The utility of HU has been overestimated: it was assumed to be the same as that of nilotinib and even higher than that of SCT, a potentially curative treatment option.
- The OS gain on HU treatment has been overestimated as it was based on data from the first line setting. OS on HU in the second-line setting is expected to be worse that in the first line setting.

Novartis conducted additional analyses using the AG model to address these concerns, taking into account the application of a patient access scheme (PAS). The additional

analyses comparing nilotinib with HU (an artificial comparator in this setting) resulted in an ICER of £22,792 per QALY gained for 6.5 years treatment duration. When the more conservative assumption of 10 years treatment duration is used, the ICER is £24,993 per QALY gained. These updated results show that nilotinib is a cost-effective treatment option for imatinib-resistant patients, even when compared with an inappropriate comparator in this setting. Nilotinib is highly cost-effective (i.e. cheaper and more effective) when HU is excluded and is compared with the standard of care (HD imatinib) in all the economic models submitted to NICE.

Nilotinib is a necessary treatment with important benefits for patients with chronic phase CML. Nilotinib has been found to be both clinically and cost-effective based on the updated analysis using the independent Assessment Group model. In view of the small number of patients likely to be eligible for treatment, the budget impact of a positive recommendation for nilotinib is likely to be relative low. Our estimates suggest that there will be 21 new chronic phase resistant patients per year in England and Wales, with an associated budget impact of around £500K in year 1 rising to £1.3m in year 5. Furthermore nilotinib is already routinely prescribed and funded in most geographies in England and, under the AWMSG process, dasatinib is also already funded in Wales.

2. HU is not the appropriate comparator in this setting

2.1. Introduction

The choice of comparator is of fundamental importance in this and every appraisal. Recommendations based on a comparison with a treatment that does not reflect current use and is associated with no evidence of benefit does not constitute useful guidance to the NHS. As explained in responses to the draft scope, HU is not and has never been used routinely for the treatment of imatinib-resistant CML and therefore is not the treatment that would be displaced should the second-generation TKIs be recommended for use in NHS patients.

Accordingly, the assessment of cost effectiveness of nilotinib compared with HU is of limited relevance to the NHS and the clinical community because, in clinical practice, patients who become resistant to imatinib are rarely treated with HU unless there are specific reasons not to receive nilotinib e.g. pregnancy. HU is thus an inappropriate comparator in this setting with no credible evidence on its use nor likely benefit in this setting. A comparison with HU does not provide a proper basis for guidance to the NHS in relation to the use of nilotinib for the treatment of adults with imatinib-resistant chronic phase CML.

2.2 Clinical expert evidence

The inclusion of HU as the principal comparator in this appraisal ignores clinical expert opinion and clinical guidelines, all of which show that HU is not routinely used or recommended to treat all patients who are imatinib-resistant.

Clinical experts have consistently stated that, in the absence of nilotinib and dasatinib, standard clinical practice would be to dose escalate those patients who become resistant to 400mg imatinib to HD imatinib. For example the Royal College of Physicians stated in their response to the assessment report (AR) that:

> *"If neither nilotinib nor dasatinib were available, most UK clinicians would opt for high dose imatinib (or stem cell transplantation in the ~20% of patients in whom this is feasible), and it therefore is logical (and clinically relevant) to compare the second generation agents to high dose imatinib."*

The evidence shows that HU will only be used in specific patient groups unable to receive TKI treatment, otherwise patients will continue on 400mg imatinib or dose escalate to HD imatinib, depending on the level of loss of response. In these circumstances Novartis believes it is unreasonable for NICE to base guidance for the treatment patients who develop resistance to standard dose imatinib on a comparison with HU because the use of HU in this indication is not supported by evidence and is not reflective of clinical practice and opinion. If, contrary to our view, NICE does have evidence indicating that HU is used in standard practice in this indication (save in patients who are unable to receive TKIs), we would ask that this evidence is identified and disclosed to us at this stage in the appraisal.

2.3 Appropriate subgroup for HU

Novartis is aware of no evidence for HU providing benefit in patients with imatinib-resistant chronic phase CML. It is therefore viewed as consistent with the provision of best supportive care (BSC) and reserved for a very specific group of patients who are ineligible for TKIs e.g. due to pregnancy, or as a holding dose before their treatment options have been decided. The effect of the current preliminary recommendations in the ACD is therefore to exclude nilotinib, a treatment with demonstrated effectiveness and to restrict patients to use of HU – a treatment that will result in little or no benefit in this setting.

The ELN recommendations endorse this position that treatment with HU is appropriate for only a very small subgroup of patients. The guidelines state that HU may still be used only for a short period of time and the only place for HU is "in a patient in whom a TKI is not advised".[1] The same view was expressed by the clinical experts for this appraisal (Professors Apperley and Clark).

The decision by the Appraisal Committee to ignore the fact that HU is not a universal comparator in this setting is perverse in light of the evidence available on the use of TKIs in clinical practice. The Committee should consider the comparison of HU and SCT as specific to a very small group of patients with CML who are unable to receive nilotinib or other TKIs.

Current practice is that patients would be offered nilotinib, dasatinib or HD imatinib if they are not eligible for stem cell transplant and therefore the analysis should be a comparison of the TKIs excluding HU in this setting.

2.4 Patients are not switched to HU when they become resistant to 400 mg imatinib

The basis of the current assessment suggests that, when patients on 400 mg imatinib become resistant, they should all be switched to HU. However, in the absence of nilotinib, dasatinib and HD imatinib, some patients could still benefit from continuing 400 mg imatinib, depending on the level of resistance. Patients defined as resistant because of loss of complete cytogenetic response could (in the absence of nilotinib, dasatinib and HD imatinib) continue on 400mg imatinib because they might benefit from further imatinib treatment. Clinical experts have stated that when patients lose complete cytogenetic response, in this hypothetical situation of no TKIs, they would continue on 400mg imatinib. It is only when patients lose complete haematological response that clinicians might consider switching them to HU (a treatment option considered to be BSC) because, at that point, there would be no additional benefit from imatinib treatment. The current analysis in the ACD on which the preliminary decision is based implies that when patients become resistant to 400mg imatinib they should all be switched to HU. Novartis believes that this is both inaccurate and does not reflect clinical practice because, depending on the level of resistance, they might continue on 400mg imatinib even when HD imatinib is assumed to be unavailable to patients.

3. HD imatinib is the appropriate comparator in this setting

3.1. NICE's own guidelines support that HD imatinib should be the reference case comparator

The NICE "Guide to the Methods of Technology Appraisal", dated June 2008 states that, for the reference case, comparators should be "*Therapies routinely used in the NHS, including technologies regarded as current best practice*". There is overwhelming evidence showing that current standard practice is to dose escalate normal dose imatinib or switch to nilotinib or dasatinib and not switch patients to HU. All the evidence we have submitted showing that a standard of care in this setting is HD imatinib has been completely ignored. We therefore emphasise as per our responses to the Assessment Report that the decision of interest to the clinical community is whether nilotinib, dasatinib and HD imatinib are cost-effective when compared head to head with each other. Whether nilotinib and dasatinib are cost-effective compared with HU is of limited relevance to the NHS and the clinical community because, in clinical practice, patients who become resistant to imatinib are rarely treated with HU. Imatinib resistance did not, and could not, exist prior to the availability of imatinib. Once imatinib resistance emerged, dose escalation became standard clinical practice.

The consultees, including clinical experts, share the same view that HD imatinib is the comparator in this setting. We note that clinical experts from NCRI, RCP, RCR, ACP and JCCO, whose views were submitted as part of their comments on the draft scope, agreed that HD imatinib, nilotinib or dasatinib are the standards of care in clinical practice. Evidence from written expert personal statements submitted during the original multiple technology appraisal, that considered both imatinib-resistant and imatinib-intolerant patients, also supports this view.

3.2. **Clinical guidelines confirm that HD imatinib would be standard of care for resistant patients in the absence of second generation TKIs**

The 2006 European Leukaemia Net Recommendations which were current prior to the availability of dasatinib and nilotinib state "*…the first choice of treatment in patients with imatinib resistance is allogeneic stem cell transplantation. If this is not possible dose escalation of imatinib to 600 or 800mg daily is an option, provided that 400mg daily is tolerated and that resistance to imatinib is not associated with a BCR-ABL mutation with a high level of insensitivity to imatinib.*" These clinical recommendations provide further evidence that, in the absence of the availability of nilotinib and dasatinib, high-dose imatinib would represent the standard of care for resistant patients. The other alternative, allogeneic SCT, is only suitable for a very small population of patients because they need an appropriate donor and also must be healthy enough for the transplant.

3.3. **UK practice confirms the use of HD imatinib in the NHS**

Results from an analysis of UK patients who participated in an expanded access trial for nilotinib, prior to nilotinib becoming licensed, confirm that high-dose imatinib is used within the NHS for the treatment of resistant chronic phase CML. In this trial, 91% (41/45) of patients with imatinib-resistant chronic phase CML were treated with doses of imatinib at or above 600mg per day prior to entering the trial and receiving nilotinib.

Cancer Network guidelines for the treatment of imatinib-resistant CML routinely include the option of using HD imatinib. Once again, this confirms the routine use of HD imatinib in this setting within the NHS.

The results from a market research study[2] demonstrate that in the absence of second generation TKIs (i.e. nilotinib and dasatinib), 100% of the 65 responding clinicians would consider high-dose imatinib to be the treatment of choice for chronic phase resistant patients and therefore high-dose imatinib would be used routinely in the NHS. The analysis in this setting should therefore be a comparison of the TKIs excluding HU.

In the face of all this evidence, the Appraisal Committee is required to explain why it has rejected HD imatinib as the appropriate comparator for the reference case assessment

of nilotinib and why this comparison has not been used as the basis of guidance to the NHS.

4. Base case treatment duration of 10 years is inappropriate

The treatment duration of 10 years relied upon by the Appraisal Committee is neither reflective of clinical expert opinion nor is it a reasonable interpretation of the evidence. Clinical experts (see response dated 22 March 2011 from the RCP to the Assessment Report) have estimated that the average survival for responders and non-responders to be 6.6 years. This estimation is based on the following:

- Average age at treatment initiation with nilotinib is 60 years.
- 40% of these patients will achieve complete cytogenetic response and survive for about 15 years. Treatment with nilotinib will therefore continue for 15 years.
- 60% of patients will be non-responders whose treatment will be withdrawn after 1 year.
- Average treatment duration will therefore be 6.6 years (40% of 15 years (6) plus 60% of 1 year (0.6)).

The results of a study conducted in Scotland[3] support the view that CML patients will not stay on treatment for as long as 10 years as the Appraisal Committee has concluded. The study collected data on tolerability and clinical outcome of patients treated with second generation TKI following discontinuation of imatinib therapy because of adverse events or failed response. The definition of event free survival in the study included patients discontinuing imatinib because of toxicity or failed response according to ELN recommendations. The results of the study showed that only about 50% of patients resistant to normal dose imatinib were still event free at approximately 18 months. This study therefore partly confirms the clinical expert conclusions that not all patients will respond to a second generation TKIs for a very long time and thus the average survival on second line therapy cannot be as high as 10 years. For the average survival to be as high as 10 years the overall survival of all CML patients from diagnosis (using the same estimates for responders and non-responders) should be at least 25 years. This implies that all CML patients will survive to the age of 85 years at least, an unrealistic assumption given the starting age for treatment of about 60 years, the effects of natural mortality on life expectancy and the impact of the mortality of non-responders on average survival.

It should also be noted that nilotinib is offered as a second line treatment option in this setting after failure of imatinib. It is illogical to expect better survival and therefore a longer treatment duration in the second line setting than the first line setting. Based on data available and our estimations of treatment duration in the first line setting, 10 years as an average estimate of survival and therefore duration of treatment for the second line setting would seem excessive. Given that the average age of CML patients is approximately 60 years, the current assumption implies that survival of CML patients in the first line setting will be shorter than in second line given the life expectancy of 85

years. This is contrary to clinical opinion and the evidence suggesting that patients would benefit more and therefore survive longer in the first line setting compared with the second line setting. It is therefore clear that the 10 years treatment duration is an overestimate of the likely time patients will be treated in the second line setting. Novartis therefore believes that the 6.6 years is a more realistic treatment duration for CML patients in the second line setting and not 10 years. This is consistent with the view expressed by the RCP as referred to above.

The decision to consider 10 years as base line treatment duration and conclude that it is conservative does not therefore reflect the available evidence from studies investigating survival of CML patients and expert clinical opinion. We would ask the Appraisal Committee to explain its reliance on the 10 year figure and why it has seemingly rejected the evidence referenced above indicating that a shorter period is more plausible.

In Novartis' view, the 10 years treatment duration is less plausible and should be considered as the upper bound of the treatment duration that might be considered in this second line setting. The results from a more realistic treatment duration of 6.5 years should also be considered and taken into account by the Committee as this is closer to the treatment duration estimated by clinical experts.

5. Inappropriate assumptions in the assessment group model

The Committee concluded that the least implausible ICER was £43,800 per QALY gained based on the additional analysis from SHTAC. Novartis maintains that flaws in the structure of the SHTAC model (updated PenTAG model) cause underestimates of the potential benefits of nilotinib resulting in a higher ICER for nilotinib. In addition the SHTAC analysis did not take into account several factors that lead to an improvement in the ICER for nilotinib. These issues are discussed in detail below.

When the concerns discussed in this section are taken into account in the AG model and a patient access scheme is considered, the ICER for nilotinib compared with HU for 6.5 years treatment is reduced to £24,993 per QALY gained. When the less plausible assumption of 10 years treatment duration is assumed, the ICER is reduced to £24,993 per QALY gained. The ICER results with and without the PAS can be summarised as follows:

Treatment duration	6.5 years	10 years
Base case (no PAS)	£37,562	£45,685
Results with PAS	£27,035	£30,776
Results with PAS plus 1,2,3 and 4	£22,792	£24,993
1.Dose intensity adjusted to 84%; 2. Assume same QALY gain as dasatinib; 3. Lower utility value for HU (0.78); 4. Lower OS for HU (3 years)		

5.1 Nilotinib dose intensity

The SHTAC analysis did not take into account the impact of dose intensity on the cost effectiveness of nilotinib. In the model that is largely unchanged from the original PenTAG model, the dose intensity of nilotinib is assumed to be 100% when the evidence from the pivotal nilotinib trial showed that the mean dose intensity for imatinib resistant patients was [redacted]. The original PenTAG analysis acknowledged that dose intensity was an important consideration and suggested that, for the economic model, the mean is required, not the median dose intensity (page 172 of PenTAG AR, 10 August 2009).

In the SHTAC analysis, dose intensity for HD imatinib was considered to be 76%, based on the lower bound of the mean in the Jabbour publication. However the dose intensity for nilotinib was based on the median dose intensity that is far higher than the mean. Novartis concurs with PenTAG's conclusions that the mean should be used instead and the mean dose intensity from the pivotal nilotinib trial has been used in the updated Novartis analysis (see appendix 1).

5.2 No link between PFS and major cytogenetic response (MCyR)

The SHTAC model did not address the fundamental concern that the MCyR rates were not linked to progression-free survival (PFS) in the model. PFS is used to estimate the treatment duration in the model and the evidence shows that a higher response is associated with better PFS which in turn leads to better survival. It seems reasonable to link PFS with MCyR because PFS reflects both the level of response and is also used to estimate the treatment duration. Instead, the current model structure assumes that MCyR is linked to OS and not PFS. This approach by SHTAC leads to an underestimate of the benefits of nilotinib in this setting. Novartis cannot address this limitation because it requires a structural change to the AG model.

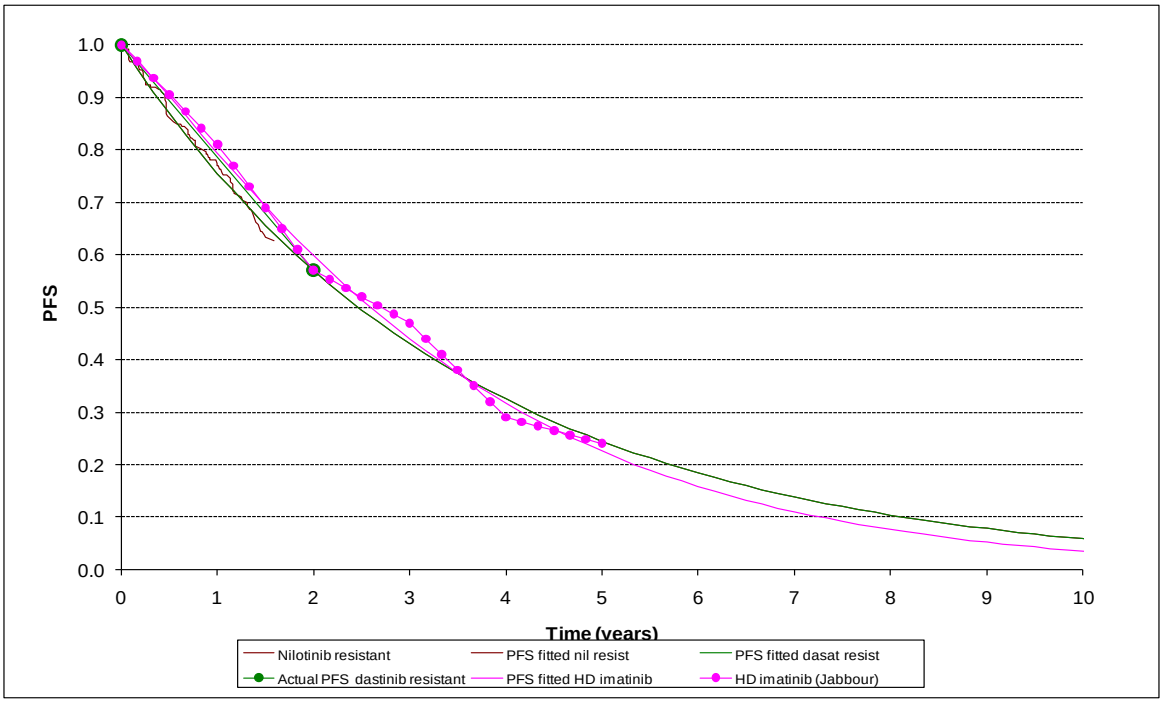
5.3 The treatment duration for nilotinib and dasatinib of 10 years is not supported by any data

The initial analysis that was conducted by both PenTAG and SHTAC on treatment duration was based on PFS data and discontinuation rates from the pivotal trials of both nilotinib and dasatinib. These data showed that dasatinib had lower discontinuation rates when compared with nilotinib resulting in higher treatments costs for the former when the discontinuation rates were applied in the model. In the updated SHTAC analysis, the lambda values for PFS have been adjusted to reflect 6.5 years and 10 years treatment durations. However the predicted PFS curves are not extrapolations based on any data as is expected in economic modelling.

To illustrate this point Novartis has extracted the PFS curves from the AG model. Figure 1 shows the fitted PFS for the original SHTAC base case analysis. Figure 2 shows the

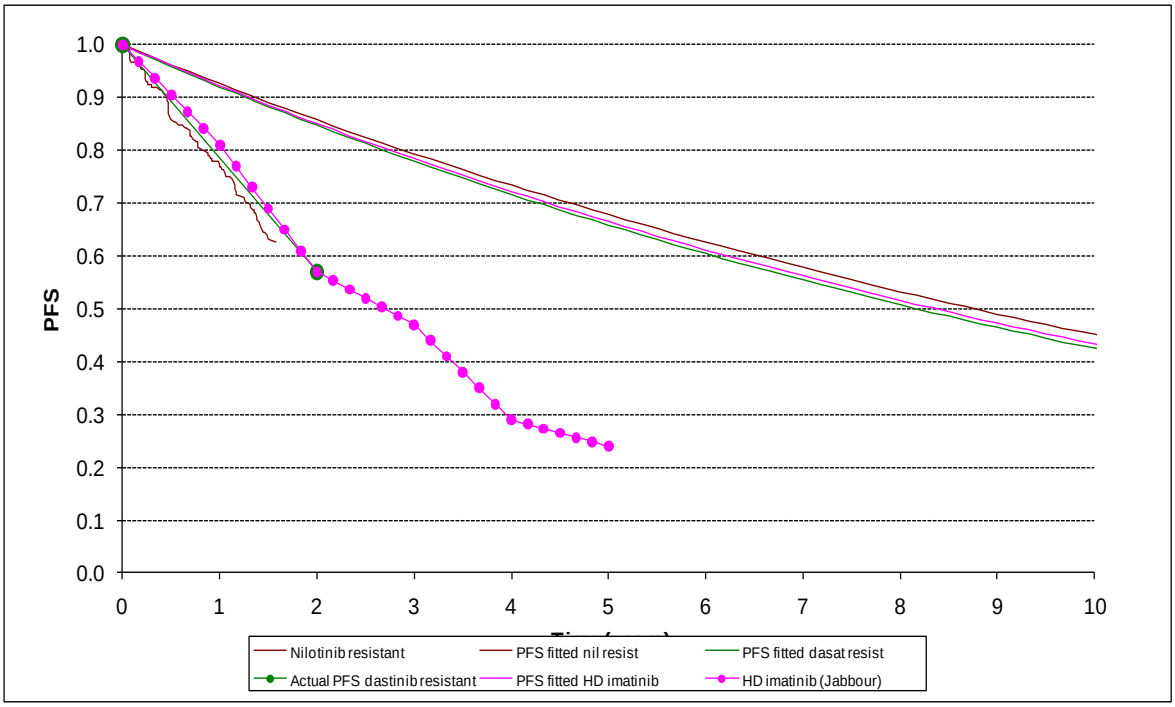
PFS curves estimating the most optimistic assumption of 10 year treatment duration compared with trial data.

Figure 1: PFS original analysis based on trial data



As can be seen in Figure 1 above, the original SHTAC base case analysis is based on extrapolations from the data. However the 10 years treatment duration PFS is not based on any fit to the data as can be seen in Figure 2. This is a limitation in the analysis because the type of curve fitted is determined by the type of data available. In the absence of data as in Figure 2, it is hard to justify such a PFS fit in the model. This issue is compounded further by the fact that the model does not link the PFS to OS as discussed earlier. All this adds to the uncertainty in the model and it is likely that the model is underestimating the benefits of nilotinib by not linking PFS to OS.

Figure 2: Predicted PFS: equal to 10 years treatment duration



5.4 The survival benefit for nilotinib assumed in the model should be the same as that of dasatinib

Although the Committee accepts clinical opinion that nilotinib and dasatinib are broadly the same with respect to their benefits, they have assumed a longer overall survival and hence a higher QALY gain for dasatinib based on the dasatinib MCyR. If the treatment duration is assumed to be the same (an unsubstantiated assumption) then it is logical to also assume the same survival benefit for the two drugs. In the base case SHTAC analysis, dasatinib's treatment duration was based on data from the pivotal dasatinib trial and this also translated into a higher benefit through the MCyR. In the additional scenario analysis, the Committee has assumed equal treatment durations based on no data, suggesting that the survival benefit should also be assumed to be the same (in the absence of data). Novartis views the approach by the Committee to be unfair and suggests that the same survival gain for nilotinib and dasatinib is assumed.

However the above not withstanding, if survival for nilotinib is to be based on observed MCyR rates from the pivotal trials, then the most up to date data should be used i.e. a MCyR of 56% for nilotinib. This estimate was noted in the SHTAC AR but was not applied in either the SHTAC's base case or updated scenario analyses. When this rate is applied in the model, the life years gained are 13.25 compared to life years gained of 13.40 for dasatinib. This confirms our view (consistent with that of clinical experts and

the Appraisal Committee) that the efficacy of the two drugs should be treated as the same.

To ensure fairness, Novartis suggests that the same life years, and hence same QALYs gained, for the two drugs be used in their considerations. With this in mind, the conclusion in paragraph 4.3.12 of the ACD that dasatinib dominates nilotinib is incorrect. Novartis has conducted updated analysis assuming the same survival gain as dasatinib (see appendix 1).

5.5 Utility of HU overestimated

The utility of HU in the chronic phase (CP) has been assumed to be the same as that of the second generation TKIs - that is 0.85. Clinical opinion (as discussed earlier) suggested that HU does not lead to any improvement in either PFS or OS. For HU to have the same utility as nilotinib which was specifically designed to delay disease progression and therefore lead to better survival is perverse and overestimates the benefit of HU in this setting. It is significant that Professor Clark has suggested that patients with chronic phase CML treated with nilotinib have a near normal quality of life.

Patients who receive SCT, a potentially curative treatment option, have a utility of 0.71 in the model, implying that a patient on HU will do better than a patient who has undergone a successful transplant. This is both counterintuitive and inaccurate and is a clear indication that the utility benefits of HU have been exaggerated. There are no published utility values for HU in this setting but given the limited benefits HU confers on patients based on clinical expert opinion, it could be argued that the utility of HU in CP could be between the utility of SCT and that of nilotinib. Novartis has therefore decided to consider the average of utility of SCT and nilotinib. This gives an average utility of 0.78 and this value is applied in the updated analysis (see appendix 1).

5.6 OS benefit for HU overestimated

The SHTAC analysis that informs the Committee's decision utilises the survival estimates of HU from the Novartis model. The survival estimates of HU are very likely to be overestimated as in the absence of any other HU data, Novartis resorted to using first line HU efficacy data.. Again this reflects the fact that HU is not used and therefore there is no evidence on its efficacy in this setting.

Novartis convened an advisory board meeting to gather clinical opinion on the efficacy of the artificial comparators such as HU. The clinical experts at the advisory board suggested that in the absence of any data on the use of HU in the second line setting, the only evidence (albeit with many limitations) will be the first line HU data from the various published trials of patients with a high Sokal risk score. The clinical experts explained that 5 year OS for HU in the second line will be expected to be less than 10% given that HU does not induce CCyR, a marker for improved survival. Novartis

calculated a 5 year survival on HU of 16% based on first line data. It should be noted that this survival is an overestimate because this is from the first line setting for patients who are not resistant to imatinib. Given that clinical experts suggested that the 5 year OS of patients on HU will be less than 10%, the use of the 16% survival in the Novartis model was an overestimate of the OS of patients on in the CP. Although this survival estimate for HU was used in the model, Novartis noted that the results were to be treated with caution because of the limitations discussed earlier. Novartis therefore believes that the survival of patients on HU has been overestimated in the SHTAC model resulting in a reduced incremental survival benefit for nilotinib.

Novartis has therefore conducted updated scenario analyses in the AG model to address this concern by assuming that the OS for HU was 3 years (See appendix 1).

6. Comments on errors in the ACD

Page 5, Section 2.6
This section states, after its mention that the treatment option of imatinib dose escalation is recommended in TA70 only in the context of clinical trials, that:

"Other treatment options for people with imatinib-resistant CML include interferon alfa, hydroxycarbamide, allogeneic stem cell transplantation, dasatinib and nilotinib".

It should be noted that TA70 was issued in 2003 and that treatment has advanced during the eight year period since that date. Today, interferon alfa (IFN) and hydroxyurea (HU) are not standard treatment options. Clinical experts have indicated that IFN and HU are, in fact, only prescribed in rare situations as a fall-back where a second line TKI cannot be used e.g. during pregnancy, or as a holding treatment until long term treatment has been decided.

Results from a market research study (2010)[2] confirm that high-dose imatinib should be the principal comparator for patients with resistance. 100% of the 65 clinicians responding stated that they would consider high-dose imatinib in the absence of second line TKIs.

Page 8, Section 3.7
This section, which does not accurately reflect nilotinib's mode of action, states:

"*Nilotinib does not inhibit the Scr family of tyrosine kinases."*

This statement implies that the Committee consider that the inhibition of the Src pathway as instrumental in the development of CML and by not inhibiting this pathway, nilotinib is not best placed to combat CML.

On the contrary, it should be noted that the known cause of CML is in fact Bcr-Abl. The role of Src in CML is not recognised and is therefore irrelevant in the context of this appraisal.

It should also be noted that, in contrast to the multi-targeted action of dasatinib, nilotinib was rationally designed to build on the considerable success of the imatinib molecule, and target Bcr-Abl more specifically than imatinib. It is 20-30 times more potent *in-vitro and* studies performed *in-vitro* show that nilotinib inhibits 32/33 known imatinib resistant Bcr-Abl mutations.

Page 9, Section 4
This section states

"In November 2009, NICE issued preliminary recommendations for a multiple technology appraisal (MTA) appraising the use of dasatinib and nilotinib for chronic myeloid leukaemia (CML) inpatients whose treatment with imatinib has failed because of resistance and/or intolerance. As a result of comments received during consultation, it was agreed to combine an appraisal of the three technologies, dasatinib, high-dose imatinib (600 mg and 800 mg) and nilotinib, to establish their comparative incremental clinical effectiveness and cost effectiveness."

This section is misleading since there was agreement from all the professional bodies (Royal College of Physicians, Royal College of Pathologists/British Committee for Standards in Haematology, Royal College of Nursing) and a clinical expert that high-dose imatinib should be the appropriate comparator, not one of the interventions. All agreed that HU is an inappropriate comparator.

This opinion continued to be expressed as evidenced by the comments on the draft scope from the Royal College of Physicians, which stated that "..in chronic phase the only appropriate comparator is escalation of imatinib to 600 or 800 mg daily, from standard dose of 400 mg daily."

Page 10, Section 4.1.2
This section states that:

"The SHTAC Assessment Group did not identify any new or updated studies of nilotinib for imatinib-resistant CML."

There have been several references to paucity of data and the fact that nilotinib data are immature. The Committee has not considered recent data up to a minimum follow-up of 24 months, despite clear reference to this in the Novartis submission.

In the chronic phase, 6 month follow up of nilotinib was published in Blood in 2007 by Kantarjian. This was followed by abstracts showing minimum follow up of 24 months by Kantarjian in both Haematologica 2009 and Blood 2009 and since then a full publication has been released, again authored by Kantarjian in Blood, February 2011.[4] The Assessment Group was therefore aware of the existence of the data as a result of the abstracts published in 2009 and the full reports were published at around the same time as the Assessment Report in February 2011. While supplementary reports were subsequently prepared by the Assessment Group and issued on 25 March and 4 April, there was no attempt to review and analyse the important long-term data in relation to nilotinib, before the meeting of the Appraisal Committee on 12 April 2011. The failure to take into account the 24 month data was unfair as was the criticism of the data for milotinib by the Committee in this context. This is particularly important in the context of the economic analysis where benefit is directly derived from the MCyR rate. It is noted that the most up to date and published 24 month results have not been utilised in the SHTAC economic model. These 24 month data include the following overall results:

Rates	% overall
CCyR	44%[4]
MCyR	56%[4]
CHR	85% (72% in resistant-only patients)[5]
Overall survival	64% at 24 months[4]

The Committee also state that there were data only 'from some patients' in the accelerated phase from a single-arm cohort study. It fails to take into consideration the data published by Le Coutre in Blood in February 2008 which showed 6 month follow up of 137 patients, or the subsequent abstract citing minimum follow up of 24 months.

In addition to the abstracts and publications from the registration trial highlighted above, there is further evidence to support both chronic and accelerated phase nilotinib treatment in the ENACT expanded access study authored by Nicolini (Haematologica 2009). This study reports results on 1,422 chronic phase patients and 181 accelerated phase patients and again, the Committee fails to take into consideration these data.

It is particularly surprising that these data have not been taken into account in the context of the Appraisal Committee's criticism of the evidence base relating to nilotinib (paragraph 4.3.6 of the ACD), a concern which Novartis does not believe is valid.

Page 11, Section 4.1.3

The ACD states that results from the Start R study treatment arms should be considered separately due to methodological limitations and the high level of cross over from imatinib to dasatinib at 12 weeks. Novartis agrees that this is a fair approach.

Page 14, Section 4.1.12

This section refers to only immature CML-CP data being available for nilotinib with lengthier follow-up being available only in abstract form. Novartis would like to clarify that the abstract form of the data which was publically available at the time of submission of this appraisal in October 2010, confirms results up to a minimum follow-up of 24 months and these figures have since been published in Blood (Kantarjian et al, Blood 2011 117: 1141-1145) in full. Novartis would request that the full publication is recognised as substantiating the data in the abstracts and that the 24 month data is used. Our comments in relation to section 4.1.2 are repeated here.

Page 14, Section 4.1.13

This section states that the nilotinib data for chronic phase was pooled. Novartis would like to highlight that these pooled data reflect not only the responses achieved on the licensed dose of 400mg nilotinib but also on the range of doses that were analysed in the phase I trial. The results therefore appear lower than when referring to the trial data for the licensed dose. Additionally, only 6 month cut-off is considered. However, as already stated, minimum follow-up of 24 months was available at the time in abstract form and fully published in Blood in February 2011 (Kantarjian et al, Blood 2011 117: 1141-1145).

Novartis requests that the full publication is used which substantiates the data in the abstracts of a minimum follow-up 24 month data which shows: CCyR rates of 44% overall, MCyR of 56% overall[3] and CHR of 85% overall (72% CHR in resistant only patients)[4].

Page 15, Section 4.1.14
This section states:

"Limited data on progression free survival were available and no published studies were identified. No data were available that provided results separately for participants with imatinib resistance and those with imatinib-intolerance".

Whilst it is true, as stated, that progression free survival is not available in the public domain for resistant only patients, the combined data for resistant and intolerant patients at a minimum of 24 month follow-up is clearly shown in the abstract presented as a poster at ASH 2009. Progression free survival was 64% at 24 months and the figures have since been published in Blood in February this year.[4]

In particular it should be noted that a new analysis of the data was carried out for the submission specifically on imatinib resistant patients and this data was fully described in our submission. It is therefore incorrect to say that no data were available that provided results separately for patients with imatinib resistance.

Page 15, Section 4.1.15
This section states:

"No studies of nilotinib provided rates of haematological adverse events separately for people with imatinib resistance."

Once again, we would like to point out that, while such data is not published, it was provided to support our submission. Our comments in relation to section 4.1.14 are repeated here.

Page 17, Section 4.1.21
This section refers to a single arm cohort study with "*some participants with accelerated phase CML. This was a dose-ranging phase one study, and as such the results of this study were viewed with caution by the Assessment Groups".*

Novartis would like to highlight that the 6 month follow up of 137 patients in the accelerated phase arm of the 2101 trial was published in Blood in 2008, authored by Le Coutre. This was subsequently updated with minimum follow up of 24 months in an abstract by Hochhaus in Haematologica 2009. There are also data from the ENACT expanded access study authored by Nicolini (Haematologica 2009) which provide updates on 1,422 chronic phase patients and 181 accelerated phase patients, all of which the Committee fails to take into consideration. Our comments in relation to section 4.1.14 are repeated here.

Page 21, Section 4.2.11
This section, under the heading of Manufacturers' Submissions, states:

"Novartis presented cost-effectiveness analyses of nilotinib and high dose imatinib compared with stem cell transplantation and hydroxycarbamide in people with chronic-phase imatinib-resistant CML."

We would like to point out that this was merely an exploratory analysis presented in accordance with the Scope, despite our disagreement with HU as a comparator in this appraisal; our base case analysis presented the cost-effectiveness of nilotinib compared with high-dose imatinib.

In the case of imatinib-resistant CML, clinical practice and recent European recommendations indicate that second-generation TKIs, nilotinib and dasatinib, and stem cell transplantation (SCT) should be used. Despite this body of opinion, the scope for this appraisal determined that the interventions, including nilotinib, should be compared with hydroxycarbamide (HU) and interferon alfa (IFN-α). These comparators are not used in clinical practice as second-line therapies and very few data exist in any

second-line setting. Indeed, the introduction of imatinib rendered the use of HU and IFN-α largely obsolete. Once imatinib was available, clinical practice evolved to dose-escalate imatinib to either 600 mg/day or 800 mg/day as the emergence of imatinib resistance came to light. For patients not able to access nilotinib and dasatinib, accepted clinical practice is to use HD imatinib and not HU or IFN-α. This means that, according to NICE's guiding principles, HD imatinib should be the comparator in this appraisal because it is the treatment that will be displaced should nilotinib and dasatinib be accepted for use in the NHS. Accordingly, we have presented an analysis in which HD imatinib is treated as a comparator.

Page 29, Section 4.2.15
This section states:

"In the first scenario (treatment duration set to 10 years..."

This should read "In the second scenario..."

Page 29, Section 4.2.29
This section states:

"The SHTAC Assessment Group noted that the economic models provided by PenTAG, Bristol-Myers Squibb and Novartis resulted in ICERs greater than £30,000 per QALY gained for all treatments."

This is not correct since, in the Novartis base case analysis of nilotinib vs high-dose imatinib, nilotinib dominated high-dose imatinib.

Page 30, Section 4.3.2 This section states:

"...high-dose imatinib followed by dasatinib and nilotinib are in widespread use and are a major advantage over the therapies previously available: that is interferon and hydroxycarbamide."

This statement is misleading and suggests that dasatinib and nilotinib are a third line treatment after high-dose imatinib; however this is not the case. We assume the text is intended to refer to "high-dose imatinib and more recently-introduced products dasatinib and nilotinib..." and would suggest that the wording is amended to avoid misinterpretation and confusion.

For the avoidance of doubt, as per the licences for nilotinib and dasatinib, and as is clear from the ELN recommendations 2009, nilotinib, dasatinib and high-dose imatinib are all options as a second line treatment and, in current clinical practice, one of these options would be selected by the clinician upon a patient failing on imatinib.

Page 32, Section 4.3.4
This section comments on the use of MCyR as a surrogate for OS and states:

" ...and heard from the clinical specialists that the strongest link was between major molecular response and overall survival."

Novartis questions the interpretation of this discussion between the Committee and the clinicians and is unaware of the evidence relied upon. The Committee seem to imply that CCyR is not important and does not link to OS. However, our own discussions with clinicians indicate that CCyR is the first main goal of treatment and that, as highlighted in a publication by Hughes from the IRIS trial, there is a clear correlation between achievement of CCyR, overall survival and PFS. MMR is effectively the next step in treatment goals and it is widely understood that achievement of MMR protects the CCyR response (patients with an MMR maintain a CCyR for longer than those who don't achieve an MMR). There is also increasing evidence that MMR itself correlates with overall survival and progression free survival.

In these circumstances, Novartis would ask NICE to clarify the evidence from clinical specialists relied upon by the Committee and identify any data in support of their position.

Page 33, Section 4.3.5
This section states:

"The Committee also agreed that there was no good evidence to distinguish between dasatinib and nilotinib, a conclusion also supported by the clinical experts."

If this conclusion is accepted, then the economic evaluation should also use same QALY for nilotinib and dasatinib in the calculation of the ICER (refer to our discussion in point 5.4 of this document).

Page 35, Section 4.3.8
This section states:

"The Committee first noted that the acquisition costs of all three interventions are in excess of £30,000 per person per year and that the cost of imatinib has recently increased;"

Novartis would like to point out that the imatinib price increase was introduced in accordance with the 2009 Pharmaceutical Price Regulation Scheme (PPRS) whereby scheme members can modulate the pricing of pharmaceuticals, but must still deliver price adjustment savings required under the PPRS agreement. It should also be noted

that the annual costs of imatinib were higher than annual costs of nilotinib before the imatinib price increase, meaning that the pivotal decision that nilotinib is cheaper and more effective remains even with the previous imatinib price.

Page 35, Section 4.3.8
This section further states that:

"The Committee also considered that if each year of life were adjusted by quality of life the resulting costs per QALY would be likely to be higher than the annual costs of the drugs."

Although the above statement is correct on a theoretical basis it assumes that the new technology is compared to nothing i.e. no costs to the comparative arm of the analysis. In this particular instance the current routine treatment option for CML patients who are resistant to 400mg imatinib is HD imatinib and the annual costs of HD imatinib are higher than those of nilotinib. Thus although the annual cost of nilotinib is in excess of £30,000 per year, it is still cheaper but more beneficial than the current treatment option in the NHS (HD imatinib). This will be the treatment option that will be displaced if nilotinib were to be recommended. We therefore request NICE to consider removing section 4.3.8 or at worst reword the section to ensure that facts are represented correctly.

Page 41, Section 4.3.17
This section states:

"The Committee considered that the development of dasatinib and nilotinib, in terms of pharmacological progress beyond imatinib was not innovative."

We believe that this view regarding nilotinib is incorrect and does not reflect the innovative approach to the development of the molecule.

As imatinib data matured, it was noted that not all imatinib patients achieved an optimal response on therapy and it is known that many have to discontinue due to adverse events. The unmet clinical need was recognised and nilotinib was specifically designed to address these issues.

Tasigna was rationally designed based on the imatinib molecule but to be more specific in its binding to the Bcr-Abl kinase domain, the single known cause of CML. This targeted design resulted in improved responses and an improved safety profile in the second line setting. Nilotinib represents a step-change in the benefits provided by imatinib, the first TKI in class and an important development in the treatment of CML. These factors do not appear to have been taken into account by the Committee in preparation section 4.3.17 of the ACD.

This innovative approach was recognised when nilotinib was commended by judges, including Sir Michael Rawlins, of the Prix Galien award in 2008 for innovation in research and development in the orphan drug category for rare conditions. It was recognised that nilotinib targets the definitive cause of CML, has improved and more flexible binding to Bcr-Abl, thereby overcoming drug resistance to imatinib, and preferentially targets Bcr-Abl, reducing the risk of unwanted off-target side effects.

7. The provisional recommendations are not a suitable basis for guidance

Novartis does not agree that the provisional recommendations are sound or a suitable basis for guidance to the NHS.

As was stated by the clinical experts and reported in the ACD section 4.3.3 *"For people receiving hydroxycarbamide, the prognosis is poor with a median life expectancy of around 5 years".* Notwithstanding this view, the preliminary decision is based on the comparison of nilotinib with HU – a treatment option that is neither relevant in this setting nor reflective of clinical practice in England and Wales.

It is simply not credible to issue guidance which has the effect of excluding what are now standard therapies for CML resistant to standard-dose imatinib, based on a comparison with a treatment which is not used in current NHS practice. Indeed, the Committee has accepted these as considerably superior interventions to HU as stated in Section 4.3.2: *"high-dose imatinib followed by dasatinib and nilotinib are in widespread use and are a major advantage over the therapies previously available: that is interferon and hydroxycarbamide"*.

The draft recommendations, if passed into final guidance, will condemn patients who have limited treatment options to an ineffective treatment (HU) that has never been used routinely for treating patients in this setting. They also represent a retrograde step in the treatment in resistant CML patients, a position which is not consistent with NICE's stated aim to promote the longer term interest of the NHS in the development of innovative treatments for the future.

The Committee stated that *"they understand that the side-effect profile of treatment is an important factor when considering the treatment options for people with CML that is resistant to standard-dose imatinib" (section 4.3.7).* However, if a negative ACD is allowed to develop into a subsequent negative FAD, the Committee are removing the clinicians' option to individualise treatment based on side effect profiles because the ACD does not recommend either nilotinib, dasatinib or high-dose imatinib. As a result,

only palliative treatment options with considerably poorer side effect profiles will be the forced drugs of choice.

It is highly unlikely that any formal clinical trial comparing the TKIs to HU – the comparator selected by the Committee in this appraisal. It will be unethical to expect patients to recruit to a trial where one of the treatment options (HU) is clearly not beneficial because it does not induce any form of response that leads to better survival outcomes. Clinical experts have stated to NICE, as part of the consultation process, that because the efficacy and tolerability of nilotinib and dasatinib might be similar, the sample size required to show meaningful and statistically significant differences of the two drugs will be large and yet the eligible patient population is very small. Due to the ethical issues and the potential practical difficulties in conducting such a trial, no new evidence will be available in the future on the comparisons of the TKIs with HU. This view is supported by CML patient groups who stated that:

> *"The ethical as well as practical dimensions involved in recruiting patients to such trials from an extremely small patient population, who are already subject to recruitment to existing trials, must lead us to the conclusion that this is likely to remain an aspiration of regulators rather than a reality."*

The current preliminary recommendation if passed into final guidance will therefore not change in the future when the guidance is reviewed. It is therefore unlikely that any new head to head data will be available to inform a guidance review in this respect. This will effectively mean that CML patients in England and Wales will not have access to life saving treatment when they fail on imatinib, thereby reducing the life expectancy of these patients. This is counter to NICE's core values of ensuring that patients have access to cost effective treatment options. In the opinion of leading clinicians[3] this will potentially leave patients with imatinib-resistant CML in England and Wales in a disadvantaged position compared to those in Europe. The provisional recommendations are therefore not sound and suitable basis for guidance to the NHS.

8. Conclusion

In conclusion, the ACD does not reflect the available evidence and, accordingly, the preliminary recommendations do not constitute a reasonable or scientifically sound or suitable basis on which to base guidance to the NHS.

In particular the inclusion of HU as the principal comparator for resistant patients is inconsistent with NICE's procedures and current clinical practice within the NHS and elsewhere. The comparison of nilotinib with HU relied upon by the Committee does not represent a valid basis for excluding nilotinib from NHS use.

We also submit that consideration of a 10 year treatment duration is not based on any evidence and clinical opinion suggests that this is an overestimate of the treatment duration in the second line setting. Clinical experts suggested that the average treatment duration is approximately 6.6 years when various factors discussed earlier were taken into account.

The survival benefit of nilotinib and dasatinib should have been assumed to be the same and nilotinib mean dose intensity should have been taken into account. We also believe that the overall survival and utility gain for HU in the CP has been overestimated. We have conducted additional analysis based on the AG model addressing these concerns and comparing nilotinib with HU (a comparator we strongly object to).

Despite the fact that nilotinib is cost-effective versus high-dose imatinib and will be cost-effective versus HU if our concerns are addressed, we want to ensure that imatinib-resistant CML patients will not be condemned to inferior treatment if our concerns are ignored. We have therefore offered a patient access scheme and the impact of this scheme is included in the analyses presented.

The analysis, taking our proposed PAS into account, resulted in a reduced ICER of £22,792 per QALY gained for 6.5 years treatment. When the more optimistic assumption of 10 years treatment duration is assumed, the ICER is reduced to £24,993 per QALY gained.

Nilotinib is highly cost effective (i.e. cheaper and more effective) when compared with the standard of care in the NHS (HD imatinib). The results of all the economic models submitted to NICE showed that nilotinib dominates HD imatinib. Nilotinib therefore represents a cost effective treatment option for imatinib-resistant patients as it is cheaper and more effective than the current standard of care in the NHS. Our updated analysis has shown that nilotinib is also cost effective when compared with HU, an inappropriate comparator.

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APPENDIX 1

Additional scenario analyses applying amended model assumptions and a patient access scheme

In this section, Novartis addresses the concerns discussed in section 5 of our comments on the ACD. Using the Assessment Group model, a series of parameters were adjusted as described below. In addition, a patient access scheme (PAS) has been applied.

Nilotinib mean dose intensity (see also section 5.1 of comments on ACD)

In the SHTAC base case analysis, a dose intensity of 100% was assumed for nilotinib. However the mean dose intensity for nilotinib from the pivotal trial should be applied in the AG model to reflect the actual average dose from the trial (data on file).

Dose intensity is an important issue in this analysis because of two main factors: firstly, the AG model is extremely sensitive to this parameter and this is confirmed in the original PenTAG AR. The PenTAG AR results showed that changing the dose intensity for HD imatinib from a base case value of 76% to 100% resulted in HD imatinib ICER changing from about £13,000 to over £170,000 per QALY gained (PenTAG AR page 237). The second point is that, because the treatment duration has been increased substantially in the SHTAC scenario analysis, the biggest proportion of the costs predicted in the model are drug costs. Novartis has applied a dose intensity of [redacted] for nilotinib based on the average dose for imatinib-resistant patients without dose escalation.

Same survival and therefore same QALY gain as dasatinib (see also section 5.4 of comments on ACD)

In the base case analysis, the dasatinib and nilotinib OS was based on MCyR from the pivotal trials. The base case analysis also considered the lower discontinuation rates for dasatinib compared with nilotinib. However in the updated scenario analysis, both the nilotinib and dasatinib PFS were adjusted via the lambda values to reflect similar treatment duration. This adjustment was based, not on any evidence, but on the fact that clinical opinion has indicated that the drugs are broadly the same. Novartis believes that in the absence of data the two drugs should be treated as being the same in all respects in including survival. Consequently, Novartis has applied the same survival and therefore QALY benefit for nilotinib in the AG model.

HU utility adjustment (see also section 5.5 of comments on ACD)

In the AG model, the utility of HU in the CP was assumed to be 0.85, the same utility in CP for patients on nilotinib and dasatinib. We are of the opinion that this utility of HU has been overestimated given clinical expert opinion suggesting that there is limited benefit for patients treated with HU in this setting. A more realistic utility estimate should be a value between the 0.85 and the SCT utility of 0.71. In the absence of utility data on HU in this setting, Novartis has applied an average of the nilotinib and SCT utility values (0.78) in the AG model.

Adjustment to the OS for HU (see also section 5.6 of comments on ACD)

As highlighted in the main response document clinical expert opinion suggested that imatinib resistant patients who move to HU do not gain any PFS or OS from this treatment. It is therefore an overestimate to assume that patients on HU will survive for an extra 3.5 years after imatinib failure. In addition Novartis has highlighted the limitations in the HU data that was used in the AG model to estimate the OS for HU. Thus HU survival is assumed to be 3 years in the Novartis scenario analysis.

In summary, the following parameter changes were made using in the Assessment Group's model:

- 1. Nilotinib dose intensity reduced from 100% to [redacted]
- 2. Same survival and therefore same QALY gain for dasatinib and nilotinib
- 4. HU utility reduced from 0.85 to 0.78
- 5. HU survival gain reduced from 3.5 years to 3 years

We have highlighted in our comments on the ACD (section 4) that we believe that a base case treatment duration of 10 years is inappropriate. Treatment duration of 6.5 years is more consistent with expert clinical opinion.

A patient access scheme, [redacted]

Results are presented showing the impact of incorporating the changed discussed above alone, as well as the PAS, for both 6.5 years and 10 years treatment duration. Please note that the ICERs are cumulative. For example the ICER for assumption 4 includes assumptions 1, 2 and 3.

Table 1: Results incorporating amended model assumptions and the application of a PAS for 6.5 years treatment duration. All ICERs are for nilotinib compared with HU.

	6.5 years		
	Total cost	**QALYs**	**ICER**
Base case vs HU	£222,093	7.63	£37,562*
1. Dose intensity adjusted to [redacted]	£196,710	7.63	£32,887*
2. Assume same QALY gain as dasatinib plus 1	£200,007	7.85	£32,213*
3. Lower utility value for HU (0.78) plus 1 & 2	£200,007	7.85	£31,676*
4. Lower OS for HU (3 years) plus 1,2 & 3	£200,007	7.85	**£30,722***
*Estimates do not include PAS			
PAS plus 1, 2, 3, and 4	[redacted]	[redacted]	**£22,792**
PAS only (without assumptions 1,2,3 and 4)	[redacted]	[redacted]	**£27,035**

Table 2: Results incorporating amended assumptions and the application of a PAS for 10 years treatment duration. All ICERs are for nilotinib compared with HU.

	Total cost	10 years QALYs	ICER
Base case vs HU	£266,204	7.63	£45,685*
1. Dose intensity adjusted to [redacted]	£230,253	7.63	£39,064*
2. Assume same QALY gain as dasatinib plus 1	£233,552	7.85	£38,154*
3. Lower utility value for HU (0.78) plus 1 & 2	£233,552	7.85	£37,518*
4. Lower OS for HU (3 years) plus 1,2 & 3	£233,552	7.85	**£36,225***
*Estimates do not include PAS			
PAS plus 1, 2, 3, and 4	[redacted]	[redacted]	**£24,993**
PAS only (without assumptions1,2,3 and 4)	[redacted]	[redacted]	**£30,776**

Incremental analysis

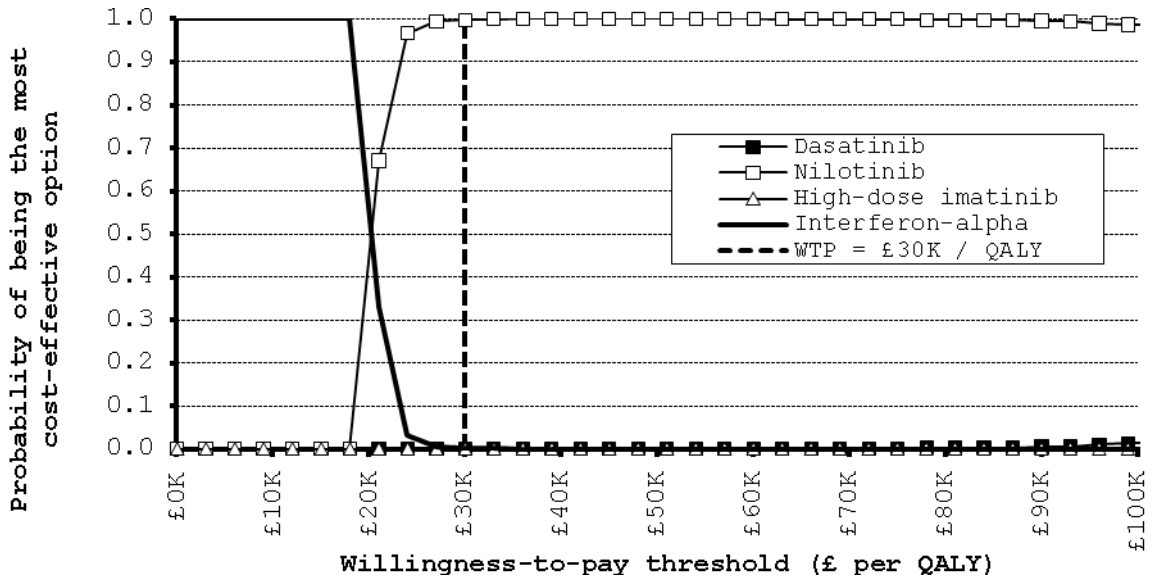
The incremental analysis could not be presented because we were unable to fully replicate all the AG scenarios with the PFS lambda values the AG supplied for both 2 and 3 decimal places.

Probabilistic Sensitivity Analysis

The focus should be on the PSA results for nilotinib compared with HU only. The full PSA could not run (error message) when the lambda values for HD imatinib were changed and therefore the lambda values for HD imatinib were left unchanged to ensure that the PSA was functional. However for the deterministic analysis all lambda values were changed.

Probabilistic Sensitivity Analysis: 6.5 years treatment duration (PAS plus 1,2,3 and 4)

The probability of cost effectiveness (nilotinib compared with HU) at WTP of £30K is 99.8%



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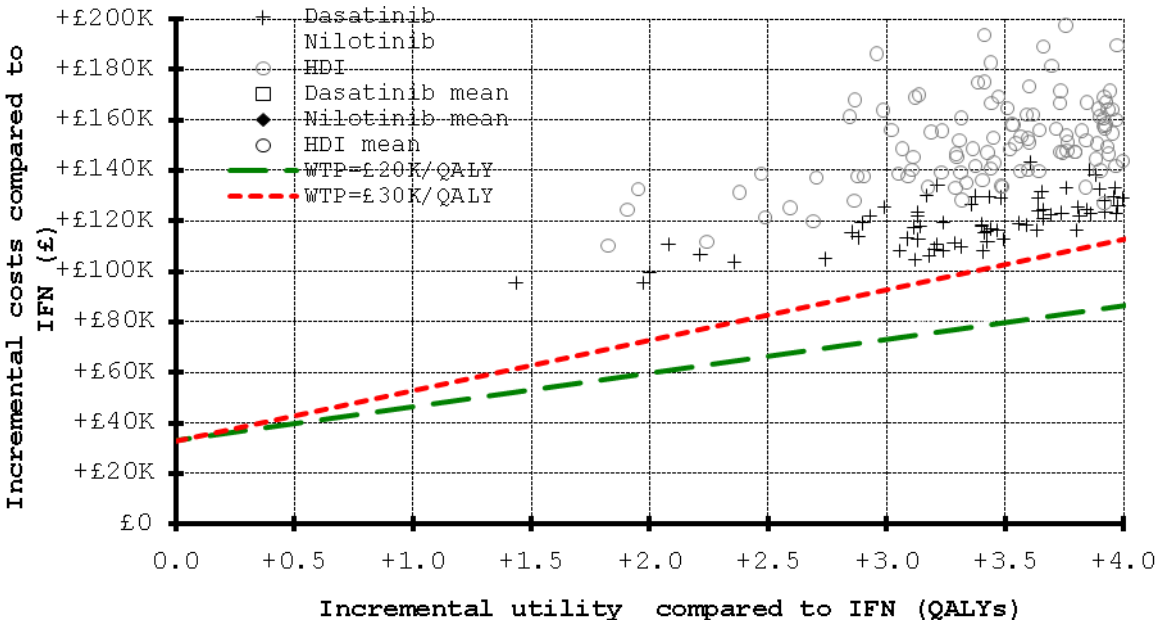
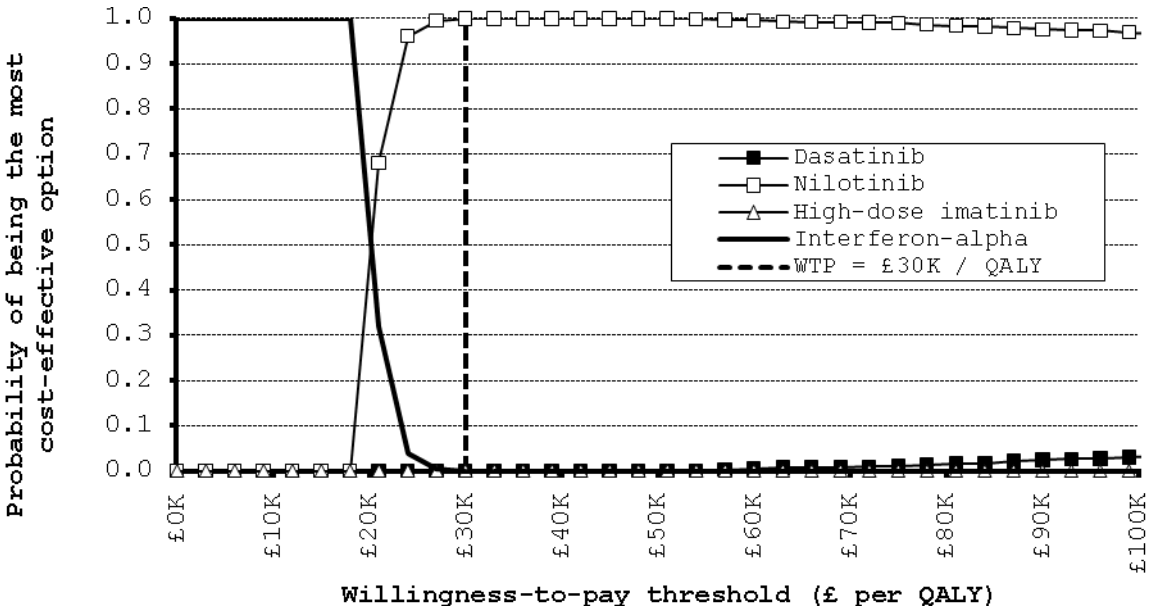
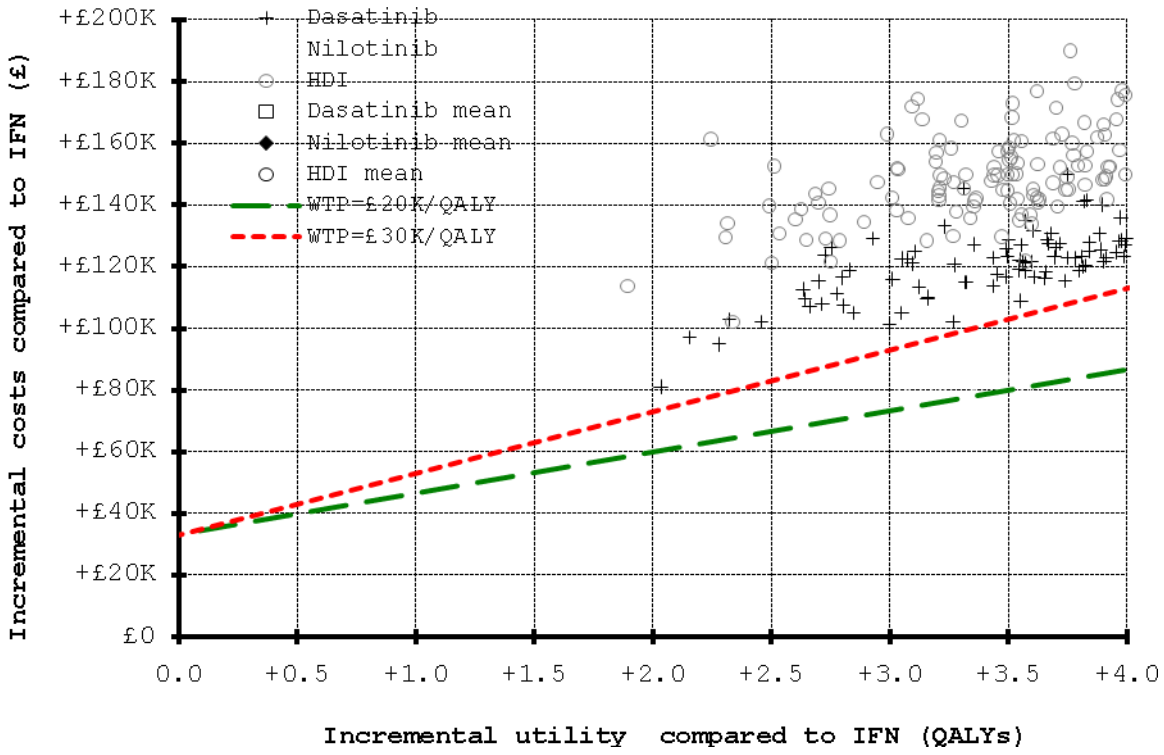


Probabilistic Sensitivity Analysis: 10 years treatment duration (PAS plus 1,2,3 and 4)

The probability of cost effectiveness (nilotinib compared with HU) at WTP of £30K is about 100%.



Scatter plot



NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Technology appraisals

Patient access scheme submission template

October 2009

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Clinical Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Clinical Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Nilotinib (Tasigna)

3.2 Please outline the rationale for developing the patient access scheme.

The PAS is a mechanism through which the NHS will be able to procure nilotinib at a price lower than list price, and equal to the current standard of care. The rationale for developing this scheme is to provide a cost-effective therapy to the NHS, thereby facilitating access for imatinib-resistant CML patients.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

This is a financially-based scheme, [redacted]

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The patient access scheme will apply to all supplies and preparations of nilotinib and will be applicable to all current and future indication.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The scheme will be applied as from positive NICE guidance for nilotinib in the second-line setting.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

100% of patients

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

[redacted].

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

The discount will be applied directly on delivery as per the standard NHS procurement procedure. No additional information will be required.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

NHS hospital trusts sign procurement agreement with Novartis UK

Invoice and payment at discounted price

Hospital pharmacy finance team

Locally negotiated tariff for nilotinib

PCO commissioner

3.10 Please provide details of the duration of the scheme.

The scheme will be in place until NICE review of guidance for the second-line treatment of CML and will be subject to Department of Health agreement.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equalities issues relating to the scheme.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

No additional forms, guides or patient information documents are required by this scheme.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

This scheme relates to the whole licensed population

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

N/A

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

The AG conducted additional scenario analysis for 6.5 and 10 years treatment duration that resulted in ICERs of £37,562 and £45,685 per QALY gained for nilotinib compared with hyroxycarbamide. Before implementing the PAS, Novartis attempted to replicate the AG ICERs by changing the PFS lambda values that were supplied by the AG. The lambda values were to 3 decimal places and the values were as follows:

6.5 years treatment duration

- Nilotinib resistant: 0.118
- Dasatinib resistant: 0.130
- HD imatinib: 0.125

10 years treatment duration

- Nilotinib resistant: 0.071
- Dasatinib resistant: 0.077
- HD imatinib: 0.075

Cells changed in model:

- Nilotinib resistant: (Treatment duration'!$BE$12)
- Dasatinib resistant: (Treatment duration'!$BE$14)
- HD imatinib: (Treatment duration'!$BE$16)

On the advice of the AG that all gamma values should be 1, a further change was made to the HD imatinib gamma value:

- Original HD imatinib gamma value: 1.16
- New HD imatinib gamma value: 1.00

Cell changed in model:

- Treatment duration'!treatment_gamma_HD_imatinib (BD16)

Novartis made changes to some of the assumptions in the AG model. These changes were as follows:

- Dose intensity adjusted to [redacted]
    - Cell changed in model: (Costs & utilities'!$F$2)
- Assume same QALY gain as dasatinib

    - Cell changed in model: (Overall survival'!$AB$9)
- Lower utility value for HU (0.78)
    - Cell changed in model: (Costs & utilities'!$N$54)
- Lower OS for HU (3 years)
    - Cell changed in model: (Costs & utilities'!$N$51)

No further changes were made to the model and a PAS (as described earlier) was implemented after the above changes:

Cell changed in model: (Costs & utilities'!$F$22)

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

Not applicable

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

There are no costs associated with the implementation and operation of the PAS.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Not applicable

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

Table 3 Base-case cost-effectiveness results for scenario 1: 6.5 years treatment duration (AG model)

6.5 years treatment duration						
	Results no PAS		**Results with PAS**		**Results with PAS plus 1,2,3,and 4[(a)]**	
	Nilotinib	**HU**	**Nilotinib**	**HU**	**Nilotinib**	**HU**
Drug cost (£)	164,475	213	[redacted]	[redacted]	[redacted]	[redacted]
Other costs (£)	57,619	17,915	[redacted]	[redacted]	[redacted]	[redacted]
Total costs (£)	222,093	18,128	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs (£)	203,965		[redacted]		[redacted]	
QALYs	7.63	2.20	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs	5.43		[redacted]		[redacted]	
ICER (£)	**37,562**		27,035		22,792	

(a)
1. Dose intensity adjusted to [redacted]
2. Assume same QALY gain as dasatinib
3. Lower utility value for HU (0.78)
4. Lower OS for HU (3 years)

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 4 Base-case cost-effectiveness results for scenario 2: 10 years treatment duration (AG model)

10 years treatment duration						
	Results no PAS		**Results with PAS**		**Results with PAS plus 1,2,3,and 4[(a)]**	
	Nilotinib	**HU**	**Nilotinib**	**HU**	**Nilotinib**	**HU**
Drug cost (£)	232,954	213	[redacted]	[redacted]	[redacted]	[redacted]
Other costs (£)	33,251	17,915	[redacted]	[redacted]	[redacted]	[redacted]
Total costs (£)	266,204	18,128	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs (£)	232,741		[redacted]		[redacted]	
QALYs	7.63	2.20	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs	5.43		[redacted]		[redacted]	
ICER (£)	**45,685**		**30,776**		**24,993**	

(a)
1. Dose intensity adjusted to [redacted]
2. Assume same QALY gain as dasatinib
3. Lower utility value for HU (0.78)
4. Lower OS for HU (3 years)

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 4 Base-case incremental results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

We are unable to present incremental analysis of all intervention because we were unable to replicate all the updated scenario analysis ICERs with the lambda values we were given by the AG for both 2 and 3 decimal places.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Not applicable

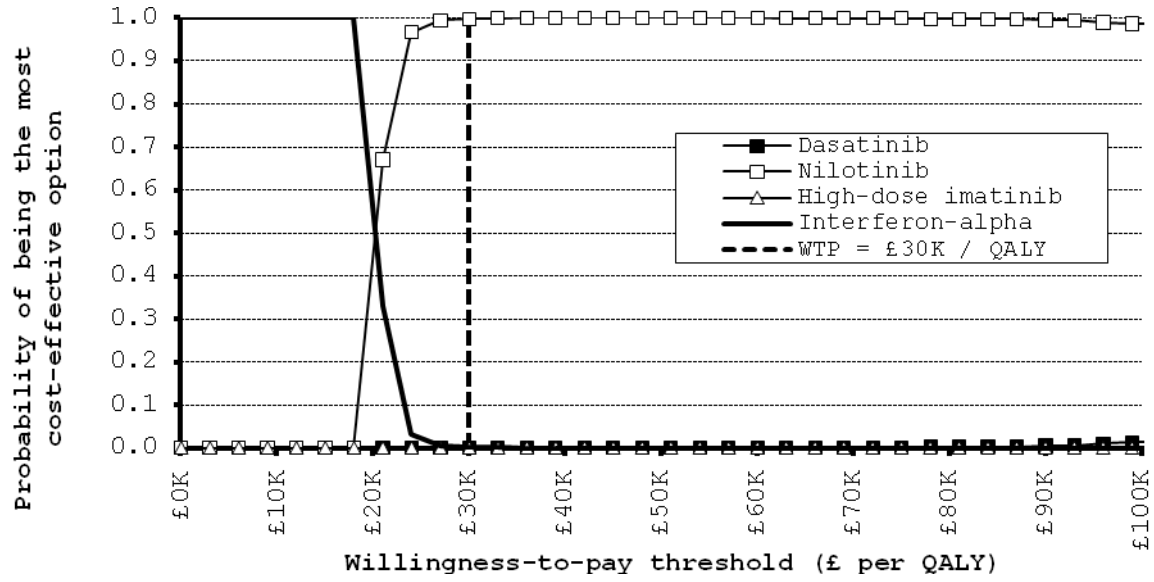
4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

The focus should be on the PSA results for nilotinib compared with HU only. The full PSA could not run (error message) when the lambda values for HD imatinib were changed and therefore the lambda values for HD imatinib were left unchanged to ensure that the PSA was functional. However for the deterministic analysis all lambda values were changed.

Probabilistic Sensitivity Analysis

Probabilistic Sensitivity Analysis: 6.5 years treatment duration (PAS plus 1,2,3 and 4)

The probability of cost effectiveness (nilotinib compared with HU) at WTP of £30K is 99.8%.



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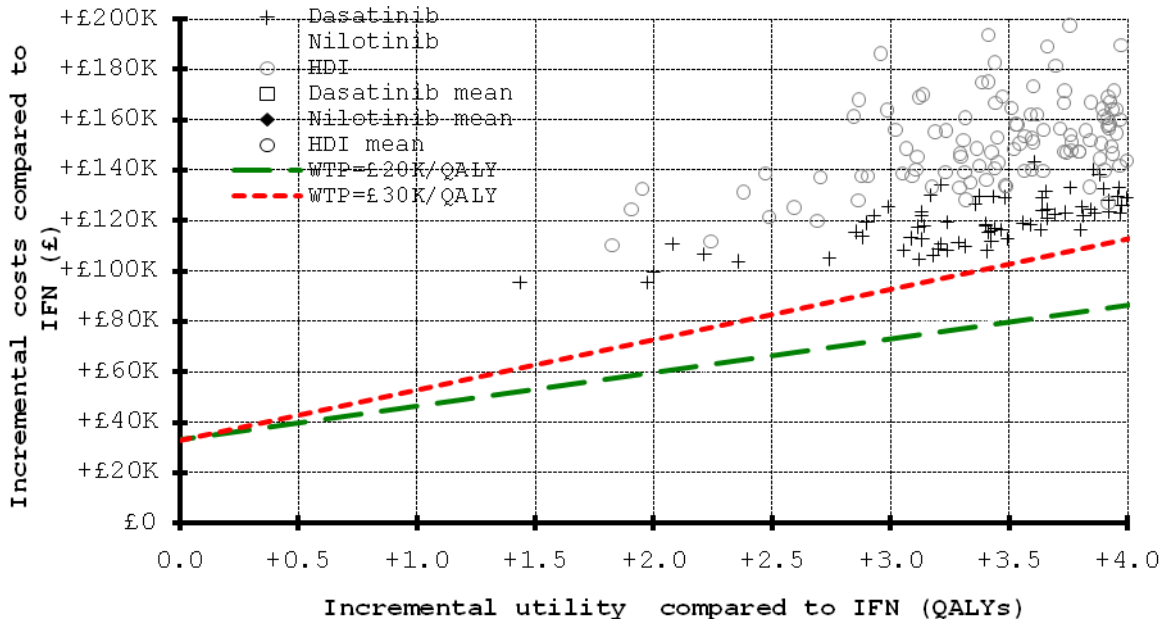
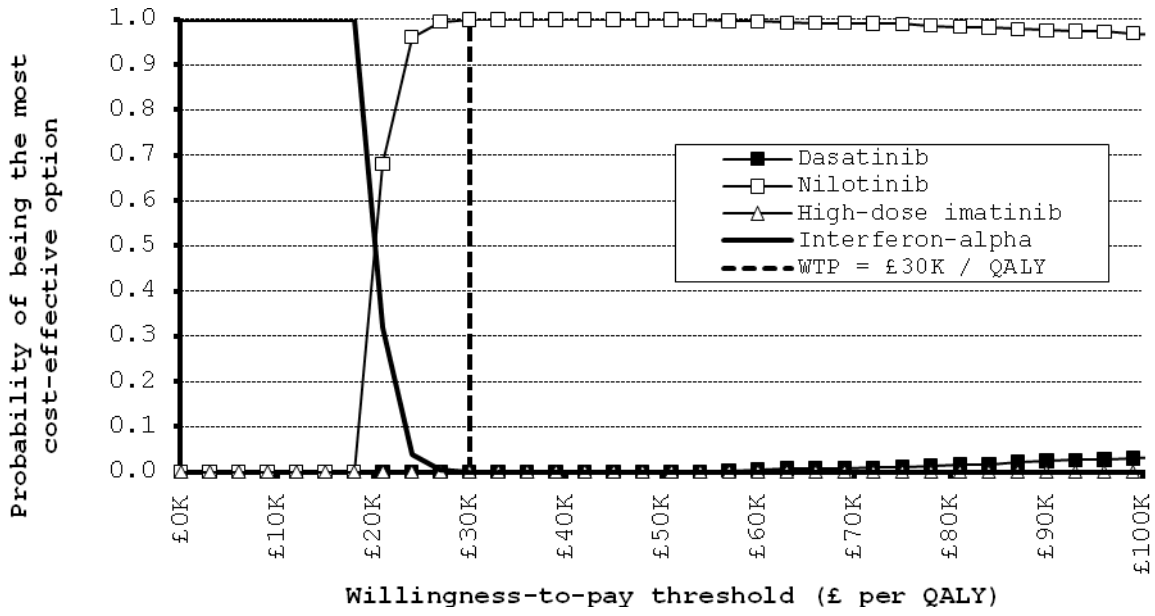
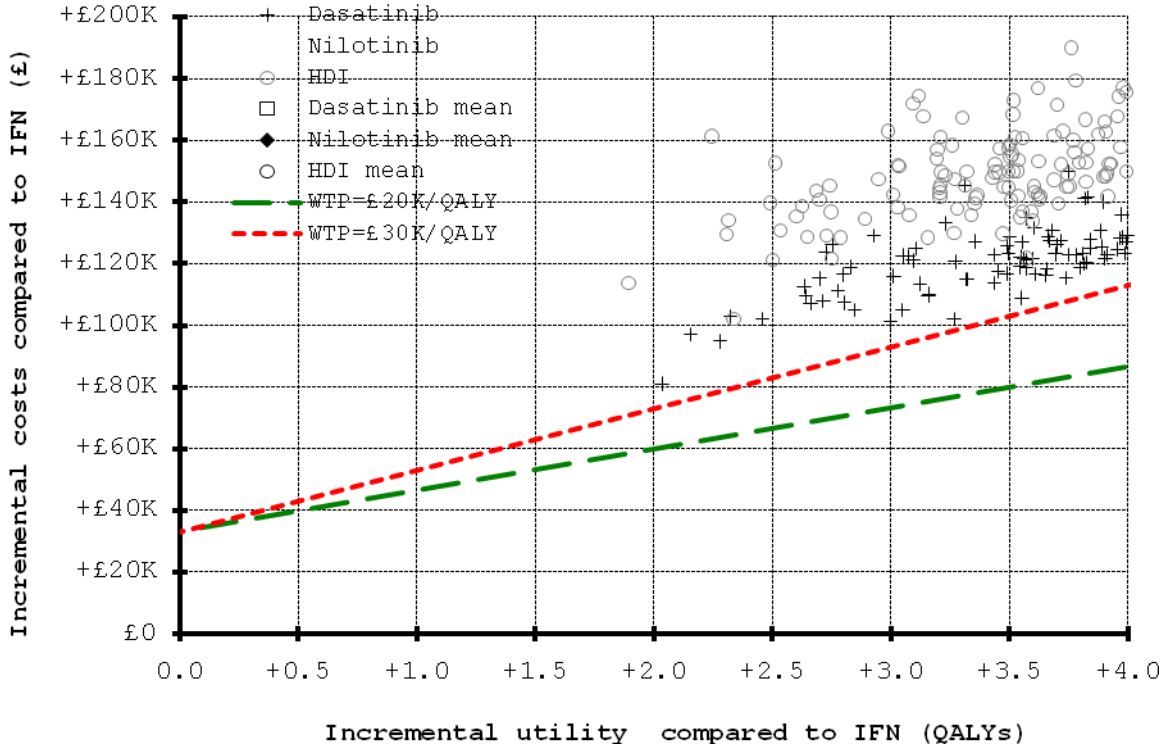


Probabilistic Sensitivity Analysis: 10 years treatment duration (PAS plus 1,2,3 and 4)

The probability of cost effectiveness (nilotinib compared with HU) at WTP of £30K is about 100%.



Scatter plot



4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

Not applicable

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Table 5 Results showing the impact of patient access scheme on ICERs

	ICER for intervention versus:				
	Comparator 1		**Comparator 2**		**…**
	Without PAS	**With PAS**	**Without PAS**	**With PAS**	
Scenario 1 (base-case)					
Scenario 2					
Scenario 3					
Scenario 4					
…					

PAS: patient access scheme.

Not applicable

Appendices

4.14 Appendix A: Additional documents

4.14.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Response

4.15 Appendix B: Details of outcome-based schemes

4.15.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Response

4.15.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Response

4.15.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Response

4.15.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Response

4.15.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Response

4.15.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Response

4.15.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Response

4.15.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

4.15.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Comparison of ICERs from the AG scenario analysis and ICERs from Novartis after applying the lambda values supplied by the AG

Comparison of ICERs: Lambda values to 3 decimal places

6.5 years PFS

Novartis				NICE			
	QALY	Cost	ICER vs HU		QALY	Cost	ICER vs HU
HU	2,20	18 128		HU	2,20	18 033	
HD Imat	7,31	242 579	43 910	HD Imat	7,31	238 594	43 151
Nilotinib	7,63	222 093	37 562	Nilotinib	7,63	222 093	37 562
Dasatinib	7,85	221 879	36 086	Dasatinib	7,85	221 325	36 007

10 years PFS

Novartis				NICE			
	QALY	Cost	ICER vs HU		QALY	Cost	ICER vs HU
HU	2,20	18 128		HU	2,20	18 033	
HD Imat	7,31	297 678	54 689	HD Imat	7,31	300 182	55 179
Nilotinib	7,63	267 474	45 919	Nilotinib	7,63	266 204	45 685
Dasatinib	7,85	265 521	43 816	Dasatinib	7,85	265 521	43 816

Comparison of ICERs: Lambda values to 2 decimal places

6.5 years PFS

Novartis				NICE			
	QALY	Cost	ICER vs HU		QALY	Cost	ICER vs HU
HU	2,20	18 128		HU	2,20	18 033	
HD Imat	7,31	238,594	43,130	HD Imat	7,31	238 594	43 151
Nilotinib	7,63	220,660	37,298	Nilotinib	7,63	222 093	37 562
Dasatinib	7,85	221,879	36,086	Dasatinib	7,85	221 325	36 007

10 years PFS

Novartis				NICE			
	QALY	Cost	ICER vs HU		QALY	Cost	ICER vs HU
HU	2,20	18 128		HU	2,20	18 033	
HD Imat	7,31	290,542	53,293	HD Imat	7,31	300 182	55 179
Nilotinib	7,63	268,760	46,156	Nilotinib	7,63	266 204	45 685
Dasatinib	7,85	262,239	43,235	Dasatinib	7,85	265 521	43 816

National Institute for Health and Clinical Excellence

Dasatinib, high dose imatinib and nilotinib for the treatment of chronic myeloid leukaemia (part review of TA70

Royal College of Nursing

Introduction

The Royal College of Nursing (RCN) was invited to review the Appraisal Consultation Document (ACD) for Dasatinib, high dose imatinib and nilotinib for the treatment of chronic myeloid leukaemia (part review of TA70.

Nurses caring for people with 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, and are the preliminary views on the resource impact and implications for the NHS appropriate?**

We would ask that the summaries of the clinical and cost effectiveness of this appraisal 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 of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?**

Nurses caring for people with chronic myeloid leukaemia have reviewed the recommendations of the Appraisal Committee. It is a bit confusing to understand the rationale for the draft recommendations. We note that the document does not recommend the use of dasatininb/nilotinib for treatment of imatinib-resistant CML. However it acknowledges that clinical specialists report that the drug is effective in those patients who have shown themselves to be imatinib-resistant, whilst noting that there is little in the way of hard evidence from clinical trials. The report also notes that treatment is £30,000 per annum for dasatinib/noliotinib and that, because it works, the patient is likely to be taking it until they die (from other causes). So it appears that this technology is not being recommended because it is too expensive as patients are likely to live too long! We also note that it is recommended that patients already on it should stay on it.

The alternatives for the treatment of people with this condition are either inadequate drugs or stem cell transplant. The latter has higher upfront costs, but is potentially curative; however only suitable for the younger, fitter patients. What is not stated in the document is the increase in mortality rate by up to 20% during the treatment and subsequent mortality and ongoing complications at 3, 6, 12 months and ongoing.

Further, it is now standard routine practice to use both of these drugs in imatinib resistant/refractory patients.

In view of the points raised, we consider that the provisional recommendations do not sound or constitute suitable basis for guidance to the NHS. They seem to have paid more emphasis on cost than on the clinical effectiveness of the technology.

iv) **Are there any equality related issues that need special consideration that are not covered in the ACD?**

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.

NICE appraisal of dasatinib, nilotinib and high-dose imatinib for patients with chronic myeloid leukaemia (CML) failing standard dose imatinib

Response on behalf of Royal College of Pathologists and BSH to the Appraisal Consultation Document (ACD) of 6th May 2011, from [redacted].

The above ACD indicates that the NICE appraisal committee's preliminary recommendations are that dasatinib, high-dose imatinib and nilotinib are not recommended for patients with chronic phase CML resistant to the NICE approved first line agent imatinib (Glivec).

1) Unfortunately, this is not good news for CML patients who are currently receiving imatinib at the standard dose (400 mg daily), nor for future patients yet to be diagnosed. This decision denies access to the second generation agents dasatinib and nilotinib, for patients whose leukaemia becomes resistant to imatinib. This is approximately 40% of CML patients, which is about 300 patients per annum across the UK.

We have very recently been carrying out a population study of CML outcome in the geographically contiguous area of Merseyside, Cheshire, Isle of Man and the North Wales coastal strip (total population = 2.0 million). During the 7 year period 2003-2009, 192 patients were newly diagnosed, of whom 9 presented with advanced disease, 3 did not receive a tyrosine kinase inhibitor (TKI) because of extreme age, and 20 received a second generation TKI as first line treatment as part of a clinical trial. A total of 160 therefore received first line imatinib, and 123 are assessable at 36 months, of which 69 (56%) have achieved adequate responses (at least complete cytogenetic remission). Thirty-three patients (which are approx. 40% of cases diagnosed since second generation TKI became locally available in Jan 2006) required switching to a second generation TKI because of imatinib resistance (18 cases) or intolerance (15 cases). Of these, 21 of 30 (70%) assessable cases have achieved not only complete cytogenetic remission but major molecular response, and no patient has lost this response at latest follow-up.

It is known from the IRIS study that the progression rate to advanced disease for patients unable to achieve complete cytogenetic response on imatinib is substantial, of the order of 10% over the subsequent 3-5 years. However, the progression rate for patients in major molecular response is less than 1%. In this population study, second generation TKI have therefore converted 70% of imatinib resistant/intolerant patients from a progression risk of 10% to <1%. It is too soon to detect an effect on progression free survival (though a trend is

currently apparent), but the overall rate of complete cytogenetic response is superior for patients diagnosed since 1/1/2006 (p = 0.04), which is when second generation TKI became locally available for imatinib resistance/intolerance.

In summary, these very recent population data provide evidence that second generation TKI benefit 70% of the 40% of CML patients in whom they are indicated.

2) There are problems with all of the 4 health economic models used in the NICE assessment. In addition, each of these has used the wrong comparator; either hydroxycarbamide, interferon or stem cell transplantation. In earlier meetings and documentation (and in the response from this college to the first appraisal meeting), it was recommended that the appropriate comparator should be high-dose imatinib. This has however been included as an appraisal technology instead. In this case, assuming that high-dose imatinib were also unavailable, then the relevant comparator should be maintaining the patients on standard dose imatinib. A detailed discussion of these points is given in the attached response to NICE from the NCRI CML subgroup (attached).

<u>Summary</u>

The appraisal committee has acknowledged that the appraisal technologies provide clinical benefit in imatinib-resistant CML (paragraph 4.3.6). We of course agree with this. It is therefore plausible that these technologies (especially dasatinib and nilotinib) may well achieve an ICER below the £30,000 threshold, if their NHS price were reduced. Novartis have recently dropped the effective NHS price of nilotinib for **first line** use (at a dose of 300mg twice daily) to match that of imatinib, whilst leaving the price of the licensed dose for second line use (400mg twice daily) unaltered. If there were downward movement of the price also for second line use, and a similar move from Bristol Myers Squibb for dasatinib, these drugs may then achieve the NICE model of cost-effectiveness. It is however difficult for the College or for individual clinicians to take a view on the detail of this; discussion between the manufacturers and the Department of Health are therefore required. One suggestion is that this could be pegged to the establishment of a CML registry across the UK, as already in place for the North of England and Wales; the UK clinical CML community would welcome and support this.

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National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London
WC1V 6NA

From [redacted]

24 May 2011

Dear [redacted]

Re: NICE appraisal of dasatinib, nilotinib and high-dose imatinib for patients with chronic myeloid leukaemia (CML) failing standard dose imatinib – Appraisal Consultation Document (ACD)

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 25,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

I write on behalf of the NCRI/RCP/RCR/ACP/JCCO with relation to this ACD consultation. We are grateful for the opportunity to respond and would like thank Professor Richard Clark for coordinating the following comments with other experts in this area.

We note that the ACD indicates that the NICE appraisal committee's preliminary recommendations are that dasatinib, high-dose imatinib and nilotinib are not recommended for patients with chronic phase CML resistant to imatinib. Our experts believe that this is firmly not in the interests of CML patients and would like to raise the following problems associated with the assessment.

- The ACD makes the point, several times, that there are insufficient data. In fact, there are 11 studies available, which were considered by the SHTAC assessment group; four of these are new since the earlier PENTAG assessment of 2009. Whilst these data are not ideal (there are no phase III RCT with survival outcomes), several clinical study groups including the NCRI Haematological Oncology (CML subgroup) Clinical Studies Group have felt it impossible to design an RCT of the appraisal technologies against standard dose imatinib, in a population of patients in whom the latter has already failed. It is therefore highly unlikely, and probably unethical, to design further studies to investigate the efficacy of these technologies. The appraisal committee has acknowledged this problem, since it supports the view that the appraisal technologies provide clinical benefit in imatinib-resistant CML (paragraph 4.3.6). We would of course agree with this.

- The analysis considered four different models, all of which are considered flawed by our experts. That from Bristol Myers Squibb assumes that chronic phase patients can only progress; there is no possibility

of progressing patients being able to achieve a second chronic phase (which is achievable clinically in approximately 30% of cases). This model uses 5 'disease states' linked to prognosis; these do not reflect real clinical practice, as they assume that once a response is achieved, it does not change until disease progression. For example, it does not encompass slow responding patients who may take time to move from no response to cytogenetic response and then molecular response. The treatment options at imatinib failure were obtained from a postal survey, but it is not clear whether continuance of standard dose imatinib was presented as an option if none of the appraisal technologies were available. Interferon was used as the comparator, apparently using first-line efficacy data from the 1990s. Apart from being an inappropriate comparator, these data are likely to be overoptimistic when applied to imatinib resistant patients, who are 'selected' for having unfavourable disease. Interestingly, the costs of nilotinib and high-dose imatinib in this model are more than double that in the other models.

- The model from Novartis compared nilotinib and high dose imatinib against the comparators stem cell transplantation (SCT) and hydroxycarbamide. Apart from being inappropriate comparators, this model also assumed that CML phases are only consecutive (ie that second chronic phase is not possible). The assumption that 75% of patients under 65 can undergo allogeneic SCT, and that all other patients receive hydroxycarbamide is considered unrealistic.

- That from PENTAG uses a model in which chronic phase patients have only 2 states; those with a major cytogenetic response and those without. There is no distinction between a patient with only a partial (ie not complete) cytogenetic response at say 18 months and beyond (who has failed according to ELN recommendations and has a significant probability of disease progression) and a patient who achieves not only complete cytogenetic response but also a deep molecular response (in whom the risk of progression is very low, <1%). Interferon is again used as a comparator, to derive ICERs that are in each case well in excess of a £30,000 threshold. However, our experts believe that the interferon data appear highly unusual (treatment for 2.04 years with interferon is associated with 10.75 years of survival; paragraph 4.2.19). This analysis also predicts overall survival of 12.98 and 13.4 years of survival with nilotinib and dasatinib respectively, despite the fact that neither drug was available in any trial until 2004/5, so long term survival is unknown. It also does not take account of the clinical observation that responses to dasatinib/nilotinib vary from minimal right through to complete molecular remissions, which are likely to have very different resultant survivals.

- The final model is from SHTAC, and addresses some of the deficiencies in the other models (eg the PENTAG assumption that treatment duration is twice as long for nilotinib as for dasatinib). However, the derivations of overall survival are made 'by a pragmatic approach' which is not made clear. No allowance is made for varying depths of response, in which long term outcome varies widely. How would this model look if patients with minimal response ceased treatment after say 12 months, with only those in complete cytogenetic remission or better continuing treatment after this time? The comparators used for deriving the ICERs of the appraisal technologies (paragraph 4.2.26) are considered inappropriate; hydroxycarbamide, interferon and SCT. It appears that at a threshold of £30,000 per QALY gained, nilotinib and dasatinib have probabilities of being cost effective of 60% and 28% respectively.

- Our experts believe that the wrong comparator has been used in each of the models. If none of the appraisal technologies were available, it is highly likely that the majority of patients would simply remain on standard dose imatinib. The statement that hydroxycarbamide is associated with a median survival of 5 years in the setting of imatinib resistance (paragraph 4.3.3) is not based on any data and appears extremely overoptimistic. We note that the issue of comparators is incorrectly summarised at point 4.3.2. We are aware that in the written evidence to the committee from the Royal College of Pathologists, it is stated that if neither dasatinib nor nilotinib were available, then most clinicians would opt for high-dose imatinib. However, hitherto the question had not arisen of what to do if high-dose imatinib were also not available. In this case, we believe that most clinicians would advise remaining on standard dose imatinib. We understand that this was also stated at the appraisal meeting.

- There are several reasons why continuing standard dose imatinib in imatinib resistance may be reasonable:

    a) In the majority, haematological response is maintained. Most would be reluctant to change to therapies that need to be given by injection and associated with many side effects (interferon) or risk cytogenetic deterioration (hydroxycarbamide).

    b) There is laboratory evidence to support the notion that disease progression may commonly arise in a mature progenitor cell compartment, rather than the leukaemic stem cell. Whilst imatinib does not target the latter, it does reduce the progenitor cell compartment, unlike hydroxycarbamide. This observation may explain the paradox that imatinib decreases progression rates whilst being ineffective against leukaemic stem cells.

    c) The only other treatment that is logical is stem cell transplantation (SCT). However, this is only feasible for fewer than 30% of patients, because of age and donor availability. Even if feasible, SCT is associated with significant permanent morbidity and some mortality, and some patients will opt to wait until clear evidence of disease progression before accepting SCT.

- Once patients progress to blast crisis, the only option likely to achieve long term good health is SCT. This is typically preceded by acute leukaemia style chemotherapy (usually 2 courses) with a concurrent second generation TKI, rather than the TKI alone. Unfortunately, SCT in this situation has a mortality approaching 50% (partly due to relapse), and is in any case only feasible in about 30% of patients, as above. The outlook for those who cannot receive SCT is grave, with a median survival of less than 24 months; those who are too unfit to withstand acute leukaemia treatment fare particularly badly. Only dasatinib has a product licence for blast crisis, but clinical experience suggests that it may palliate the unpleasant symptoms of blast crisis for many months, ensuring reasonable quality of life for the majority of patients. This is especially important for the considerable number of patients who cannot undergo acute leukaemia-style treatment. It appears that blast crisis may therefore meet NICE criteria for 'end of life', and indeed this point was made at the April appraisal committee meeting.

Summary

The appraisal committee has 'concluded that it is clear that dasatinib, high-dose imatinib and nilotinib provide clinical benefit for …imatinib-resistant CML' [paragraph 4.3.6]. We agree that these drugs may be effective in 50-75% of patients. However, since none of the technologies pass below the ICER threshold of £30,000 per QALY, the issue may centre on the drugs price, especially for dasatinib and nilotinib. For example, if the effective price to the NHS of each drug were to drop by say 30% (eg to the current price of imatinib), it may well be that the ICER for both drugs would fall below the £30,000 threshold. Whilst we appreciate that NICE is not in a position to negotiate pricing directly with manufacturers, it is possible that the effective price could be reduced through patient access schemes. Of note, Novartis have recently dropped the effective NHS price of nilotinib for **first line** use (at a dose of 300mg twice daily) to match that of imatinib, whilst leaving the price of the licensed dose for second line use (400mg twice daily) unaltered.

We agree that these drugs offer valuable options in imatinib resistant CML, but understand that at current prices, these do not meet the standard NICE cost-effectiveness thresholds. We would suggest that the appraisal panel consider the following:

- an interval for the manufacturers to consider patient access scheme options that may in effect reduce the drug price, perhaps linked to a national register for imatinib-resistant patients.

- that patients with advanced phase disease (accelerated phase and blast crisis) meet the 'end of life' criteria.

We would also support the comments in Appendix 1.

Yours sincerely

[redacted]

APPENDIX 1

Comments on the appraisal consultation document (ACD)

Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (part review of NICE technology appraisal guidance 70)

Jane Apperley, May 2011

An addendum to the NCRI/RCP/RCR/ACP/JCCO response

The preliminary decision not to recommend dasatinib, nilotinib and high dose imatinib for the treatment of chronic myeloid leukaemia (CML) resistant to standard doses of imatinib is most regrettable and disappointing,. 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 Panel prioritisation exercise, applications for exceptionality to relevant PCT or most recently from the Cancer Drug Fund. Several hundreds of patients in the UK have benefited from their prescription and now lead productive lives of good quality having been restored to a near normal life expectancy The removal of these drugs from the UK's armamentarium against CML is a retrograde step and in complete contrast to the practice in the rest of the European Union, the USA, Australia and New Zealand, amongst others. Yet again the decision is based not on efficacy, which was broadly accepted by the Committee, but on a putative cost produced by only certain analyses within the economic model.

The decision making process is based on the results of complicated statistical models, understood in their entirety by few of the medical and pharmacological experts. These models are exactly that, models. The results can be altered quite dramatically by introducing changes in any number of variables and they can only be as accurate as the information that is used for the original assumptions. In this particular case the statisticians responsible for the modelling freely acknowledge that the relatively short follow-up of these drugs that was reported in the publications, has been inadequate to guarantee their accuracy. In addition there are no data available for the outcome of the use of the various comparators in situations of imatinib resistance for the simple reason that they are ineffective and no patient or physician would accept their use when potentially effective drugs are available. The following statement was made on page 74 of the Technology Assessment Report (TAR) produced by the Southampton Health Technology Assessments Centre (SHTAC), 'However, it must be stressed that because of the concerns relating to data for the comparators, results should be treated with due caution.'

As a consequence SHTAC produced a number of results regarding the cost effectiveness of these drugs, altered considerably by altering the duration of treatment and the duration of survival. For many of these, the QALY of the technologies was within the range deemed acceptable. By altering these parameters and by choosing an effective but exceptionally inexpensive comparator, hydroxycarbamide, the QALY became unacceptably large and it was on this basis that the decision was reached. In contrast the following statements were made in the summary of the findings of the SHTAC model (page 86 of the TAR)

- Results suggest that the three interventions, dasatinib, nilotinib and high dose imatinib, have similar costs and effectiveness.
- Nilotinib, dasatinib and high dose imatinib are all cost-effective when compared with hydroxycarbamide, for a willingness to pay of about £30,000 per QALY.

Hydroxycarbamide is not a realistic choice as a comparator as it does not confer any survival benefit in CML, it merely controls symptoms. It will not be used in CML in chronic phase (CP) resistant to imatinib unless effective agents such as the second generation tyrosine kinase inhibitors (2G-TKI) are completely removed from the market and there is complete loss of control of the blood counts. Either a 2G-TKI will be

used, or in their absence, standard dose imatinib will be used. To insist in the use of hydroxycarbamide as the comparator is simply not to recognise modern leukaemic management.
In responding to this appraisal we are requested to consider a number of questions and these responses are set out by question for the remainder of this submission.

Has all of the relevant evidence been taken into account?
In section 4.1.2 of the ACD there is the following statement:'The SHTAC Assessment Group did not identify any new or updated studies of nilotinib for imatinib-resistant CML'
The phase II study of nilotinib for imatinib resistant CML was published online in November 2010 and in hard copy in January 2011 (Kantarjian HM et al. Blood. 2011 Jan 27;117(4):1141-5. Epub 2010 Nov 22). It provides the 24 month follow-up of this study and has not been considered.
In addition the clinical experts repeatedly stated that hydroxycarbamide, a palliative therapy, is not considered an appropriate treatment for patients who have demonstrated resistance to imatinib but still have a 50% chance of excellent responses and long overall survivals with high quality of life. Their written and verbal evidence was not taken into account.
With respect to the use of the technologies in accelerated phase and blast crisis, the 'end of life' criteria are clearly met, as without treatment these two conditions have a median life expectancy of considerably less than 24 months

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Comments regarding the interpretation of the cost-effectiveness have been made in the introduction to this document. In addition it is important to note that the final economic model was tabled at the meeting of the Appraisal Committee without providing members and clinical experts any time to seek critical review of the methodology. The individual presenting the data was one of very few people in the room who would have appreciated the complexity (and accuracy or inaccuracy) of the model so the chance of critical interpretation was low. In addition he moved through complex slides at a rapid rate, precluding rational discussion and challenge.
There are undoubtedly some mistakes in the ACD, of variable importance. For completeness these are acknowledged below. Unfortunately these mistakes reflect the fact that the ACD has been put together by researchers unfamiliar with the disease, its management and expected outcomes. Although in general they have interpreted data correctly there are sufficient numbers of errors to cast doubt on the final decision being based on accurate information.

Examples include
2.5 'After the introduction of imatinib into routine clinical practice, 5-year relative survival increased from 27.1% in 1990–92 to 48.7% in 2002–4 for all age groups combined ($p < 0.0001$ for the trend).'
Since imatinib became frontline treatment in the UK only after the initial results of the phase III study (IRIS) became available and the drug had been approved by NICE (TA 70 issued October 2003), 5 year survival rates could not have been available in 2002-2004. The figure of 48.7% underestimates considerably the impact of this drug on the outcome of this disease. The real value is of the order of that quoted for the IRIS study of 85% at 8 years.
3.1 'Dasatinib ... It is an orally active inhibitor of SRC and the Src-family of kinases.'
This is true but the action of dasatinib in CML is because of its inhibition of BCR-ABL in a very similar manner to imatinib and nilotinib.
4.1.3 'The Assessment Groups expressed concerns that none of the RCTs reported methods of allocation concealment, all were of an open-label design and none presented power calculations.'
When imatinib is ineffective and the patient is not eligible for an allogeneic stem cell transplant, their disease will be fatal. Dasatinib and nilotinib were drugs that were rationally designed to act in cases of imatinib failure. It is always easy to produce criticisms of studies when not personally responsible for a better design but these criticisms seem banal. How could they be anything other than open label? There is no alternative chemotherapeutic agent that can induce major or complete cytogenetic responses in patients with imatinib failure so any power calculations would be worthless. Many patients were included in these studies so it is very easy to perform a power calculation retrospectively and see that the numbers

recruited would have exceeded any requirement. These are therefore petty criticisms, which when written down and unchallenged, serve to undermine the efficacy of these agents.

4.1.4 'All other studies used higher dosages of nilotinib'

This statement should read 'All other studies used higher dosages of dasatinib'

4.1.8 'Three single-arm cohort studies that assessed high-dose imatinib and an update to the comparative RCT of dasatinib and high-dose imatinib were identified. As previously noted, this RCT was considered to be of limited use because of the extent of crossover and the study design, and the treatment arms were considered separately.'

The dismissal of the RCT of high dose imatinib versus dasatinib because of early cross-over is unfortunate since useful information can be obtained from this study. There are a number of aspects of study design which include an ethical element alongside the statistical considerations. Patients failing standard dose imatinib are aware that they once more have a fatal disease. It is unethical to ask them to consider entry to a trial in which they could be randomised to an ineffective agent and expect them to remain on this arm indefinitely to satisfy the statisticians. At some point the treatment must be considered to have failed so that they can be offered alternatives, including stem cell transplantation. Three months was not an unreasonable period of time to expect some degree of cytogenetic response. Irrespective of the early cross-over this study showed that high dose imatinib could not achieve complete cytogenetic responses in patients who had failed to show any degree of cytogenetic response on standard dose imatinib. These data have since been confirmed in other studies and suggest the futility of his approach in certain patient sub-populations.

4.2.1 'The SHTAC Assessment Group considered that although the results of this study were credible, there were some methodological limitations and it was unclear how generalisable the model parameters and the results are to the UK'

Rather than simply stating that the results might not be generalisable to the UK and thereby undermining the value of the study, could SHTAC explain why results obtained in a Northern European population, with whom the UK share considerable ancestry and genotypes, might not be valuable.

4.2.27 'The SHTAC Assessment Group explored the case in which dasatinib has a longer treatment duration than high-dose imatinib and nilotinib by varying the progression-free survival for dasatinib between 3.1 years (as in the SHTAC base case) and 6.5 years (as in the PenTAG base case), while keeping progression-free survival for high-dose imatinib and nilotinib constant. Extending the progression-free survival and treatment duration of dasatinib results in higher costs for dasatinib with no change in QALYs. Therefore the longer the treatment duration the less favourable the results compared with the other interventions. The SHTAC Assessment Group explored the case in which dasatinib has a longer treatment duration than high-dose imatinib and nilotinib by varying the progression-free survival for dasatinib between 3.1 years (as in the SHTAC base case) and 6.5 years (as in the PenTAG base case), while keeping progression-free survival for high-dose imatinib and nilotinib constant. Extending the progression-free survival and treatment duration of dasatinib results in higher costs for dasatinib with no change in QALYs. Therefore the longer the treatment duration the less favourable the results compared with the other interventions.

Why was this analysis done? As the evidence suggests that dasatinib and nilotinib are equally efficacious (a statement accepted by SHTAC) what is the value of trying to model a situation in which dasatinib is given for a longer duration than nilotinib or high dose imatinib?

4.3.2 'The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people with CML would most commonly receive treatment with hydroxycarbamide or stem cell transplantation, if possible, and that these were the appropriate comparators for dasatinib, high-dose imatinib and nilotinib.'

The clinical specialists stated on many occasions that if a patient was resistant to imatinib but remained in chronic phase that the most likely scenario would be that they remined in imatinib 400mg or where possible were given an increased dose.

4.3.3 'It heard from the clinical specialists that high-dose imatinib is being used in clinical practice but only in people whose CML has previously shown a good response to initial treatment with standard-dose imatinib; that is, good blood count response, complete cytogenetic response and complete molecular response.'

The clinical experts did not state this. They said without any qualifications that high dose imatinib was being widely used in patients who had failed standard dose imatinib. They did say that it was most likely to be effective in inducing a cytogenetic response if the patient had previously had such a response but had subsequently lost this response.

'The Committee heard from the clinical specialists that people whose CML does not respond to dasatinib or nilotinib within 12 months would receive treatment with hydroxycarbamide or, if suitable, stem cell transplantation.'

This statement is misleading because the clinical experts qualified their answer by saying that if there was good haematological control then the patient would probably stay on the current drug but some might be give the alternative second generation TKI.

'For people receiving hydroxycarbamide, the prognosis is poor, with a median life expectancy of around 5 years'

This is true for patients receiving hydroxycarbamide form diagnosis, not after failing both first and second generation TKI

4.3.4 'The Committee noted the poor evidence base for all interventions for people whose CML is resistant to standard-dose imatinib. It was aware of only one comparative trial, which compared dasatinib with high-dose imatinib, but noted the comments from the Assessment Groups on the poor study design and the interpretation problems with this trial.'

Although this might be the Committee's statement it is evidently untrue. There is excellent evidence that dasatinib and nilotinib are able to induce a complete cytogenetic response in approximately 50% of patients who fail to achieve or who lose CCyR on imatinib. There is not a single CML expert in the world who would argue that these drugs are ineffective. The criticism is of the trial design not of the drugs.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
The provisional recommendations are not sound (if only because the economic model is based on shaky foundations) and are certainly not a suitable basis for guidance in the NHS. CML is a rare disease but has an influence far beyond its incidence. It provides a story of remarkable success by using the molecular understanding of the basis of the disease to design successful targeted agents, the mechanism and unwanted side effects of which are radically different from conventional chemotherapy. The outcome of cancer treatment in the UK has been the subject of much criticism in future years and enormous effort is being expended in trying to correct this. Limiting the use of highly effective drugs in an eminently treatable condition will perpetuate the contrast between the UK and the rest of the developed world.

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?
The proposed recommendation of the Committee has a number of ramifications for inequality. First, if these drugs are denied to those who are resistant to standard dose imatinib , then more patients will be referred for allogeneic stem cell transplantation (allo-SCT). The success of allo-SCT is dependent on the degree of tissue match between recipient and donor. Any patient of non-Caucasian origin is less likely to find a compatible unrelated donor and therefore less likely to benefit from this treatment and more likely to die of their disease.

Furthermore, as has been stated above there will be inequality of access to effective therapy in the European Union.

COMMISSIONING SUPPORT

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11th May 2011

Dear Ms Farrar

Regarding: MTA on dasatinib, high-dose imatinib or nilotinib for imatinib-resistant chronic myeloid leukaemia (CML)

On behalf of the Commissioning Support, Appraisals Service (CSAS), I would like to submit our comments on the appraisal consultation document for the Multiple Technology Appraisal on dasatinib, high-dose imatinib or nilotinib for imatinib-resistant chronic myeloid leukaemia (CML) in the NHS in England and Wales. CSAS is in agreement with the appraisal committee's decision that this technology does not represent a cost effective use of scarce NHS resources.

Unit costs: Dasatinib costs £83.50 per 100mg tablet (excluding VAT; 'British national formulary' [BNF] edition 61). Assuming a treatment regimen of 100mg once daily the per person cost of dasatinib treatment is £30,477 per year. Imatinib costs £53.47 per 400mg tablet (excluding VAT; BNF edition 61) and at a maximum dose of 400mg twice daily this would result in an annual per person cost of £39,032.61. However, the cost of imatinib increased in December 2010 to £57.48 per 400mg tablet (excluding VAT; 'Monthly Index of Medical Specialties' [MIMS] April 2011), which would now make the annual cost at the 400mg twice daily dose, £41,960. The cost of nilotinib is £21.72 per 200mg tablet (excluding VAT; BNF edition 61), and assuming a dose of 400mg twice daily this makes an annual cost £31,711. Costs of all drugs may vary in different settings because of negotiated procurement discounts.

Affordability: An estimated 560 people are diagnosed with CML in the UK each year, an age standardised rate of 1.2 per 100,000 men and 0.7 per 100,000. The CSAS rapid evidence review estimated that 80% of people with CML receive standard dose imatinib, and 12% of these will be resistant. As such with a CML population prevalence of 0.001% it was estimated that in a PCT of average size 300,000 was one person every three years would be eligible for these treatments.

Efficacy: The Assessment Group conducted a systematic review of evidence on the clinical efficacy of dasatinib, nilotinib and high-dose imatinib compared with each other, and with other treatment options, in people with CML resistant to standard-dose imatinib, and identified only one RCT directly comparing dasatinib and high-dose imatinib. All other trials were single arm. The comparative RCT had methodological limitations and a high level of crossover (80% switched from imatinib to dasatinib after 13 weeks). In this trial the outcome of complete cytogenetic response (considered a surrogate outcome for overall survival) was reached by 26 months in 43.6% of those receiving

dasatanib, 63.4% of whom had a major molecular response. It was reported that 74% of those receiving high-dose imatinib achieved complete cytogenetic response at 18 months, 55.6% of whom had a major molecular response. Median survival was not reached in the trial. Due to the study design and high crossover the Assessment Group considered that the treatment arms could not be compared.

Appraisal of the evidence: The Appraisal Committee noted the short trial duration in terms of expected survival, and the overall poor evidence base for all interventions in people whose CML is resistant to standard-dose imatinib. The Committee also aware noted that no evidence was presented on the use of dasatinib, high-dose imatinib and nilotinib adjuvant to intensive chemotherapy for people with advanced disease, as would be used in practice. Also, specialists considered that the people included in clinical trials had worse disease prognoses than would be seen for treatment in current clinical practice. It was agreed that dasatinib, high-dose imatinib and nilotinib would provide clinical benefit for people with imatinib-resistant CML, and the Committee agreed with specialists that in practice, dasatinib and nilotinib would be preferred over high-dose imatinib for people with imatinib-resistant CML. However, there was agreement that there was no good evidence to distinguish between dasatinib and nilotinib, and that the poor evidence base means that the magnitude of the benefit is uncertain.

Safety: The Committee heard from specialists that dasatinib and nilotinib are better tolerated than imatinib, and it was also considered that older treatments such as interferon alfa are poorly tolerated.

Cost effectiveness: The Appraisal Committee considered two Markov models submitted by the manufacturers of dasatanib (Bristol-Myers Squibb) and nilotinib (Novartis), and a model developed by PenTAG in the original appraisal of imatinib-resistant and imatinib-intolerant CML. Bristol-Myers Squibb assessed the cost effectiveness of dasatinib, high-dose imatinib and nilotinib compared with standard-dose imatinib, allogeneic stem cell transplantation and interferon alfa in people with imatinib-resistant CML. Data on progression came from a dose-ranging RCT of dasatinib, other clinical studies and opinion. Data from the RCT were limited to 48 months of follow-up and the manufacturer extrapolated longer-term progression-free survival by assuming that the monthly rate of progression after 48 months was equal to that observed during the final year of the published data. Drug acquisition costs came from BNF60. High-dose imatinib and nilotinib were dominated by dasatinib, and the base-case ICER of dasatinib compared with interferon alfa was £38,883 per QALY gained. Novartis assessed nilotinib and high-dose imatinib compared with SCT and hydroxycarbamide in people with chronic-phase imatinib-resistant CML. Drug acquisition costs came from BNF60. Base-case results showed that high-dose imatinib was dominated by nilotinib, and the ICER of nilotinib compared with hydroxycarbamide and stem cell transplantation was £44,028 per QALY. PenTAG estimated the cost effectiveness of dasatinib, high-dose imatinib and nilotinib in people with imatinib-resistant chronic-phase CML, but the Assessment Group was unable to identify suitable effectiveness data for comparator treatments in people with advanced CML with which to populate the model. Drug acquisition costs came from BNF58. In the base-case high-dose imatinib was dominated by nilotinib. The ICER of nilotinib compared with interferon alfa was £44,600 per QALY gained, and dasatinib compared with interferon alfa resulted in an ICER of £75,800 per QALY gained. Dasatinib compared with nilotinib resulted in an ICER of £277,700 per QALY gained.

Appraisal of the economic evaluation: The Appraisal Committee noted the use of complete cytogenetic response as a surrogate outcome for overall survival and heard from the clinical specialists that the strongest link was between major molecular response and overall survival. The Committee also noted that the acquisition costs of all three interventions are in excess of £30,000 per person per year, and that the recently increased cost of imatinib is included in only one of the economic models (Novartis). In the Bristol-Myers Squibb the Committee noted the cost of interferon alfa was almost double that in other models and that there was no comparison to hydroxycarbamide. They also did not consider the extrapolation of longer-term progression-free survival to be appropriate. The Novartis model was notable in having no comparison with dasatanib and no separate comparisons for interferon and hydroxycarbamide. The economic models provided by PenTAG, Bristol-Myers Squibb and Novartis resulted in ICERs greater than £30,000 per QALY gained for all treatments. In all of the models, nilotinib had the lowest ICERs. The Committee did not consider that a plausible ICER had been presented. All models were considered to have treatment durations different from what would be seen in current practice where people would be treated until death. They concluded that there is no evidence to distinguish between dasatinib and nilotinib and that the ICERs for these treatments compared with hydroxycarbamide would both be higher than £43,800 per QALY gained and could be considerably more if treatment were continued for the person's lifetime. The Committee also noted that high-dose imatinib was dominated in all models and therefore could not be recommended as a cost-effective use of NHS resources for the treatment of chronic-phase CML that is resistant to standard-dose imatinib.

Additional factors: The Committee was aware that end-of-life criteria may be met by people with accelerated or blast phase CML who are resistant to imatinib. However, though life expectancy at this stage is less than 24 months and less than 10% of all people with CML would present at this stage, the Committee agreed that the available evidence on life extension was too weak and not robust, and that no data were presented for the interventions as used in clinical practice. The Committee concluded that high-dose imatinib, dasatinib and nilotinib do not fulfil end-of-life criteria for people with advanced CML.

If you require any further information please contact CSAS at; AskAppraisals@sph.nhs.uk

Yours sincerely

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HEALTH TECHNOLOGY APPRAISAL: NICE Health Technology Appraisal - Appraisal Consultation Document On Dasatinib, high-dose imatinib and nilotinib for the treatment of chronic myeloid leukaemia (review)	
TO: NICE	**FROM: Healthcare Improvement Scotland 26 May 2011**

1. Do you consider that all the relevant evidence has been taken into account? *If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results?*

We have conducted a West of Scotland and Lothian audit for all patients treated initially with imatinib 400mg per day from diagnosis. Restricted access to second generation tyrosine kinase inhibitors in the UK could result in suboptimal treatment for almost half of chronic myeloid leukaemia patients: results from a West of Scotland and Lothian population study.Gallipoli P, Shepherd P, Irvine D, Drummond M, Holyoake T. Br J Haematol. 2011 Apr 22. doi: 10.1111/j.1365-2141.2011.08653.x

This audit demonstrates that in the real world approximately 50% of patients who are started on imatinib at diagnosis will remain on imatinib and in good response 5 years later. However 50% of patients will have discontinued imatinib therapy. These patients include a tiny number who proceed to stem cell transplant, some who have intolerance to imatinib (nearly 20%) and switch to one of the second generation agents, either dasatinib or nilotinib, some who fail imatinib and switch to dasatinib or nilotinib and some who are deemed to have a sub-optimal response to imatinib and are switched to dasatinib or nilotinib. The study included 122 patients diagnosed between 2002 and 2010. 44 patients of 122 stopped imatinib because of intolerance or failed response of whom 39 went onto second generation drugs dasatinib or nilotinib. For these 39 patients the median time on imatinib was 13.2 months but 19.2 months on second generation strongly suggesting the the second generation drugs were both tolerated and effective. Indeed 25 of 39 patients were deemed to have had a satisfactory response, 10 were intolerant and 4 failed to respond. The EFS on second generation drugs was 58% which was better than for imatinib first line at 53%. Both the intolerant to imatinib and the failed imatinib groups did equally well on

second generation drugs going against the idea of reviewing intolerance separately to resistance. In other words 60% of patients who do not do well with imatinib will be rescued by dasatinib or nilotinib.

2. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? *If not, in which areas do you consider that the summaries are not reasonable interpretations*?

   My take on this is that both nilotinib and dasatinib are exceptionally good drugs when used for those who fail imatinib either for INTOLERANCE or for RESISTANCE. In the worst case scenario (hypothetical) if a patient became imatinib resistant and imatinib was discontinued the person might die the following day, whilst in the very best case scenario they would go on to dasatinib or nilotinib and live a normal life (eg more than 10 years). If in this setting the drug price is too high then the threshold for QALY set at £30,000 is likely to be bridged simply because dying immediately is cheaper than living on drug for 10 years. In reality if we stop imatinib in these cases they will not die the following day but their life expectancy would be limited to months/few years as they are already a high risk group as they are imatinib resistant and given palliative therapy with hydroxyurea they would all enter blast crisis and die with a median somewhere around 24 months. If these same patients were given dasatinib or nilotinib we know from the audit above, performed in Scotland on real Scottish CML patients, that their EFS would be 57.9% at 3 years and overall survival 91% (only 4 deaths 2 of which were CML unrelated caused, 1 post-transplant and 1 from CML).

   These drugs cannot be any better from a response point of view therefore the only way to reduce the QALY threshold is to cut the cost of the drugs.

3. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? *If not, why do you consider that the recommendations are not sound?*

   The recommendations are completely out of line with our clinical experience of using these drugs. These drugs work in 60% of patients who become resistant to imatinib. These drugs are very well tolerated and given on an out patient basis. Only today I have been in a clinic full of patients on second generation TKI dasatinib and nilotinib who would have died from disease progression had they not been given these drugs. The doctors all know that this is FACT. The decision by NICE is only made on the basis of cost – this being the case the only way out of this situation is to try to force the drug companies to lower their price.

4. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? *If not, how do they differ in Scotland?*

   What happens in Scotland currently is that every patient diagnosed with CML is commenced on imatinib 400mg or entered into SPIRIT 2 trial which offers a 50:50 randomisation between dasatinib and imatinib. The patients are monitored every 3 months. We apply the ELN recommendations (JCO 2009, Baccarani M et al,). If the patients fail imatinib they either go onto dasatinib or nilotinib (95%) or are considered for a stem cell transplant (no one recently in Glasgow). Similarly if patients show a suboptimal response according to ELN they go onto dasatinib or nilotinib. Similarly if intolerant they switch to one of these agents. In a tiny number of patients we find they develop

haematological toxicity with all 3 available TKI and if not fit for stem cell transplant (the vast majority) we use hydroxycarbamide. NO patient is on interferon for treatment of CML in WOSCC.

5. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? *If so, please describe what these changes would be.*

   Absolutely. If we cannot give the 50% of patients who become intolerant or resistant to imatinib either nilotinib or dasatinib then we would use stem cell transplant with mortality of 10-40% depending on age and with +++ long term complications (only applicable in a small minority of cases <15%) or hydroxycarbamide a palliative agent thus condeming these patients to disease related death within a short time window when we know there are good drugs out there for these patients. I hope that by applying for each case individually we would still be able to prescribe nilotinib or dasatinib for all those cases who develop imatinib resistance as there is really no other choice that makes any sense.

6. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? *If yes, please explain why this is the case.*

   I would hope our extensive experience with these drugs in Scotland and our careful audit and analysis of outcome would be taken into account. I have led these studies from the beginning (PI Scotland for all imatinib, nilotinib and dasatinib trials to date) with huge input from Dr Mark Drummond. It has been our privilege to be able to secure amazingly good drugs for patients with CML all over the country – Arran, the Borders, Fife, Wick etc (even one case by sleeper from Kent and another from London). Please ensure we can continue to serve our patients as we have been doing until now.

7. Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment

   Simply please do everything you can to reverse this decision.

Comment provided by [redacted]

1. Do you consider that all the relevant evidence has been taken into account? *If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results?*

I would suggest reading the following article:

Restricted access to second generation tyrosine kinase inhibitors in the UK could result in suboptimal treatment for almost half of chronic myeloid leukaemia patients: results from a West of Scotland and Lothian population study.Gallipoli P, Shepherd P, Irvine D, Drummond M, Holyoake T. Br J Haematol. 2011 Apr 22. doi: 10.1111/j.1365-2141.2011.08653.x

As with the use of all TKIs since they became available in 2002 we have audited their use extensively in Scotland. This clearly illustrates that we would be doing almost 50% of our CML population a disservice by removing their availability. These patients MAY have recourse to transplant (approximately a 30% mortality rate depending on source data used and pt factors) a procedure which costs £70,000 with approx £2,400 ongoing monthly cost thereafter (which includes a £21,000 per readmission sum). In the NICE economic model this probably looks fairly attractive; killing patients with the treatment certainly does reduce ongoing drug costs.

How out of step this decision is can be easily gleaned from the literature on the subject (see ELN Guideleines, JCO 2009 Baccarini et al). This is a Europe-wide consensus guideline produced with UK representation. Our audit results show that 60% of patients who go onto these drugs achieve an excellent response. Without them this group would now comprise patients on high dose imatinib (600-800mg daily, expensive, toxic & less effective than nil or das, dead as a result of

transplant, some cured and well as a result of transplant with a significant cohort alive but with serious transplant induced co-morbidities including downstream secondary cancers, heart disease etc, patients on palliation with hydroxycarbamide, a useless- but cheap-treatment but keeps white cell count down, and perhaps a few individuals on interferon. The latter remains expensive (approx £1000 per month) and produces acceptable responses in only 10-20%, with considerable toxicity. In short treatment would return to a hodge-podge of unsatisfactory treatments from the useless to reasonably effective (HD IM) to the downright lethal.

2 Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? *If not, in which areas do you consider that the summaries are not reasonable interpretations*?

Any drug that prevents death, but demands ongoing administration, is going to be unattractive to our current economic modelling systems. It is my understanding that the economic model used by NICE (& produced by PENTAG) was hugely flawed, specifically with regard to the comparator drugs in which Hydroxycarbamide (which costs pennies) featured highly. This comparator is laughably inappropriate, as all doctors asked to comment on the model (including myself) pointed out. The correct comparator should have been high dose imatinib. This is even more expensive (approx £40,000 pa) and significantly more toxic than either dasatinib or nilotinib.

I appreciate that cost-modelling does not take into account the 'social' costs of therapy however I would appeal to the SMC / QIS to give some thought to this: CML patients may now have a near normal life expectancy thanks to these drugs. This is entirely down to scientific and pharmaceutical advances and is a triumph of modern medicine. Furthermore, these patients also function normally and importantly RETURN TO WORK. If we didn't have 2nd line TKIs many patients would be held on imatinib either at standard or high dose; this would still cost a significant amount (in the case of high dose IM considerably more than das or nil). Uncomfortable imatinib side effects would have to be tolerated (after all the alternative is not there) and QoL would suffer. Many patients would stop functioning and many would stop work. I cannot think of a single working patient in our large CML practice (60-80 patients) who has stopped work for disease or treatment related reasons.

2. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? *If not, why do you consider that the recommendations are not sound?*

No. For all the reasons above.

4. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? *If not, how do they differ in Scotland?*

I refer you to the comment of Professor Holyoake provided under this section, with whom I share a large WoS CML practice:

> "What happens in Scotland currently is that every patient diagnosed with CML is commenced on imatinib 400mg or entered into SPIRIT 2 trial which offers a 50:50 randomisation between dasatinib and imatinib. The patients are monitored every 3 months. We apply the ELN recommendations (JCO 2009, Baccarani M et al,). If the patients fail imatinib they either go onto dasatinib or nilotinib (95%) or are considered for a stem cell transplant (no one recently in Glasgow). Similarly if patients show a suboptimal response according to ELN they go onto dasatinib or nilotinib. Similarly if intolerant they switch to one of these agents. In a tiny number of patients we find they develop haematological toxicity with all 3 available TKI and if not fit for stem cell transplant (the vast majority) we use hydroxycarbamide. NO patient is on interferon for treatment of CML in WOSCC".

5. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? *If so, please describe what these changes would be.*

   Yes. We would do more transplants, have more transplant related deaths and have more patients remaining on imatinib (including high dose) with chronic toxicity. We would use interferon in some circumstances (again at considerable expense & toxicity) in the knowledge it would only benefit a minority (10-20% at most). For those denied 2nd Gen TKIs a proportion would still get them; we would make a good case on a non-formulary / exceptionality basis. Please note; while I am no health economist I rather suspect that by the time you add all these cases up (HD IM, Transplant, 2GTKIs granted on a NF application) and factor in the chronically ill who are unable to work we are not going to be saving very much money after 'unapproving' these drugs.

6. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? *If yes, please explain why this is the case.*

   We have a strong CML background in this country with a Scotland-wide network of interested expert clinicians and a nationwide Treatment Guideline in preparation. This will incorporate the role of nilotinib as first line therapy if approved (see below). These drugs are used within tight local guidelines and are audited regularly (as we have demonstrated). The same cannot be said for England outwith the larger interested centres.

   A final and important comment is with regards the availability of Nilotinib as a first line treatment. I understand that this is currently going through the SMC and will involve a price reduction to that of Imatinib when used first line. The implications of this for the use of the second line agents are two-fold:

   1. **Less patients will fail first line therapy. Nilotinib is more effective than imatinib. My estimates from the literature are that 10-20% of patients will require a 2nd line agent with nil as compared to 30-40% in our IM audit / literature. Furthermore, for patients intolerant of nil, imatinib will be used (cost neutral) as a second line therapy (a major**

shift in Scottish practice). Therefore we are looking at only 10% or so of patients escalating to dasatinib, a marked reduction from before. I would therefore expect the treatment of CML to become gradually more cost effective with less use of these agents in the second line.

2. **Nilotinib cost reduction. This is available for patients treated with nilotinib as first line. This immediately produces a grey 'first line area'. What if a patient is rapidly intolerant of imatinib, say within days or even 4-6 weeks, who has not yet achieved a remission (and this does happen)? I would still consider use of nilotinib here as 'first-line' as far as long-term disease control is concerned. Thus a proportion of what we would have considered 2nd line (and paid for accordingly) might, quite legitimately, be accepted for first line discounted therapy. I should point out that I have discussed this issue with Novartis (in my view the fairest and most ethical company involved in treating blood cancers) and they agree that the line is a blurred in this regard but that they would honour the agreement (indeed they do not ask for evidence re line of therapy).**

These two important issues need to be taken into account when making the decision on 2G TKIs in a Scottish context.

7. Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment

   I would reiterate Professor Holyoake's plea to reverse this NICE MTA. As I have illustrated above it is based on a flawed economic model with unrealistic cost comparators. First line Nilotinib will alter the picture in the coming years. If these drugs are refused we can safely predict that many patients will die unnecessarily from inappropriate and ineffective treatments in the years to come. I think it would be a grave error to align ourselves with this decision while the rest of Europe looks on in disbelief.

Comment provided by [redacted]

Healthcare Improvement Scotland
Delta House, 50 West Nile Street
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Comments on the appraisal consultation document (ACD)

Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (part review of NICE technology appraisal guidance 70)

Jane Apperley, May 2011

The preliminary decision not to recommend dasatinib, nilotinib and high dose imatinib for the treatment of chronic myeloid leukaemia (CML) resistant to standard doses of imatinib is most regrettable and disappointing,. 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 Panel prioritisation exercise, applications for exceptionality to relevant PCT or most recently from the Cancer Drug Fund. Several hundreds of patients in the UK have benefited from their prescription and now lead productive lives of good quality having been restored to a near normal life expectancy The removal of these drugs from the UK's armamentarium against CML is a retrograde step and in complete contrast to the practice in the rest of the European Union, the USA, Australia and New Zealand, amongst others. Yet again the decision is based not on efficacy, which was broadly accepted by the Committee, but on a putative cost produced by only certain analyses within the economic model.

The decision making process is based on the results of complicated statistical models, understood in their entirety by few of the medical and pharmacological experts. These models are exactly that, models. The results can be altered quite dramatically by introducing changes in any number of variables and they can only be as accurate as the information that is used for the original assumptions. In this particular case the statisticians responsible for the modelling freely acknowledge that the relatively short follow-up of these drugs that was reported in the publications, has been inadequate to guarantee their accuracy. In addition there are no data available for the outcome of the use of the various comparators in situations of imatinib resistance for the simple reason that they are ineffective and no patient or physician would accept their use when potentially effective drugs are available. The following statement was made on page 74 of the Technology Assessment Report (TAR) produced by the Southampton Health Technology Assessments Centre (SHTAC), 'However, it must be stressed that because of the concerns relating to data for the comparators, results should be treated with due caution.'

As a consequence SHTAC produced a number of results regarding the cost effectiveness of these drugs, altered considerably by altering the duration of treatment and the duration of survival. For many of these, the QALY of the technologies was within the range deemed acceptable. By altering

these parameters and by choosing an effective but exceptionally inexpensive comparator, hydroxycarbamide, the QALY became unacceptably large and it was on this basis that the decision was reached. In contrast the following statements were made in the summary of the findings of the SHTAC model (page 86 of the TAR)

- Results suggest that the three interventions, dasatinib, nilotinib and high dose imatinib, have similar costs and effectiveness.
- Nilotinib, dasatinib and high dose imatinib are all cost-effective when compared with hydroxycarbamide, for a willingness to pay of about £30,000 per QALY.

Hydroxycarbamide is not a realistic choice as a comparator as it does not confer any survival benefit in CML, it merely controls symptoms. It will not be used in CML in chronic phase (CP) resistant to imatinib unless effective agents such as the second generation tyrosine kinase inhibitors (2G-TKI) are completely removed from the market and there is complete loss of control of the blood counts. Either a 2G-TKI will be used, or in their absence, standard dose imatinib will be used. To insist in the use of hydroxycarbamide as the comparator is simply not to recognise modern leukaemic management.

In responding to this appraisal we are requested to consider a number of questions and these responses are set out by question for the remainder of this submission.

Has all of the relevant evidence been taken into account?

In section 4.1.2 of the ACD there is the following statement:'The SHTAC Assessment Group did not identify any new or updated studies of nilotinib for imatinib-resistant CML'

The phase II study of nilotinib for imatinib resistant CML was published online in November 2010 and in hard copy in January 2011 (Kantarjian HM et al. Blood. 2011 Jan 27;117(4):1141-5. Epub 2010 Nov 22). It provides the 24 month follow-up of this study and has not been considered.

In addition the clinical experts repeatedly stated that hydroxycarbamide, a palliative therapy, is not considered an appropriate treatment for patients who have demonstrated resistance to imatinib but still have a 50% chance of excellent responses and long overall survivals with high quality of life. Their written and verbal evidence was not taken into account.

With respect to the use of the technologies in accelerated phase and blast crisis, the 'end of life' criteria are clearly met, as without treatment these two conditions have a median life expectancy of considerably less than 24 months

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

Comments regarding the interpretation of the cost-effectiveness have been made in the introduction to this document. In addition it is important to note that the final economic model was tabled at the meeting of the Appraisal Committee without providing members and clinical

experts any time to seek critical review of the methodology. The individual presenting the data was one of very few people in the room who would have appreciated the complexity (and accuracy or inaccuracy) of the model so the chance of critical interpretation was low. In addition he moved through complex slides at a rapid rate, precluding rational discussion and challenge.

There are undoubtedly some mistakes in the ACD, of variable importance. For completeness these are acknowledged below. Unfortunately these mistakes reflect the fact that the ACD has been put together by researchers unfamiliar with the disease, its management and expected outcomes. Although in general they have interpreted data correctly there are sufficient numbers of errors to cast doubt on the final decision being based on accurate information.

Examples include

2.5 'After the introduction of imatinib into routine clinical practice, 5-year relative survival increased from 27.1% in 1990–92 to 48.7% in 2002–4 for all age groups combined ($p < 0.0001$ for the trend).'

Since imatinib became frontline treatment in the UK only after the initial results of the phase III study (IRIS) became available and the drug had been approved by NICE (TA 70 issued October 2003), 5 year survival rates could not have been available in 2002-2004. The figure of 48.7% underestimates considerably the impact of this drug on the outcome of this disease. The real value is of the order of that quoted for the IRIS study of 85% at 8 years.

3.1 'Dasatinib ... It is an orally active inhibitor of SRC and the Src-family of kinases.'

This is true but the action of dasatinib in CML is because of its inhibition of BCR-ABL in a very similar manner to imatinib and nilotinib.

4.1.3 'The Assessment Groups expressed concerns that none of the RCTs reported methods of allocation concealment, all were of an open-label design and none presented power calculations.'

When imatinib is ineffective and the patient is not eligible for an allogeneic stem cell transplant, their disease will be fatal. Dasatinib and nilotinib were drugs that were rationally designed to act in cases of imatinib failure. It is always easy to produce criticisms of studies when not personally responsible for a better design but these criticisms seem banal. How could they be anything other than open label? There is no alternative chemotherapeutic agent that can induce major or complete cytogenetic responses in patients with imatinib failure so any power calculations would be worthless. Many patients were included in these studies so it is very easy to perform a power calculation retrospectively and see that the numbers recruited would have exceeded any requirement. These are therefore petty criticisms, which when written down and unchallenged, serve to undermine the efficacy of these agents.

4.1.4 'All other studies used higher dosages of nilotinib'

This statement should read 'All other studies used higher dosages of dasatinib'

4.1.8 'Three single-arm cohort studies that assessed high-dose imatinib and an update to the comparative RCT of dasatinib and high-dose imatinib were identified. As previously noted, this RCT was considered to be of limited use because of the extent of crossover and the study design, and the treatment arms were considered separately.'

The dismissal of the RCT of high dose imatinib versus dasatinib because of early cross-over is unfortunate since useful information can be obtained from this study. There are a number of aspects of study design which include an ethical element alongside the statistical considerations. Patients failing standard dose imatinib are aware that they once more have a fatal disease. It is unethical to ask them to consider entry to a trial in which they could be randomised to an ineffective agent and expect them to remain on this arm indefinitely to satisfy the statisticians. At some point the treatment must be considered to have failed so that they can be offered alternatives, including stem cell transplantation. Three months was not an unreasonable period of time to expect some degree of cytogenetic response. Irrespective of the early cross-over this study showed that high dose imatinib could not achieve complete cytogenetic responses in patients who had failed to show any degree of cytogenetic response on standard dose imatinib. These data have since been confirmed in other studies and suggest the futility of his approach in certain patient sub-populations.

4.2.1 'The SHTAC Assessment Group considered that although the results of this study were credible, there were some methodological limitations and it was unclear how generalisable the model parameters and the results are to the UK'

Rather than simply stating that the results might not be generalisable to the UK and thereby undermining the value of the study, could SHTAC explain why results obtained in a Northern European population, with whom the UK share considerable ancestry and genotypes, might not be valuable.

4.2.27 'The SHTAC Assessment Group explored the case in which dasatinib has a longer treatment duration than high-dose imatinib and nilotinib by varying the progression-free survival for dasatinib between 3.1 years (as in the SHTAC base case) and 6.5 years (as in the PenTAG base case), while keeping progression-free survival for high-dose imatinib and nilotinib constant. Extending the progression-free survival and treatment duration of dasatinib results in higher costs for dasatinib with no change in QALYs. Therefore the longer the treatment duration the less favourable the results compared with the other interventions. The SHTAC Assessment Group explored the case in which dasatinib has a longer treatment duration than high-dose imatinib and nilotinib by varying the progression-free survival for dasatinib between 3.1 years (as in the SHTAC base case) and 6.5 years (as in the PenTAG base case), while keeping progression-free survival for high-dose imatinib and nilotinib constant. Extending the progression-free survival and treatment duration of dasatinib results in higher costs for dasatinib with no change in QALYs. Therefore the longer the treatment duration the less favourable the results compared with the other interventions.

Why was this analysis done? As the evidence suggests that dasatinib and nilotinib are equally efficacious (a statement accepted by SHTAC) what is the value of trying to model a situation in which dasatinib is given for a longer duration than nilotinib or high dose imatinib?

4.3.2 'The clinical specialists suggested that if dasatinib, high-dose imatinib or nilotinib were not available, people with CML would most commonly receive treatment with hydroxycarbamide or stem cell transplantation, if possible, and that these were the appropriate comparators for dasatinib, high-dose imatinib and nilotinib.'

The clinical specialists stated on many occasions that if a patient was resistant to imatinib but remained in chronic phase that the most likely scenario would be that they remined in imatinib 400mg or where possible were given an increased dose.

4.3.3 'It heard from the clinical specialists that high-dose imatinib is being used in clinical practice but only in people whose CML has previously shown a good response to initial treatment with standard-dose imatinib; that is, good blood count response, complete cytogenetic response and complete molecular response.'

The clinical experts did not state this. They said without any qualifications that high dose imatinib was being widely used in patients who had failed standard dose imatinib. They did say that it was most likely to be effective in inducing a cytogenetic response if the patient had previously had such a response but had subsequently lost this response.

'The Committee heard from the clinical specialists that people whose CML does not respond to dasatinib or nilotinib within 12 months would receive treatment with hydroxycarbamide or, if suitable, stem cell transplantation.'

This statement is misleading because the clinical experts qualified their answer by saying that if there was good haematological control then the patient would probably stay on the current drug but some might be give the alternative second generation TKI.

'For people receiving hydroxycarbamide, the prognosis is poor, with a median life expectancy of around 5 years'

This is true for patients receiving hydroxycarbamide form diagnosis, not after failing both first and second generation TKI

4.3.4 'The Committee noted the poor evidence base for all interventions for people whose CML is resistant to standard-dose imatinib. It was aware of only one comparative trial, which compared dasatinib with high-dose imatinib, but noted the comments from the Assessment Groups on the poor study design and the interpretation problems with this trial.'

Although this might be the Committee's statement it is evidently untrue. There is excellent evidence that dasatinib and nilotinib are able to induce a complete cytogenetic response in approximately 50% of patients who fail to achieve or who lose CCyR on imatinib. There is not a single CML expert in the world who would argue that these drugs are ineffective. The criticism is of the trial design not of the drugs.

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

The provisional recommendations are not sound (if only because the economic model is based on shaky foundations) and are certainly not a suitable basis for guidance in the NHS. CML is a

rare disease but has an influence far beyond its incidence. It provides a story of remarkable success by using the molecular understanding of the basis of the disease to design successful targeted agents, the mechanism and unwanted side effects of which are radically different from conventional chemotherapy. The outcome of cancer treatment in the UK has been the subject of much criticism in future years and enormous effort is being expended in trying to correct this. Limiting the use of highly effective drugs in an eminently treatable condition will perpetuate the contrast between the UK and the rest of the developed world.

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?

The proposed recommendation of the Committee has a number of ramifications for inequality. First, if these drugs are denied to those who are resistant to standard dose imatinib , then more patients will be referred for allogeneic stem cell transplantation (allo-SCT). The success of allo-SCT is dependent on the degree of tissue match between recipient and donor. Any patient of non-Caucasian origin is less likely to find a compatible unrelated donor and therefore less likely to benefit from this treatment and more likely to die of their disease.

Furthermore, as has been stated above there will be inequality of access to effective therapy in the European Union.

Multiple Technology Appraisal

Dasatinib, high dose imatinib and nilotinib for the treatment of chronic myeloid leukaemia (part review of TA70)

Appraisal Consultation Document

Summary

We have strong objections to the above ACD as detailed below.

We join with leading expert CML clinicians (letter to The Daily Telegraph 23rd May) in considering the reasoning that resulted in the preliminary negative recommendation to be *"inconsistent"* and *"perverse"*.

In addition we think that the methodology implicitly advocated to provide the *"strong"* evidence base that the Committee concluded is absent here, is impossible to mobilise and that it is disingenuous of the Committee to suggest it could be.

We also think that, more fundamentally, NICE should think very seriously about reforming its procedures and processes for the appraisal (and assessment) of TKIs, or more generally pharmacogenomic therapies, for rare diseases with correspondingly small patient populations.

Finally we also feel that NICE has not clearly articulated their policy concerning pharmaceutical innovation; there is no set of transparent criteria to establish its status in any particular case or measure of innovation once established. Granting of innovation status appears to proceed on an ad hoc basis with the Committee supporting its award with, in this case, over generalized assertions based on dubious scientific judgement.

Inconsistency in assigning value to clinicians life expectancy evidence

The Committee accepts that all three drugs do *"provide clinical benefit"* when prescribed for this group of patients. This concurs with the review commissioned by the Committee from the Health Technology Assessment (HTA) provider (SHTAC) as it does with the evidence presented by leading specialist haematologists.
The Committee also say:
".... the paucity of the evidence base means that the magnitude of the benefit is uncertain." (ACD: 4.3.6.)

The SHTAC notes that *"Limitations in the data exist ..."* (SHTAC: Assessment Report p.5)

However, the Committee notes, and later resorts to, evidence presented by the same expert haematologists that shows that in imatinib resistant CML:

"...over 50% of people with CML treated with dasatinib or nilotinib, but not with high-dose imatinib, there is a good response to treatment and that this response is usually as good as the initial response to standard-dose imatinib. The clinical specialists expected that these people would receive dasatinib or nilotinib for the rest of their lives, possibly with a near normal life expectancy (that is, at least 10 more years) " (ACD 4.3.3)

The Committee rely on the *"near normal life expectancy"* observation, referred to above (ACD: 4.3.3.), on two occasions to express reservations about the economic evaluation evidence presented to them. These are:
In their examination of the economic model developed by Novartis (ACD: 4.3.10) and, secondly, in the assessment of the SHTAC model (ACD: 4.3.12).

They were critical of the *"much lower than would be expected"* treatment durations in the former and that the *"base-case treatments durations"* do not reflect likely treatment durations in the case of the latter.

In summary, the Committee seems to have no issue with the adequacy of this evidence to critique aspects of the economic modeling evidence presented. but also regards the same evidence as contributing to *"paucity"* status when commenting on the clinical effectiveness of the drugs subject to this appraisal.
It is inconsistent to rely on evidence that is later disregarded as weak.

Inconsistency in the economic evaluation evidence
The Committee is inconsistent with regard to their position taken on QALY values compared with that displayed in TA 70 (2003 Technology Appraisal 70 *"Guidance on the use of imatinib for chronic myeloid leukaemia"*).

A) QUALY values for imatinib, dasatinib and nilotinb compared to HU (hydroxycarbamide)

Noting that there was no evidence to distinguish between nilotinib and dasatinib the Committee concluded that:

"...the ICERs for these treatments compared with hydroxycarbamide would both be higher than £43,800 per QALY gained and could be considerably more" (ACD 4.3.12)

And that "*...dasatinib or nilotinib could not be recommended as a cost-effective use of NHS resources"* for this patient population.

TA 70 noted a similar conclusion with regard to imatinib:
"The results from the independent model suggested, however, that the cost effectiveness of imatinib when compared with HU was not acceptable, with an ICER of around £87,000 per QALY."
(TA 70: 4.3.7.)
But, because of known limitations concerning the clinical effectiveness data, the Committee, TA 70 notes, asked the assessment team to undertake an additional analysis which resulted in:

".... slightly improved ICERs for imatinib, to around £60,000 when compared with HU" (TA 70:4.3.8)

Nevertheless the Committee proceeded to give a positive recommendation to imatinib.

In the 2006 paper entitled "Appraising Orphan Drugs" NICE notes (4.1.2.) :
"No particular scientific or technical problems have arisen during the Institute's appraisals of those orphan drugs that have been referred to it. Many, however, have had incremental cost effectiveness ratios (ICERs) at the "high" end of what NICE and its appraisal consider to be cost effective within the NHS."

Both imatinib, dasatinib and nilotinib are at the 'high' end yet one, at standard dose, is recommended and the others not. This is inconsistent.

B) Limitation of comparators to current first line treatment therapies.

Even though it had been established that IFN-a (interferon alpha) was not to be *"considered a cost-effective treatment compared to HU"* (TA 70: 4.3.9) since its ICER was *"in excess of £1 million per QUALY"* (TA 70: 4.3.7), the Committee nevertheless decided that, since IFN-a was, at that time, a standard first line treatment for CML it was therefore appropriate to compare it to imatinib in terms of its ICER.

Having taken this decision the Committee proceeded to conclude that imatinib, as a first line treatment for CML *"may result in a better use of NHS resources for CML"* (TA 70: 4.3.10)

On this logic the current ACD should have insisted on using only standard dose imatinib as a comparator in its appraisal since this is the current first line treatment.

C) Actual comparators used in this ACD

If an argument is put forward that standard dose imatinib has no benefit and thus should not be a comparator then why did the committee not decide to abandon HU as a comparator on the grounds that HU offers no possibility of enabling patients to survive the 10 years set out in the second scenario (see below ACD: 4.3.2) selected as being the *"least implausible"*

Obviously there can be no HU ICER values entered in the second scenario table (Table 3) since all patients prescribed it would have died before the 10 year time-line set yet the Committee still insists on using it as comparator (SHTAC *"Additional scenarios analysis"* p. 2)

D) Non TKI comparators

We would argue that it is perverse to reason HU still qualifies for the status first line treatment. To do so would logically require other therapies like busulphan to also be included.
The current use of HU or busulphan is not as first line treatment but is rather either a 'conditioning treatment' prior to some other therapeutic intervention or, where no first line intervention is appropriate, as Best Supportive Care.

E) Stem cell transplantation

Stem Cell/Bone Marrow Transplantation is also absent from consideration in the *"least implausible"* scenario analysis yet it is surely more qualified for first line status than HU or bulsulphan in that it offers the possibility of long term survival for those for whom it can be considered and who manage to avoid the risks associated with its implementation.

The impossibility of mobilising a traditional evidence based methodology

The ACD Committee was also critical of the use of interferon-alpha as a comparator (in both the Bristol Myers Squibb and PenTAG models) making clear that it preferred the comparators recommended by the clinical specialists, after discounting the possibility of resort to any of the TKIs, which were HU and stem cell transplantation (SCT).

Since the Committee notes (ACD: 4.3.2.) the majority of this patient group will be likely to be unsuitable for SCT, the more so given the median age of 60 cited in the ACD, the comparator defaults to HU.

Yet the committee accepts that for HU *"...the prognosis is poor, with a median life expectancy of around 5 years"* (ACD: 4.3.3) whilst also accepting the evidence of these same clinicians that more than 50% of patients could possibly expect *"a near normal life expectancy"* if prescribed nilotinib or dasatinib with responses being *"as good as the initial response to standard-dose imatinib"* (ACD 4.3.3.)

The Committee expressed dissatisfaction with all the clinical studies reviewed by the HTA provider (SHTAC) and noted the considerable reservations expressed by the provider regarding the design, interpretation and execution of the trials/studies reviewed.

It is reasonable to assume, because of its position at the top of the hierarchy of an evidence based approach to medicine, that an acceptable trial would be a double blind randomized clinical trial (RCT).
However it is self evident that attempting to recruit patients from an already very small patient population, rendered even smaller by the availability of the drugs in question in comparable countries, presents very formidable problems.

All three TKI drugs are prescribed and reimbursed all over Western Europe, the USA, Canada, Australia and New Zealand, in some 90 nations in total.

Since the trial would use HU as the stated preferred comparator it is inevitable that there would be very considerable crossovers from the HU arm given its established lack of efficacy relative to the drugs in question.
Indeed it is highly likely that, in such circumstances, the trial would be abandoned so that even a default from the preferred intention-to-treat to a per-protocol analysis, as the Committee requested of the HTA team with regard to imatinib (TA 70: 4.3.8.), would not be possible.

Given the particular circumstances involved, and the ethical issues raised as a consequence, it is not implausible to speculate that it would prove impossible to even propose a trial which would of course act as a major deterrent to those that might fund it at the initial planning stage.

This is best described as a Catch 22 situation where a NICE ACD proposes a negative recommendation due to what the CEO, Andrew Dillon, calls *" very weak"* evidence (NICE Press Release 5th May 2011) which carries with it an implicit assumption that it would be possible to generate '*very strong'* evidence that was acceptable to the Committee.

Yet all concerned know that such evidence will never be forthcoming since the means of establishing it can and will never be operational.

It is not as if NICE is unaware of the problem.

TA 70 observes that the European Agency for the Evaluation of Medicinal Products (EMEA- now EMA) marketing authorization of imatinib in November 2001 was granted on the basis of surrogate measures which included haematological (HR) and cytogenetic response (CR) rates, and progression free survival rather than Randomized Clinical Trial (RCT) data.

The EMEA (EMA) argued this was because:
" the indications for which the medicinal product in question (imatinib) is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence/data on the quality, safety and efficacy of the medicinal product." (TA 70: 3.2.)

TA 70 noted that the previous Guidance TA 50, for the current licensed indications was "based on evidence primarily from case series" (TA 70: 4.3.2.)

TA 70 is based on a reliance on a single open label, non randomized RCT (IRIS) and three case studies but:
" .. the published supportive evidence from the RCT relied principally on surrogate measures of efficacy such as the achievement of an HR and/or a CR" (TA 70: 4.3.2.) because of the absence of long term survival data.

However the Committee considered that:
" ..based on current evidence of the significance of CR and HR in CML, and knowledge of the effect of imatinib – that the relationship between CR and survival is sufficiently strong to support the use of CR, in particular, as a surrogate measure of survival in people with chronic-phase CML." (TA 70: 4.3.3.)
but:
"the Committee did not believe it was possible, based on the current evidence, to determine precisely the absolute survival gain that would result from switching from IFN-α to imatinib as first-line treatment." (TA 70: 4.3.4.) -in part because the Committee was aware of *"high crossover rates in the IRIS trial"* (the RCT referred to) (TA 70: 4.3.5.)

Nevertheless the Committee recommended that, even with such a "paucity" of data,
"Imatinib is recommended as first-line treatment for people with Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) in the chronic phase." (TA 70:1.1.)

Yet the committee came to the opposite conclusion, with its negative recommendation, in this ACD even though the evidence was also, similarly not comprehensive.

There is a more general criticism applicable here concerning the particular genetic mutations for which a TKI is active against. The principle underlining a TKI is that it is effective only against those mutations for which it was designed and that it is counter intuitive and counter productive to deploy it when they are not present.

We argue that, with likely recipient minute patient populations for what are already rare diseases, RCTs, as currently designed, should be abandoned altogether and substituted with a more appropriate design based on a Bayesian approach.
Bayesian approaches imply updating prior probability distributions of efficacy through new data in order to give rise to posterior probability distributions.

There is a requirement for sufficient information to be available to empower the statistics required which would be sourced from clinical practice and biological evidence, other clinical studies, the natural history of the disease, analogies with more frequently occurring diseases etc.

The ongoing development of digitalized e-health records with common design matrixes accumulated in instantly accessible data warehouses offer tantalizing possibilities in terms of the contribution they could make to such an approach.

Innovation status: criteria for qualification

The Committee does not find nilotinib and dasatinib to be innovative *"in terms of pharmacological progress beyond imatinib"*

Imatinib is, however, a drug that does attract their innovation classification. They give no substance to this decision.
There are, as far as we are aware, no publicly available NICE criteria deployed to grade the degree of innovation displayed in any particular case and it seems such classificatory work proceeds on an ad hoc basis.

Of course we accept that imatinib represented a 'step change' in cancer therapy in much the same way as penicillin represented a 'step change', as in a first of its kind, but would think it either perverse or demonstrative of a misunderstanding of the science not to regard successor generations as representing an innovation.

Pharmacogenomics, the tailoring of products to particular genetic configurations characteristic of small sub sets of patient populations for diseases like CML, sits at the leading edge of advanced manufacturing industries like pharmaceuticals.

Scientists working in research institutions and those engaged in similar work in academic institutions, would be surprised, to say the least, that their work in developing successor generations of inhibitors is not considered to represent *"pharmacological progress beyond imatinib"* and would no doubt wish the committee, or indeed NICE, to articulate their innovation policy in rather more detail than hitherto has been the case, in order to demonstrate that they had not made any *"pharmacological progress beyond imatinib"*.

Elsewhere in the appraisal the committee accepts, and indeed use as a resource in their appraisal work, evidence supplied by expert clinicians that confirms that, in more than 50% of the patients involved, a *"good response"* to nilotinib and dasatinib was achieved with patients able to anticipate living *"possibly with a near to normal life expectancy (that is, more than 10 years)"*. They also note responses were *"usually as good"* as the response to the first line drug they accept to be innovative, standard dose imatinib.

It is axiomatic that the *"more than 50%"* of patients referred to above would certainly regard dasatinib or nilotinb as representing *"pharmacological progress beyond imatinib"* especially since the alternative would be HU.

Equalities

There are issues to be considered that fall under this heading. We feel NICE need to recognise in a more policy driven manner that there are two populations that are under represented in terms of stem cell transplants. One are ethnic minorities, especially the African Caribbean community, and their gross under-representation in donor registries and the other is the population on the upper side of the current median age for stem cell transplantation.

We would like it noted that in the former case greater encouragement ought to be offered to organisations like the African Carribbean Leukaemia Trust to assist them in building ethnically diverse donor registry and secondly, that additional resources should be devoted to the research of new technologies that involve the use of inhibitors in stem cell transplants with the objective of making them safer and more easily tolerated than is the case at present.

[redacted] **and Sandy Craine**

May 27th 2011

The CML Support Group

[redacted]

[redacted]

In aid of Blood and Lymphatic cancers Leukaemia CARE supporting a quality of life

[redacted]

Leukaemia & Lymphoma Research BEATING BLOOD CANCERS

[redacted]

African Carribbean Leulaemia Trust

Promoting bone marrow & blood donation

The clinical and cost effectiveness of dasatinib, high dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia: SHTACs comments on the proposed Patient Access Scheme for nilotinib.

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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8th June 2011

SHTAC have reviewed the proposed patient access scheme (PAS) submitted by Novartis Pharmaceuticals for the appraisal of the clinical and cost effectiveness of dasatinib, high dose imatinib and nilotinib for imatinib-resistant chronic myeloid leukaemia. The PAS is a financially-based scheme (where a [redacted] discount to the list price for nilotinib is applied).

The manufacturer has applied the PAS to the SHTAC additional scenario analyses undertaken to inform the appraisal. No results of the application of the PAS on the Novartis economic model have been presented.

Two additional scenario analyses were undertaken by SHTAC to test two different durations of treatment for the three interventions. In the PAS submission, the manufacturer has applied the proposed change in cost of nilotinib to these two scenario analyses. SHTAC have assessed the results of these analyses for accuracy. SHTAC have used the same proposed discount to nilotinib and show subtly different results (see Tables 1 and 2 below) than shown by the manufacturer, owing to slightly different costs of nilotinib when the proposed discount has been applied. SHTAC calculations are shown underlined in the following two tables.

Table 1: Application of the PAS on scenario analysis 1 using 6.5 years treatment duration

	Results no PAS		**Results with PAS**		**Results with PAS plus 1,2,3,and 4[(a)]**	
	Nilotinib	**HU**	**Nilotinib**	**HU**	**Nilotinib**	**HU**
Drug cost (£)	164,475	213	[redacted]	213	[redacted]	213
Other costs (£)	57,619	17,915	[redacted]	17,915	[redacted]	12,533
Total costs (£)	222,093	18,128	[redacted]	18,128	[redacted]	12,746
Incremental costs (£)	203,965		[redacted]		[redacted]	
QALYs	7.63	2.20	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs	5.43		[redacted]		[redacted]	
ICER (£)	**37,562**		**27,035** 27,324		**22,792** 22,964	

(a)
1. Dose intensity adjusted to [redacted]
2. Assume same QALY gain as dasatinib
3. Lower utility value for HU (0.78)
4. Lower OS for HU (3 years)

Table 2: Application of the PAS on scenario analysis 2 using 10 years treatment duration

	Results no PAS[†]		**Results with PAS**		**Results with PAS plus 1,2,3,and 4**[(a)]	
	Nilotinib	**HU**	**Nilotinib**	**HU**	**Nilotinib**	**HU**
Drug cost (£)	232,954 234,924	213	[redacted]	213	[redacted]	213
Other costs (£)	33,251 32,549	17,915	[redacted]	17,915	[redacted]	12,533
Total costs (£)	266,204 267,474	18,128	[redacted]	18,128	[redacted]	12,746
Incremental costs (£)	232,741 249,393		[redacted]		[redacted]	
QALYs	7.63	2.20	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs	5.43		[redacted]		[redacted]	
ICER (£)	**45,685** 45,919		**30,776** 31,296		**24,993** 25,303	

(a)
1. Dose intensity adjusted to [redacted]
2. Assume same QALY gain as dasatinib
3. Lower utility value for HU (0.78)
4. Lower OS for HU (3 years)

[†]Costs of nilotinib in this column were corrected by the assessment group in correspondence with NICE following a question raised by Novartis pharmaceuticals on the 17th May, however, the costs applied in the PAS submission do not reflect these corrections.

The manufacturer also applied the proposed change in cost together with a number of changes to assumptions, as shown in the last column of Tables 1 and 2. No justification was provided for these changes in assumptions in the PAS submission document.

The manufacturer have not presented base case incremental results stating that they are unable to replicate all the updated scenario analyses ICERs from the SHTAC analyses. The assessment group are unsure why this could not be replicated, and have presented incremental results applying the PAS to the two analyses as seen in Tables 3 and 4 below for completeness. As in the original SHTAC scenario analyses, the comparators interferon-alfa, standard dose imatinib, and stem cell transplantation are not presented as these were dominated or extendedly dominated in the base case analyses. For consistency the costs of high dose imatinib are as those presented in the original SHTAC assessment report.

Table 3: Application of PAS on incremental analysis using scenario of 6.5 years treatment duration

Original Analysis				
	QALY	**Cost, £**	**ICER vs HU (£/QALY)**	**ICER vs next best option (£/QALY)**
HU	2.2	£18,128		
High dose imatinib	7.311	£242,579	£43,910	Dominated
Nilotinib	7.630	£222,093	£37,562	Dominated
Dasatinib	7.846	£221,879	£36,086	£36,086
PAS Analysis				
	QALY	**Cost, £**	**ICER vs HU (£/QALY)**	**ICER vs next best option (£/QALY)**
HU	2.2	£18,128		
Nilotinib	[redacted]	[redacted]	£27,324	£27,324
Dasatinib	7.846	£221,879	£36,086	£256,327
High dose imatinib	7.311	£242,579	£43,910	Dominated

Table 3: Application of PAS on incremental analysis using scenario of 10 years treatment duration

Original Analysis				
	QALY	**Cost, £**	**ICER vs HU (£/QALY)**	**ICER vs next best option (£/QALY)**
HU	2.2	£18,128		
High dose imatinib	7.31	£297,678	£54,689	Dominated
Nilotinib	[redacted]	[redacted]	£45,919	Dominated
Dasatinib	7.846	£265,521	£43,816	£43,816
PAS Analysis				
	QALY	**Cost, £**	**ICER vs HU (£/QALY)**	**ICER vs next best option (£/QALY)**
HU	2.2	£18,128		
Nilotinib	[redacted]	[redacted]	£31,296	£31,296
Dasatinib	7.846	£265,521	£43,816	£358,500
High dose imatinib	7.311	£297,678	£54,689	Dominated

Applying the PAS costs for nilotinib to the scenario analyses (Table 3 and 4) suggests that nilotinib is more cost effective than both dasatinib and high dose imatinib.

SHTAC have also checked the probabilistic sensitivity analyses presented in the PAS submission and can confirm the results presented as correct for the given input values and assumptions.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE
SPECIAL HEALTH AUTHORITY

Multiple Technology Appraisal (MTA)

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

Report to the Appraisal Committee summarising public comments on the Appraisal Consultation Document (ACD) issued in May 2011 (including comments from patients, carers and health professionals)

1 Executive summary

In total 657 members of the public responded to the consultation on the draft guidance relating to the appraisal of dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (part review of technology appraisal guidance 70). There were 352(53.6%) letters and emails, 206 (31.4%) web comments, and 99(15.1%) letters and emails sent to the Enquiry handling team at NICE. Of the 206 web comments, 150 respondents identified themselves as patients, carers or members of the general public and 59 respondents identified themselves as healthcare professionals. The web comments, emails and letters were read and the key themes were identified, coded and analysed. This report summarises the findings.

Two of the respondents partially agreed, and all the other 655 respondents disagreed with NICE's preliminary decision not to recommend dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (part review of technology appraisal guidance 70). Respondents argued that there is a clinical need for dasatinib, high-dose imatinib and nilotinib, particularly given that comparator drugs and bone marrow transplants are not as effective or are not appropriate. People were concerned that the decision had been made purely on cost grounds and not on the effectiveness of the drugs. People also felt that the Committee were unfair and unrealistic in requesting a 'gold standard' clinical trial model, as such a model is impractical in the real environment. Some respondents specifically challenged the process used by NICE, arguing that there should have been an oncologist or haematologist as part of the committee membership, and that patient choice was not being considered properly.

There were also a number of comments relating to equity, equality and human rights in particular the availability of drugs in other countries.

2 Introduction

This report collates and summarises the emails, letters and web comments received from the public on NICE's draft guidance recorded in its Appraisal Consultation Document (ACD) for the appraisal of dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (part review of technology appraisal guidance 70). All emails, letters and web comments have been read by NICE, and this report collates all the responses received. NICE would like to

acknowledge the time and effort that members of the public put into preparing and sending comments as part of the consultation.

3 Numbers and format of comments received

In line with NICE's published process, the appraisal consultation document setting out NICE's draft recommendations was posted on NICE's website for the consultation period from 6 May 2011 to 27 May 2011.

In total, 657 members of the public responded to the consultation. Of these 451 people contributed by individually written email or letter and 206 people commented via the NICE website. This report summarises those 657 public comments received as emails, letters and web comments in line with NICE's processes. The issues raised in the 657 comments received from patients, carers or members of the general public are quantified in the attached coding sheet (appendix 1) and described in sections 5 and 6 of this report. The issues raised in the 59 comments received by health professionals are summarised in section 7 of this report and are also quantified in the attached coding sheet (appendix 1)

Two petitions signed by 1420 and 71 patients and members of the public, respectively, are attached in appendix 2 and appendix 3.

Two template letter examples received from a number of respondents are attached in appendix 4.

Some sample letters, emails and web comments received are attached in appendix 5.

4 How NICE dealt with the correspondence

All letters and emails were read by members of NICE staff, as discussed above. Subsequently, all the web comments and eligible letters from patients, carers and members of the general public were read and collated by the Appraisals, Patient and Public Involvement Programme, and Enquiry Handling teams at NICE.

To produce a coding template, the Technology Appraisals technical team for the topic provided a list of key themes from the Consultee and Commentator groups' consultation responses. These themes where then used to create a comprehensive formal coding list, using knowledge of concerns raised by members of the public during previous ACD consultations to add additional themes. The issues raised in the public responses were coded against this final list. As the finalised coding sheet was designed to be comprehensive, not all codes were used. The numbers of respondents who raised each issue, along with the equivalent percentage figure, is shown on the coding sheet in appendix 1. All the web comments were read by the NICE Technology Appraisals technical team and those from health professionals are summarised in section 7.

5 Main themes of comments received

Two of the respondents partially agreed, and all the other 655 respondents disagreed, objected to NICE's preliminary decision not to recommend dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia. Objections to NICE's decision focused on four main issues:

- Clinical effectiveness of high dose imatinib , dasatinib and nilotinib and comparator drugs/ bone marrow transplant
- Cost and cost effectiveness
- The nature or implementation of the NICE process
- Issues relating to equity, equality and human rights.

The sections below explore each of these themes in more detail. Quotes from individual responses are included to help illustrate some of the key issues.

6 Exploration of key themes in comments from patients, carers and members of the general public

6.1 Comments on clinical effectiveness of high dose imatinib, dasatinib and nilotinib and comparator drugs/ bone marrow transplant

Many respondents commented on the clinical effectiveness of the drugs being appraised (high dose imatinib, dasatinib and nilotinib):

- *Please could you explain me how anyone can suggest that higher doses of Imatinib treatment are not recommended or are not working? As far as I am concern and I am one of these patients as long I am alive and feeling fantastic with full haematological response to treatment it is in my opinion as effective as any cancer treatment can possibly be…*

- *She originally took the drug imatinib but suffered serious and disabling side effects which she tolerated for two years. After this time the level of the defective gene which causes CML to develop started to rise and her consultant advised changing the drug to nilotonib which she has been taking since December 2010. This drug has so far proved very effective with few troubling side effects and her levels have dropped and she is nearly in remission…*

- *…was diagnosed with CML (in chronic phase PCR 80.135) in May 07 and was initially prescribed Imatinib at 100mg/day. However, by Apr08 it was clear that the initial gradual improvement from the treatment (Nov 07 PCR 7.743) was not being sustained and things were deteriorating (Mar 08 PCR 63.476). Treatment with Dasatinib 100 mg/day started in May 08 and immediately showed significant improvement (Sep 08 PCR 0.027) representing Major Molecular Response.*

Some respondents also reported negative personal experiences of bone marrow transplants and of comparator drugs:

- *…Her bone marrow transplant failed and she was put on a drug trial for imatinib (glivec). The drug has been very effective for her – without it she would have died ten years ago…*

- *There is no viable alternative, Hydroxia Urea and Interferon, are very temporary medicines, and only hold back the disease for months.*

6.2 Comments on costs/cost effectiveness

Respondents made a number of different observations about costs:

- *These drugs have been providing most CML patients a quality and longevity of life they would not have enjoyed some 12 years ago, with a prognosis of 3 to 5 years expected then. I cannot say what these drugs have cost to the NHS in monetary terms, but balanced against their quality of life there can be no comparison… The alternative cost to the NHS of providing care to CML patients I am sure would be far greater than providing tablets to treat the problem, with periodic visits to haematology departments for health checks to monitor the individual.*

- *Many Nations around the world risk and spend millions to save lives and here your 'financial cut-backs' are going to put many lives at risk!*

- *This is not a matter of cost, this is life and death and I'm shocked a change is even being considered. Even if a handful of people benefit from the next generation of treatment it HAS to be worth it.*

Some respondents noted patients' own contributions to the NHS, as tax payers or as NHS or public sector employees:

- *The majority of CML patients have worked for the most part of their life and have paid there [sic] dues. Now they are being told that you cant [sic] have the medication that keeps you going and gives you a hope of a normal life.*

6.3 Comments on the NICE process

Comments about the NICE process focussed on two perceived problems:

Some respondents criticised NICE for not having a CML specialist as part of the committee membership:

- *It is noted that on the appraisals committee there is not one cancer specialist let alone a CML specialist.*

Some people also said that the NICE process doesn't take patient choice sufficiently into account:

- *I feel let down and disappointed – and not a little afraid. Im [sic] doing well on Imatinib 400mg but if that stops working, where does that leave me? Quite honestly, living with leukaemia is bad enough, without having the added worry of people trying to withdraw our safety net.*

6.4 Equity, equality and human rights

A number of respondents raised issues relating to equity or challenged the NICE decision within the context of human rights legislation:

- *In the Appraisal consultation document, it is concluded [ref 4.3.18] that the preliminary recommendations do not discriminate. While this may appear so on the surface, it could be argued that its implementation would in practice be age-discriminatory. While transplant treatment is a relevant treatment for younger people, it is not considered an option for those aged over 65 (like myself - but I still play squash). Removing the option of treatment with second-generation TKIs, currently available to everyone, will result in discrimination against the over 65?s and be, in effect, age-discriminatory in my view. Perhaps this would need to be tested in court to prove otherwise*

Many respondents challenged the fact that NICE was restricting use of dasatinib, high-dose imatinib and nilotinib when such restrictions did not apply to patients in other countries in Europe:

- *What we can't understand is that withdrawing alternative drugs for Imatinib resistant patients essentially leaves them with two options;1-Move to Scotland or elsewhere in the EU to get these drugs, 2-A bone marrow transplant which obviously isn't available to everybody and in itself can bring even more problems than it solves.*

- *The available annual UK patient population that would qualify is around a 120 but this would include patients in Scotland where these drugs are already available. As they are in countries in Western Europe.*

- *The draft recommendation also goes against the direction of travel we see prevailing in Scotland and other Western European countries where these drugs will continue to be available.*

6.5 Other

Some respondents commented that they agreed with the conclusion of the Southampton Health Technology Assessment Centre report commissioned by NICE and therefore did not understand the preliminary no recommendation. Most respondents also argued that the drugs are effective and thus did not agree with the decision

- *…the results of single arms studies suggest that the interventions dasatinib, nilotinib and high dose imatinib can lead to improvements in haematological and cytogenetic responses in people with imatinib resistant CML.*

- *Being a patient with cml for the past 4years and on high dose imatibib (800mg) this treatment has been a life saver, as a result cml has had almost no impact on my life, I continue to work in a demanding full time occupation and lead a normal social calendar. Without the availability of this treatment the results would probably be very different.*

- *This is a devastating blow for CML patients who are showing early signs of resistance to Imatinib (like our son in law). They are at most immediate risk, facing a bleak future and very short life expectancy on previous treatments that are known to be virtually useless, but all patients currently with a good response to standard dose Imatinib will be extremely worried that they may develop resistance.*

Some respondents also commented that the decision made did not conform to Andrew Lansley's promise of a reformed NHS that would give patients "real choice for the first time."

7. Comments raised by health professionals

Health professionals raised several issues on the themes of clinical effectiveness, cost effectiveness, comparator effectiveness and patient choice:

- *Up to 30% of CML patients will not respond adequately to standard dose imatinib. Evidence shows that many of these patients will respond to either a*

higher dose of imatinib or a second generation tyrosine kinase inhibitor. Untreated CML patients are at risk of transformation to blast crisis and death. The only other treatment option is allogeneic transplantation which carries a considerable morbidity and mortality and is not available to all patients due to lack of donor availability / patient age. Thus refusing to fund these drugs discriminates against those of ethnic minority background (where donors may not be available) and older patients in whom transplants may not be possible. These drugs clearly save lives and are associated with minimal toxicity.

- *on the evidence evaluation this would seem a reasonable conclusion, but there will be arguements in favour of continued treatment following progression/ resistance to standard dose imatinib.*
  Commissioners were unaware that many centres were dose escalating imatinib prior to the launch of Dasatinib and Nilotinib, to the extent that it has been reported as common practice. This clarification of cost-effectiveness is therefore valuable to commissioners.

- *5 patients (out of approx 20 with CML) in our hospital failed to respond to Imatinib (less than Major Cytogenetic response or worse). 4 have gained complete cytogenetic responses (or better) to Dasatinib which has been durable for years. All are very well with no significant side effects, fit and able to work (PS 0), all 4 are in their 40s or early 50s, several with young children. To deny them this drug and therefore the option of long term survival with good health (as opposed to bone marrow transplantation) is not acceptable. I cannot defend this decision to my patients. The other 1 patient on Dasatinib (who did not respond) has gone on to have a bone marrow transplant and is fairly well but has some Graft versus host disease and it is early days.*
  If a good response to TKI is achieved this is akin to a cure but without the very significant toxicity and mortality risk of a transplant. The 2 are not comparable.

Technology Appraisals Programme
Patient and Public Involvement Programme
Enquiry Handling team

June 2011

Appendix 1

Coding form showing numbers, and percentages, of responses per category

Categories	Emails & letters received (352)	Web comment (206)	Emails & letters sent to Enquiry handling (99)	Totals (657)	Percentages (% of 657)
Overall					
Agree with recommendations	-	-	-	**0**	0
Disagree with recommendations, with no critique of issues	93	78	15	**186**	28.3
Disagree with recommendations, with reasons given OR recommendations need to be reconsidered/drugs should be provided	259	127	83	**469**	71.4
Other, e.g. partially agree with ACD or no opinion stated	-	1	1	**2**	0.6
	53.6	**31.4**	**15.1**	**657**	100.3
Quality of Life/ Clinical Effectiveness issues					
Personal experience of benefit from Imatinib	53	29	16	**98**	14.9
Personal negative experience of Imatinib	23	9	1	**33**	5
Personal experience of benefit from Dasatinib	21	51	12	**84**	12.78
Personal negative experience of Dasatinib	4	1	-	**5**	0.8
Personal experience of benefit from Nilotinib	46	12	11	**69**	10.5
Personal negative experience of Nilotinib	-	-	-	**0**	0
Tiredness/ fatigue	4	-	-	**4**	0.6
All these drugs work	-	90	3	**93**	14.2
Other QoL - affect on relationships, work etc importance of hope and choice	76	22	29	**127**	19.2
Costs					
Cost cutting exercise/ rationing/ costs shouldn't be considered	94	79	33	**206**	31.4
NHS costs mentioned/ the costs have been underestimated/ failed to consider costs.	1	12	5	**18**	2.7
The pharmaceutical companies should reduce the price.	4	4	-	**8**	1.2
I am self funding treatment and worried that I will not be able to continue paying for my treatment	-	-	-	**0**	0
Other cost issues e.g. drug fund	6	11	-	**17**	2.6
Agreement with Appraisal					
Agreement that all relevant evidence has been taken into account	-	-	-	**0**	0
Equity, equality and human rights					
Drugs are funded in other countries (USA, Europe, Scotland)	118	24	26	**168**	25.6

Human rights legislation promising right to life regardless and/or right to private and family life	14	14	13	**41**	6.2
Disability discrimination.	1	-	2	**3**	0.5
Some people can afford private treatment while others can't.	2	-	-	**2**	0.3
Other equality issues - e.g. ageism	1	7	-	**8**	1.2
National Insurance/tax payer/NHS worker for many years.	20	1	12	**33**	5.0
Others					
Comparator drugs not as effective / bone marrow transplant not effective	44	46	22	**112**	17
Gold standard clinical trial model	24	7	10	**41**	6.2
Imatinib Intolerant population will be affected also	8	2	26	**36**	5.5
Not enough time to comment	1	2	1	**4**	0.6
NICE process used e.g. no Haematologist/ Oncologist on Committee, not fit for purpose	22	19	9	**50**	7.6
Inappropriate use of NHS funding – e.g. treating drug addicts	-	-	2	**2**	0.3
Negative recommendations likely to restrict innovation in pharma industry	-	8	4	**12**	1.8
Population - size/subgroup	-	11	-	**11**	1.7
More research needed before a decision	-	32	-	**32**	4.8

Appendix 2 – Petition 1

Recd 27/May/2011

2011-05-25

Dear Ms Farrar.

Please find enclosed petition with over 1000 names addresses and signatures. All these people strongly object to the NICE recommendation to stop CML patients that start to fail on the standard dose of 400mg Imatinib from then being prescribed 600mgs. They also object to the recommendation that these patients will not be allowed to start either Dasatinib or Nilotinib. Therefore the only treatment available to these patients will be obsolete drugs which are poorly effective or given by injections with many known side effects. Also what happens to the patients that these old drugs don't work for if the are denied Imatinib 600mgs, Dasatinib or Nilotinib. Is the only answer then severe illness long hospital admissions or even death. I would like this letter and petition presented at the coming Nice meeting in June. I would also like the NICE panel to consider what the impact of withholding these drugs will have upon these patients, who are trying to lead a normal life as possible with the help of these drugs. I feel that this recommendation is solely to do with cost and not what is proven to be the best treatment for CML patients. Why do 19 other major countries including Scotland allow patients with CML to be prescribe these drugs with no problems ?

Yours truly

Please note 1185 signatures

Appendix 3 – Petition 2

Appendix 3 – Petition 2

Total of 71 names

Facial alopecia

25.05.11

Dear ,

Appendix 3 – Petition 2

Total of 71 names

Facial alopecia

25.05.11

Dear ,

Please find enclosed along with my letter several pages of signatures that I obtained from the Royal Liverpool Hospital Clinic G which I attended myself, if you remember I came to your office just over 12 months ago and you took my file off me containing letters, I am again pleading with you and your company to please read enclosed letters Many Thanks

again pleading with you and your company to please read enclosed letters Many Thanks

To Whom It May Concern

My name is I . I was diagnosed with Chronic Myeloid Leukaemia some 2yrs ago now. I was devastated when given the initial news. I thought about my family, friends and what about my charity work, I have done for so long. "I DID NOT WANT TO DIE". The staff of Professor Clarke at the Royal Liverpool Hospital soon gave me so much hope and faith. I couldn't of accepted it without them. I was initially given a drug which was a trial drug, and this had to be changed quite soon as it did not agree with my immune system. I was then prescribed a drug called Tasigna, this has worked for me it has not only changed my life but most certain it has saved it. I attend the hospital every 3mths now for a check up and I am doing really well. The only reminder that I have leukaemia is when I take my meds. My life is full, with the things I hold dearest, Family, Friends and my charity work, and I thank God and the Doctors for that. One year into my illness I was told the drug Tasigna may be stopped and not given to any new sufferers needing it. I thought to myself, No man has the right to stop life ! Only God has the right to do that. So I started a campaign to which was a great success. I received over 500 letters of support from the public, to which I took to the offices of National Institute Clinical Excellence (N.I.C.E) in Manchester, to which you are based. A member of staff kindly took my folder containing copies of the letters of support and re-assured me that it would be looked at, some time later the decision to stop the drug Tasigna had itself been put on hold and the drug stayed on the shelf. Now 1yr on the same thing might be about to happen, Tasigna maybe coming to an end, how can this be allowed to happen, people need this life saving drug. I implore you please in the name of humanity, re-consider your decision and look at what you are proposing to do. I my self at the moment are one of the lucky ones, or AM I ? I just thank God for the gift he has bestowed on our scientists who have found this wonderful drug and is allowing me to live my life. Please in the name of humanity, let other people live, you have the power to do this, in Gods name use it.

Yours Sincerely

Appendix 4 – Two template letters were each used by a number of respondents

Dear Ms Farrar

We are disappointed that we feel compelled to write this e-mail after being informed about a preliminary decision by NICE not to recommend the use of certain drugs that are proven to be effective in the fight against Leukaemia. We had been hopeful that with the commitments in the Conservative election campaign and the formation of the coalition government, we were through this problem but NICE is still with us and making what we consider is a cruel and unfair decision.

Last Friday (May 5th 2011), the NICE appraisal committee published a preliminary decision not to recommend Dasatinib, Nilotinib or high dose Imatinib for NHS treatment of CML (Chronic Myeloid Leukaemia) patients who are resistant to standard dose Imatinib. This is a devastating blow for CML patients who are showing early signs of resistance to Imatinib (like our son in law). They are at most immediate risk, facing a bleak future and very short life expectancy on previous treatments that are known to be virtually useless, but all patients currently with a good response to standard dose Imatinib will be extremely worried that they may develop resistance.

The critical point is that NICE does not deny that these new drugs are more effective than Imatinib. The appraisal committee accepts the evidence from leading expert clinicians that the new drugs show clear benefits and the assessment report says "the results of single arm studies suggest that the interventions Dasatinib, Nilotinib and high dose Imatinib can lead to improvements in hematological and cytogenetic responses in people with Imatinib resistant CML."

It seems that the problem is that whilst the study data is robustly positive, the committee is dissatisfied with the design and execution of the single arm studies which, they conclude, render the data substandard. The committee insists on a gold standard clinical trial model, even though such a model is totally impractical in the real environment of a rare and potentially fatal disease. It is totally unreasonable to expect CML sufferers taking part in trials to remain on drugs that are known to be less effective or virtually useless to satisfy their requirements for trials. Those patients' lives are seriously at risk.

Whilst we are pleased that the standard dose of the front line treatment, Imatinib, continues to treat many sufferers effectively, we have always found it comforting to know that there were other drugs becoming available to fall back on if he were to become intolerant or resistant, as it has transpired today. He may now be showing early signs of resistance to standard dose Imatinib after only being diagnosed with CML in October 2010.

What we can't understand is that withdrawing alternative drugs for Imatinib resistant patients essentially leaves them with two options;

1-Move to Scotland or elsewhere in the EU to get these drugs

2-A bone marrow transplant which obviously isn't available to everybody and in itself can bring even more problems than it solves.

After so much hard work to bring CML drugs on leaps and bounds in recent years, this is one almighty backwards step, purely financially driven in our opinion.

The potential decision is ludicrous in our eyes and we implore NICE not to carry this decision through but to continue to recommend the use of Imatinib high dose, Dastanib and also Nilotinib, all of which are proven in the fight against this horrendous disease. Our son in law is only 32 years old and he still has a lot of living to do, if only NICE will allow him to do it.

We do hope that you will understand our deep concerns and do your utmost to ensure that any existing drugs are made available to those who desperately need them.

Yours sincerely

Recd
26/05/11

Attention of Lori Farrar
Technology Appraisal Project Manager
NICE
Level 1A City Tower
Piccadilly Plaza
Manchester
M1 4BD

Dear Sirs

I am writing to you in order to express my utter dismay at the National Institute for Health & Clinical Excellence (NICE) Appraisal Committee's preliminary decision not to recommend dasatanib, nilotinib or high-dose imatinib as an NHS treatment of Chronic Myeloid Leukaemia (CML) where patients are resistant to the standard dose of imatinib (Glivec).

As I am sure you will agree this is a crushing blow for those patients already diagnosed with CML and for around 40% of the 600 people who are newly diagnosed with this life threatening disease in the United Kingdom every year.

Patients who are showing early signs of resistance together with those who have sub-optimal responses to the standard dose imatinib are at the most immediate risk. Anybody suffering from this disease will face a bleak future should the committee confirm their preliminary recommendation in June of this year.

Scottish patients will continue to receive these very effective drugs as a second line therapy. The Welsh Assembly have already voted to keep this line of treatment open to all CML patients in Wales.

I am not against health technology appraisal (HTA) systems for drugs or healthcare products in general but I do object to a standard setting organisation like (NICE) that refuses to recognise that the way they conduct their appraisals is not fit for purpose for the clinical situation they are confronted with, as in this case.

Their refusal to even recognize a problem exists when confronted with products aiming to provide benefit to a very small numbers of patients appears representative to me of a well-entrenched bureaucracy comfortable in its practice and complacent in its outlook.

It's outrageous that, as a consequence, so many patients will have to lose their lives waiting for (NICE) to drag itself into the new environment initiated by these second generation inhibitors.

Can I please quote the words of Mr Andrew Lansley Parliamentary Secretary of State for Health who said "that the reform of our NHS will give all UK patients real choice for the first time?

You will no doubt understand my feelings that this potential decision that (NICE) are considering would most certainly not lie side by side with Mr Lansley's statement to the UK public.

Can I ask that my comments, together with no doubt, those of many other citizens, be passed to the committee? It must be stressed that patients / suffers and those who will be diagnosed in the coming months and years want "real choice" rather than "no choice" for all UK CML patients.

Yours sincerely,

Appendix five – Sample letters, emails and web comments

Dear Ms Farrar,

My mother was diagnosed with CML in October 2008 and received excellent care through the NHS at The City Hospital, Nottingham. She originally took the drug imatinib but suffered serious and disabling side effects which she tolerated for two years. After this time the level of the defective gene which causes CML to develop started to rise and her consultant advised changing the drug to nilotonib which she has been taking since December 2010. This drug has so far proved very effective with few troubling side effects and her levels have dropped and she is nearly in remission.

I was extremely concerned to read that NICE have issued an Appraisal Consultation Document stating that the second line drugs of dasatinib, nilotonib and high dose imatinib are not recommended for the treatment of CML that is resistant to standard dose imatinib. Patients like my mother who show early signs of resistance and who have a sub-optimal response to standard dose imatinib, are at immediate risk and could face a bleak therapeutic future should NICE confirm this preliminary recommendation.

There is good evidence that these drugs are more clinically effective than their predecessors and I note that the Appraisal Committee accepts the evidence from leading expert clinicians that there are distinct therapeutic benefits for the use of these drugs over the other options available.

The conclusion of the SHTAC assessment report commissioned by you states:

"the results of single arms studies suggest that the interventions dasatinib, nilotinib and high dose imatinib can lead to improvements in haematological and cytogenetic responses in people with imatinib resistant CML". From my family's personal experience this is definitely so.

Andrew Lansley promised that a reformed NHS would give patients “real choice for the first time”. After NICE’s announcement today this has a very hollow ring.

I urge NICE to reconsider their recommendations and give CML patients real choice in their treatment.

Yours sincerely,

[redacted]

Dear sir/madam

IT has come to my attention that there is to be a review regarding high dose imatibib, dasatinib and nilotinib is not to be recommended for the treatment of standard dose resistant cml, having read the posted documentation on the nice web site (some parts read a number of times in order to understand and digest the information and implications) the conclusions fill me with alarm.

Being a patient with cml for the past 4years and on high dose imatibib (800mg) this treatment has been a life saver, as a result cml has had almost no impact on my life, I continue to work in a demanding full time occupation and lead a normal social calendar. Without the availability of this treatment the results would probably be very different.

The treatment I am presently receiving from Liverpool Royal Hospital has been excellent and is also part of a 5year spirit trial (400mg imatibib v 800mg imatibib v interferon) which is still ongoing, so any conclusions reached by nice would seem to be prejudging such ongoing trails and makes me wonder are these trials a valuable tool if there results are seemingly to be ignored.

In the current fight against cancer why is it when we have available a treatment that works we then consider with holding it from a number of patients on what seems to be the issue of cost.

When the final appraisal conclusion is decided I hope the points and views I and hopefully others have aired are taken into consideration, as I may be secure in my continued line of treatment there will be many that will follow that will face an uncertain future or any future at all.

Yours sincerely

[redacted]

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5 patients (out of approx 20 with CML) in our hospital failed to respond to Imatinib (less than Major Cytogenetic response or worse). 4 have gained complete cytogenetic responses (or better) to Dasatinib which has been durable for years. All are very well with no significant side effects, fit and able to work (PS 0), all 4 are in their 40s or early 50s, several with young children. To deny them this drug and therefore the option of long term survival with good health (as opposed to bone marrow transplantation) is not acceptable. I cannot defend this decision to my patients. The other 1 patient on Dasatinib (who did not respond) has gone on to have

a bone marrow transplant and is fairly well but has some Graft versus host disease and it is early days.
If a good response to TKI is achieved this is akin to a cure but without the very significant toxicity and mortality risk of a transplant. The 2 are not comparable.

Dear Lori,

I would like to comment on the ACD for Leukaemia (chronic myeloid) - dasatinib, high dose imatinib and nilotinib (guidance review). Unfortunately the link from the ACD on the NICE web site to submit comments appears not to work and therefore I am e-mailing my comments with a request that these are treated in the same way as if they were submitted via the NICE web site.

My comments relate specifically to the comments made by the Committee regarding the innovative nature of the treatments under consideration:

"The Committee considered that the development of dasatinib and nilotinib, in terms of pharmacological progress beyond imatinib was not innovative".

It is our understanding that these rationally designed molecules are both second generation TKIs and should be regarded as highly innovative in nature. They were developed to address a significant and important unmet need in CML, i.e. for the benefit of those patients who are intolerant or resistant to the current standard of care, imatinib. We understand that these new medicines provide improved response rates and improved safety profiles in the second line treatment setting.

It would be helpful to understand more about the Committees views regarding the innovative nature of these treatments in the context of the second-line treatment of imatinib resistant or intolerant patients for which they have been initially developed.

Best wishes.

[redacted]