NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

HEALTH TECHNOLOGY APPRAISAL

APPEAL HEARING

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

Decision of the Panel

Introduction

1. An appeal panel was convened on Friday 4 November 2011 to consider an appeal against The Institute's Final Appraisal Determination, to the NHS, on dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (part review of NICE technology appraisal guidance 70) and dasatinib and nilotinib for people for whom treatment with imatinib has failed because of intolerance.

2. The Appeal Panel consisted of Mr Jonathan Tross (Chair), Ms Jenny Griffiths (Non-Executive Director), Dr Hugh Annett (NHS Representative), Dr Peter Brock (Industry Representative), Mr Bob Osborne (Lay Representative). Mr John Morris was present as a Panel observer.

3. None of the members of the Appeal Panel had any competing interest to declare.

4. The Appeal Panel considered appeals submitted by the company Bristol-Myers Squibb Pharmaceuticals Limited (BMS) and by the patient support group The CML Support Group.

5. BMS was represented by Mr Amadou Diarra, General Manager BMS UK, Professor Charles Craddock, Haemato-oncologist, Mr Andrew Jones, Disease Area Specialist Oncology, BMS, Mr Stuart Mealing, Health Economist, Oxford Outcomes and Miss Jemima Stratford QC, Legal Representative.

6. The CML Support Group was represented by Mr David Ryner, Ms Sandy Craine and Ms Rachael Bamford.

7. All the above declared no conflicts of interest.

8. In addition the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel: Professor Andrew Stevens, Appraisal Committee Chair, Mr Meindert Boysen, CHTE Programme Director, Ms Frances Sutcliffe, Associate Director, Scott Goulden, Technical Lead, Ms Janet Robertson, Technical Advisor and Dr Matt Stevenson, School of Health and Related Research.

9. All the above declared no conflicts of interest.

10. The Institute's legal adviser Mr Stephen Hocking (DAC Beachcroft LLP) was also present.

11. Under the Institute's appeal procedures members of the public are admitted to appeal hearings and several members of the public were present at this appeal.

12. There are three grounds under which an appeal can be lodged:

    - The Institute has failed to act fairly
    - NICE has formulated guidance which cannot reasonably be justified in the light of the evidence submitted
    - The Institute has exceeded its powers

13. The Chair of the Appeal Committee (Dr Maggie Helliwell) in preliminary correspondence had confirmed that:

    - BMS had potentially valid grounds of appeal as follows:

    Ground 1

    1.1 The splitting and subsequent combining of the appraisals of dasatinib and nilotinib for CML lacks transparency and has deprived the consultees of their procedural and administrative rights.

    1.2 The Institute's choice of comparator is inconsistent with the Methods Guide.

    1.4 The Review and Approval of Novartis' Patient Access Scheme during an on-going Multiple Technology Appraisal is procedurally unfair.

    1.6 The failure to provide BMS with a fully executable version of the PenTAG/SHTAC model lacks transparency.

    Ground 2

    2.1 Relying on outputs of the SHTAC model and utilising these to form the basis of guidance to the NHS is perverse.

    2.2 The choice of hydroxycarbamide as the most appropriate comparator is perverse.

    2.3 The decision not to apply the End-of-Life Criteria to blast crisis patients is perverse.

    2.4 The conclusion that dasatinib is not innovative is perverse.

Ground 3

3.1 The FAD recommendations are in breach of the Human Rights Act 1998.

3.2 The acceptance of the Novartis Patient Access Scheme is in breach of the PPRS.

and:

- The CML Support Group had potentially valid grounds of appeal as follows:

Ground 1

1.1 The Appraisal Committee have failed to follow the NICE procedures set out in the 2008 NICE 'Guide to the methods of technology appraisal' in the selection of a comparator, in this case hydroxycarbamide.

Ground 2

2.1 In relation to FAD section 4.3.3 the Committee's conclusion is flawed. Relevant inhibitor technologies, including standard dose imatinib, are available and are proven to be able to induce sytogenetic responses at high rates in patient populations resistant or intolerant to standard dose imatinib. Hydroxycarbamide, on an in principle basis, cannot do so, interferon has minor efficacy and low tolerability and stem cell transplantation is available to only a minority.

Ground 3

No grounds were raised.

14. Dasatinib (Sprycel, Bristol-Myers Squibb), a tyrosine kinase inhibitor (TKI), is an orally active inhibitor of Src and the Src family of tyrosine kinases. These are involved in cell growth, differentiation, migration and survival, and many are involved in oncogenesis, tumour metastasis and angiogenesis. Dasatinib has been shown to directly inhibit 21 out of 22 forms of BCR-ABL that are resistant to imatinib. Dasatinib has a marketing authorisation for the treatment of 'adult patients with newly diagnosed Philadelphia-chromosome-positive chronic myelogenous leukaemia (CML) in the chronic phase' and 'adult patients with chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib mesilate'.

15. Imatinib (Glivec, Novartis Pharmaceuticals) is an orally active TKI, designed to competitively inhibit BCR-ABL tyrosine kinase activity. By blocking specific signals in cells expressing BCR-ABL, imatinib reduces the uncontrolled proliferation of white blood cells that is a characteristic of CML. Imatinib has a marketing authorisation for the treatment of adult and paediatric patients with newly diagnosed Philadelphia-chromosome- (BCR-ABL) positive CML for whom bone marrow transplantation is not considered as the first line of treatment, and for 'adult and paediatric patients with Philadelphia-chromosome-positive CML in chronic phase after failure of interferon alfa therapy or in accelerated phase or blast crisis'.

16. Nilotinib (Tasigna, Novartis Pharmaceutical) a TKI, is an orally active phenylaminopyrimidine derivative of imatinib. Studies suggest that nilotinib inhibits 32 of 33 BCR-ABL forms that are resistant to imatinib. Nilotinib has a marketing authorisation for the treatment of 'adult patients with newly diagnosed Phildelphia-chromo-positive CML in the chronic phase' and 'adult patients with chronic phase and accelerated phase Phildelphia-chromosome-positive CML with resistance or intolerance to priori therapy including imatinib'. The SPC states that 'efficacy data in patients with CML in blast crisis are not available'.

17. The appraisal that is the subject of the current appeal is to provide advice to the NHS on dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant CML, and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance.

18. Before the Appeal Panel inquired into the detailed complaints the following made preliminary statements: Mr Amadou Diarra and Miss Jemima Stratford QC for BMS, Mr David Ryner for the CML Support Group, and Professor Andrew Stevens for NICE Appraisal Committee.

19. Mr Amadou Diarra for BMS thanked the Panel for the opportunity to appeal as BMS believed fundamental errors have been made that will make it impossible for NHS patients to have the advantage of access to dasatinib, whose value had not been fully appreciated in the appraisal. He then requested his colleague Miss Jemima Stratford QC to speak on behalf of BMS. Miss Stratford QC noted that the Appeal Panel had received written submissions and, this being so, while there are ten points for appeal, she would emphasise three.

20. The FAD uses hydroxycarbamide (Ground 1.2) as the key comparator but caveats its conclusions heavily by saying that none of the economic models provide a good ICER and chooses what it describes as 'least implausible', a model using hydroxycarbamide as the comparator, on which to base its conclusion. On no view is hydroxycarbamide routine or best practice; rather it is antiquated and mainly palliative. This is an obvious case of choosing the wrong comparator.

21. The inclusion of a patient access scheme (PAS) (Ground1.4) at the 11th hour is contrary to NICE guidance for MTAs, which states that when introducing a PAS during a MTA the ACD must be re-issued for consultation unless the guidance becomes positive or largely positive. In this case it did not; it remained negative on two of three decisions and for all in the late phase. It was therefore essential that the ACD went back so that all parties were consulted; only in this way could 'gaming' be avoided. Failure to do so was unfair to BMS.

22. The third area Miss Stratford QC addressed was the modelling, on which BMS also provided a detailed submission. The whole point about NICE appraisals is that they are evidence-based, and there comes a point when modelling is so fundamentally flawed as it was in this appraisal, that it is perverse for NICE to rely on it at all.

23. The FAD recommended nilotinib once a PAS was agreed for it. BMS does not wish the availability of nilotinib to be 'the elephant in the room'. But patients will still suffer because dasatinib has not been recommended. Some patients cannot tolerate nilotinib, for some dasatinib is the only possible 2nd line drug treatment, and dasatinib alone is licensed for use in the blast phase.

24. Mr David Ryner for the CML Support Group noted that their appeal on the 1st and 2nd grounds pivots around the use of hydroxycarbamide as the comparator. NHS best practice is only to use hydroxycarbamide for palliation. Leading clinicians and other guidelines agree that there is no place for hydroxycarbamide in treatment. Hydroxycarbamide is incapable of giving a cytogenetic response. Faced with a patient with imatinib failure no clinician would consider hydroxycarbamide, but would use one of the other tyrosine kinase inhibitors available. The FAD should not rely on the historic treatments. It is current practice that is relevant.

25. Professor Stevens for the Appraisal Committee noted the importance of CML, his satisfaction that NICE had been able to recommend imatinib previously and were now pleased to recommend nilotinib. However, the other side of the coin for any potential recommendation is that NICE must also reflect on the impact on other NHS patients and take into account what treatment is displaced if another expensive treatment is introduced. When accepting a new intervention NICE must seek to ensure that for the NHS as a whole there is not a net health loss, spread throughout the NHS. Dasatinib at £30K per patient per year pushes the NHS into that territory, in the Appraisal Committee's view. Novartis provided a price reduction but BMS adopted a different approach, reflected in the weight of paperwork before the Appeal Panel.

26. Professor Stevens continued by saying that, in everything the Appraisal Committee had done, it had sought to be fair. Both appellants would like the comparator to be high dose imatinib. When imatinib was approved NICE said that escalation of dose could not be approved without further clinical trials. However, far from selecting just hydroxycarbamide the Committee expanded the appraisal to include all comparators. The appraisal has not relied upon hydroxycarbamide as the only comparator.

27. With respect to modelling, Professor Stevens emphasised that the model does not make the decision – the committee does - and in doing so it used all of the models available to it, including those of BMS. All of the models had problems but it was very clear what all of the models were saying.

28. Concluding, Professor Stevens noted that offering a PAS is open to all manufacturers. The '12th hour' is still there for BMS. The Novartis PAS is fair to patients and to the NHS.

Appeal by BMS

Appeal Ground 1: The Institute has failed to act fairly

Appeal Ground 1.1: The splitting and subsequent combining of the appraisals of dasatinib and nilotinib for CML lacks transparency and has deprived the consultees of their procedural and administrative rights

29. Miss Jemima Stratford QC for BMS indicated that the point at issue concerns the unusual way the appraisal for imatinib resistant and intolerant patients was split but then subsequently recombined without consultation with stakeholders. When in 2010 the Appraisal Committee indicated its intention to use high dose imatinib (HDI) as a comparator (for dasatinib and nilotinib) for imatinib resistant patients but continue with a separate appraisal for imatinib intolerant patients BMS accepted this approach. It made sense because resistant and intolerant patients are different patient groups and HDI clearly could not be a comparator for intolerant patients. But as the appraisal continued the focus of the Appraisal Committee was on HDI as a technology under review rather than as a comparator. From the perspective of BMS this is where things went awry.

30. In early July 2011, BMS was told without consultation that the appraisals would be re-combined. This meant that the BMS evidence on intolerant patients was not fairly represented in the FAD. The FAD inferred that the dasatinib ICER for imatinib intolerant patients would be as good as that for imatinib resistant patients. However, the Appraisal Committee had received detailed submissions on intolerant patients. These stakeholder submissions were never properly addressed. Rather the Committee decided to proceed on the basis of inference from the ICER for resistant patients. This last minute recombination was unfair.

31. Professor Andrew Stevens for the Appraisal Committee explained that the split came about because of the recognised need at the time to appraise HDI too. The population contained both patient groups and the Appraisal Committee already had a full set of data on imatinib intolerant patients. For imatinib intolerant patients the appraisal could be completed as the Appraisal Committee had all the data available and had carried out a consultation, and this was all discussed before writing the FAD for imatinib intolerant patients. It was decided not to publish this FAD immediately in order to be fair to imatinib intolerant patients. The FAD was negative and the Appraisal Committee did not want to publish a negative message for one group of patients when it did not yet know the result for imatinib resistant patients. For the resistant patients HDI always was a comparator and remained a comparator. Separating out imatinib resistant patients allowed wider comparators to be used, and allowed HDI itself to be appraised. This process yielded two FADs and the Appraisal Committee could easily have released them separately. However, the concern was that the minority, imatinib intolerant group should not be disadvantaged and so the Appraisal Committee decided to produce one document. They did not intend that intolerant patients would get a less attractive recommendation than resistant patients. So they relaxed the intolerant recommendation to bring it into line with the resistant recommendation, and then published in one document what they could equally have published in two.

32. Responding to questioning, Professor Stevens explained that the splitting and recombining of the appraisals was transparent to stakeholders and had been approved by the Guidance Executive for reasons of fairness. NICE presented every decision point at Appraisal Committee meetings and when carrying out the scoping workshop all scopes were sent out for consultation. HDI and other comparators were all in the scoping. There had been three ACD consultations before the final FAD; these had included consideration of the appraisal with the two populations combined and each population separately. All of this was in line with Guidance Executive intentions regarding consistency and fairness.

33. Miss Stratford QC confirmed that the issue for BMS was the process of recombining. She observed that, while Professor Stevens referred to two unpublished FADs, it is the published FAD that is under consideration. The issue in dispute had not been addressed publicly and in the published FAD there is cursory and inadequate consideration of the needs of the imatinib intolerant population. While there had been opportunity to comment it was only in early July when publication of the FAD was imminent that BMS were told of the recombination.

34. The Appeal Panel noted that, once the decision was made to split the appraisal for imatinib resistant and imatinib intolerant patients and run them as two separate appraisals, this separation continued to the penultimate stage of the appraisal process. The Appeal Panel understood that this splitting was not under challenge in the appeal. The Appeal Panel also noted the Appraisal Committee's evidence that it could have published the findings and recommendations separately for imatinib resistant and intolerant patients, and that recombination came only at the very end of the decision making process. The Appeal Panel further noted that all stakeholders had opportunity to input and comment at various stages throughout the process though not upon the final decision to issue a single FAD. However, the Appeal Panel did not identify any failure to consider evidence relating to intolerant patients connected with the eventual recombination of the two appraisals, or any other unfairness. The Appeal Panel accepted that the decision to combine the separate appraisals in the published FAD was not prejudicial to the interests of any of the parties.

35. The Appeal Panel therefore dismissed this appeal point.

Appeal Ground 1.2: The Institute's choice of comparator is inconsistent with the Methods Guide.

36. Miss Stratford QC for BMS suggested that the Appeal Panel consider hearing all of the points relating to the comparator when she addressed the Appeal Panel under appeal ground 2.2. This was acceptable to the Appeal Panel but each appellant and the Appraisal Committee were given opportunity to make brief points if they so wished before postponing further discussion.

37. Miss Stratford QC for BMS stated that hydroxycarbamide is not routine treatment or best practice and therefore contrary to NICE's own guidelines.

Further, that in the FAD hydroxycarbamide is relied on as the single comparator.

38. Mr David Ryner for the CML Support Group indicated that when the point is under full discussion he would like the Appeal Panel to hear from Professor Charles Craddock on how hydroxycarbamide is actually used in clinical practice.

39. Professor Stevens for the Institute explained that the spirit of the methods guide is for inclusivity; it is permissive with the intention of putting in play all relevant comparators. It also gives primacy to the scoping workshop, as did the Appraisal Committee.

40. The full consideration of matters relevant to this appeal point is at sections 71 to 83.

41. For the reasons to be given under those sections the Appeal Panel dismissed this appeal point.

Appeal Ground 1.4: The review and approval of Novartis' Patient Access Scheme during an on-going multiple technology appraisal is procedurally unfair

42. Miss Jemima Stratford QC for BMS said this is a very important ground and referred the Appeal Panel to a letter dated 26th September 2011 from BMS to Dr Maggie Helliwell in which a full account of the BMS position is set out. There are five essential considerations. First, the Pharmaceutical Price Regulation Scheme 2009 (PPRS) states that the timing of a Patient Access Scheme should not encourage 'gaming'. To avoid 'gaming' and because of the complexity of a MTA the PPRS says that there must be a clear presumption against proposing or accepting schemes other than at the start of the MTA. Second, NICE guidance indicates that a PAS will only be accepted after the ACD in exceptional circumstances. Third, the FAD does not attempt to set out what the exception circumstances were in this case. Fourth, NICE guidance is that where a PAS is accepted, unless the recommendations become or remain largely positive, an ACD should be issued. However, this FAD remains negative for two of three technologies for 2nd line treatment and for all in the blast phase. Yet NICE pressed on and did not issue an additional ACD for consultation. Finally, according to the PPRS 2009, NICE must provide stakeholders with the opportunity to comment on any PAS. The PPRS is clear; if exceptionally NICE is minded to take a PAS at a late stage it must consult with stakeholders; this did not happen. If NICE had consulted this would have afforded procedural fairness for BMS and other stakeholders.

43. BMS is aware that it could have offered a PAS but does not wish to do so until it is convinced it would be assessed using a secure model. In such circumstances if dasatinib was not cost effective at that point BMS could consider a PAS. BMS feels very strongly that the terms of a PAS should not be offered on the basis of a flawed appraisal.

44. Mr Meindert Boysen for the Institute explained that NICE accepts a PAS at any stage in the appraisal process but realises that in a MTA there are complexities. Consideration was given to issuing another ACD, but the PAS relates to nilotinib and nothing changed for dasatinib and the case for the blast stage was unchanged (as nilotinib is not licensed for the blast stage). Therefore the Appraisal Committee did not see any unfairness in not letting BMS react. Dasatinib failed on its own account rather than on any issue connected to the PAS, so the situation for dasatinib had not changed. NICE would never issue an ACD on the grounds that a company might issue a PAS (ie, for dasatinib). That is not the business of NICE as the Department of Health alone decides on pricing. The Appraisal Committee were fair because the case of dasatinib is not influenced by the PAS for nilotinib. The PPRS is an agreement between the DoH and the ABPI, and if the ABPI is concerned about gaming, that is a matter for it to take up.

45. Dr Peter Brock for the Appeal Panel sought clarification on the relationship of the PPRS to NICE processes. Mr Boysen for the Institute explained that there is not a direct read-across. The PPRS is not a NICE document, and the relevant documents for NICE are the STA and MTA processes. The NICE process is intentionally not explicit as to when a PAS can be accepted. On consultation: there are two elements to possible consultation on a PAS. The first is the DoH consulting on whether to accept the PAS. In doing so it consults with the patient access scheme liaison unit, which whilst it is based at NICE has no specific link to technology appraisals. The second element is any consultation by NICE on the consequences of including a PAS in an appraisal. On this occasion the PAS is a simple discount. Responding to Dr Brock, Miss Stratford QC for BMS indicated that it was in June this year that BMS became aware of the Novartis PAS. She confirmed that BMS had not offered a PAS because of modelling on which key decisions were being based is structurally unsound and unreliable.

46. For the Appeal Panel, Mr Tross sought confirmation that it is common ground that the PPRS and the MTA documentation do not say the same thing. Responding, Ms Stratford QC indicated that the focus for BMS is NICE's own guidance and observed that, despite the views expressed by Mr Boysen, NICE guidance should have allowed for consultation and validation. This is a MTA and the critical point is whether guidance became or remained largely positive. The BMS view is that it did not, and the obligation to consult was triggered.

47. Responding to Mr Tross's inquiry concerning where BMS see responsibility to lie regarding a PAS, Miss Stratford QC said it is initially the responsibility of a company, then a process between the company and the Department of Health (assisted by a unit within NICE on behalf of the NHS). But, when it comes to the question of whether a PAS should be accepted into an ongoing appraisal, that is very much a NICE decision and this of course is where BMS focused attention in the context of the appeal.

48. The Appeal Panel considered that BMS were right to focus their attention on the decision by NICE to accept the fact of the PAS into the appraisal. The fact that the PAS was considered and accepted under the PPRS is a matter for the

Department of Health and not the Appraisal Committee. The Panel noted that it is not for NICE to set prices or be involved in price negotiations, or to invite a company to respond to another company's price variations (and further noted that the Department of Health itself does not set individual prices, as the PPRS is concerned with regulating the overall profitability of a company's portfolio of drugs within which the company sets prices for individual technologies).

49. The Appeal Panel considered the choice before the Appraisal Committee once the Department of Health had accepted the PAS for nilotinib. The Appeal Panel concluded that effectively the decision by the Department of Health committed the Appraisal Committee to taking account of the PAS in the appraisal even though the appraisal was then at an advanced stage. Had the Appraisal Committee not done so, it would have been appraising nilotinib on a false basis, and with the effect that what would otherwise have been a positive recommendation for that drug would have remained negative, with all that that would imply for patients. Although the Appeal Panel accepts it is important to adhere to published procedures (though it notes failure to do so is not per se an appeal ground), whether or not it amounts to an exceptional case, where a PAS has been agreed late by the Department of Health and where the effect is to make a treatment for a serious condition acceptably cost effective, the Appraisal Committee should not be criticised for considering it. The Appeal Panel had no doubt that, had the Appraisal Committee instead refused to take account of a scheme agreed between the Department of Health and the manufacturer, an appeal would have been lodged by one or more of the consultees on the grounds either that the Appraisal Committee could not ignore as a matter of process a decision made by the Department of Health to accept a PAS or that the decision to deny a technology now available at an acceptable price was irrational (or both).

50. The Appeal Panel further considered whether there were circumstances that justified the Appraisal Committee in its separate decision not to issue an ACD for consultation. There are two issues; the statement in the MTA that consultation will be undertaken unless the guidance becomes positive or largely positive, and (which is the appeal ground) procedural fairness in the round. The Appeal Panel concluded first that the Guidance had indeed become positive or largely positive from a common sense patient-centred perspective. The result of the change was that most patients would be recommended to receive a second line TKI, whereas previously that treatment option was not recommended. That can be considered a "largely positive" outcome. (Indeed, entirely positive as regards nilotinib, which may well be the correct perspective.) The Appeal Panel was not persuaded that a "drug by drug" perspective was correct, totalling up those drugs which were recommended and subtracting those that were not, at least where the drugs, whilst not entirely interchangeable, met a very similar need in a very similar way. The Appeal Panel was aware of the dasatinib blast phase licence, and that some patients would not tolerate nilotinib, but still regarded the guidance as largely positive. Second, and even if that was not correct, the Appeal Panel could not see any unfairness in the decision not to re-consult after the nilotinib PAS enabled a positive decision for that drug. The PAS did not affect dasatinib ICERs or the dasatinib recommendation, which had already been consulted on. Fairness cannot require re-consultation on issues

which have already been consulted on and which have not changed. The Panel felt it was surely inconceivable that BMS would have wished to argue against patients having access to nilotinib. That was not their position during the appeal. The Appeal Panel understood that BMS wanted to be consulted, but, as BMS had expressly ruled out submitting a PAS of their own during consultation, the Panel did not understand what it was that BMS wanted to say in that consultation that had not already been said in the previous consultations. Miss Stratford QC had not suggested anything. The Appeal Panel could not therefore see that any unfairness had been caused to BMS, or to any other party by a failure to re-consult. The Appeal Panel also observes that consultation comes at the price of delay, and that the Appraisal Committee were in the position of wanting to release guidance whose effect would be that most patients would be recommended for treatment. Whilst that consideration could not excuse unfairness, if there had been any, it is relevant context.

51. The Appeal Panel therefore dismissed this appeal point.

Appeal Ground 1.6: The failure to provide BMS with a fully executable model of PenTAG/SHTAC model lacks transparency

52. Miss Jemima Stratford QC for BMS stated that she wished to put the point differently from how it had been put in the appeal letter in that it had in fact been possible for BMS to get the model working. This had required considerable technical work and expertise but with this work the model became executable.

53. Mr Meindert Boysen for the Institute explained that it is well recognised that these models are very complex and require considerable expertise to run and that it is not the Institute's fault that this is so.

54. Mr Tross clarified with Miss Stratford QC that BMS still considered this a valid appeal point. Miss Stratford QC indicated that as provided the model had not been executable.

55. The Appeal Panel concluded, notwithstanding the technical difficulties, that BMS had been given access to an executable version of the economic model, and that the requirement of fairness had been satisfied.

56. The Appeal Panel therefore dismissed this appeal point.

Appeal by the CML Support Group

Appeal Ground 1: The Institute has failed to act fairly

Appeal Ground 1.1: The Appraisal Committee have failed to follow the NICE procedures set out in the 2008 NICE 'Guide to the methods of technology appraisal' in the selection of a comparator, in this case hydroxycarbamide

57. The CML Support Group did not make observations additional to those reported above (sections 36-41)

58. The relevant observations by the Institute on this appeal ground are found in sections 71-83.

59. The discussion of this appeal ground is found in section 71-83.

60. The Appeal Panel therefore dismissed this appeal point.

BMS

Appeal Ground 2: NICE has formulated guidance which cannot be reasonably justified in the light of the evidence submitted

Appeal Ground 2.1: Relying on outputs of the SHTAC model and utilising these to form the basis of guidance to the NHS is perverse

61. Miss Jemima Stratford QC for BMS suggested that the Appeal Panel should be looking for an error of reasoning that robs the decision by the Appraisal Committee of its logic. She noted that BMS had made detailed written submissions and from that she would highlight two points. First, this FAD is unusual in that it makes recommendations on the basis of no plausible economic model, yet the Appraisal Committee is prepared to place reliance on the SHTAC model. The fact that the Appraisal Committee acknowledges something is hopeless does not cure it of its hopelessness. While the SHTAC model attempted to modify the PenTAG model no structural changes have been made and the flaws in the original model continue to feed through.

62. Second, when the SHTAC model is set up to give ten year treatment durations it allows for individuals to spend longer in the progression-free state than alive; this is but one example of fundamental flaws. An unfortunate 'quick-fix' in relation to treatment durations leads to a model that produces impossible and perverse outputs. The model lacks face validity.

63. This model is not useful; the extent of the flaws is such that the Appraisal Committee should not have accepted the conclusions. It should not have 'thrown in its hand' when the Decision Support Unit could have assisted. But when Novartis comes along with a PAS the Appraisal Committee lightens upon it to issue the FAD.

64. Professor Andrew Stevens for the Institute reiterated that it is not the model but the Committee that makes the decision. The Appraisal Committee used all of the models - and common sense. It did not rely on the SHTAC model alone. With all three models (Novartis, BMS and PenTAG/SHTAC) the three important parameters are overall survival, treatment duration, and the costs of treatment. And the problems are of two kinds: the underlying information on this disease is problematic and all models are dealing with surrogate outcomes. Professor Stevens further explained that, on two of three key parameters, the SHTAC and BMS models were in broad agreement with the BMS model corroborating what the SHTAC model says.

65. Professor Stevens indicated however that the language used in the FAD (4.3.19) was infelicitous in not accurately reflecting the factors taken into account by the Appraisal Committee in reaching its conclusions and that it should have said that in arriving at its decision the Appraisal Committee took into account all of the models.

66. Responding to Dr Hugh Annett, Professor Stevens explained that no useful purpose would have been served in referring the difficulties with the models to the Decision Support Unit. The Appraisal Committee were aware of the BMS concerns, and would have preferred to have had sensitivity analysis on the SHTAC estimate of treatment duration and overall survival. But the Appraisal Committee also had the manufacturer's models and was confident in reaching its conclusion. In a subsequent exchange, Professor Stevens explained that referral to the Decision Support Unit is not a cost-free process and has to be related to the Appraisal Committee being impressed that such a referral could lead to a different outcome.

67. To illustrate the basis for the concerns of BMS Mr Stuart Mealing described some of the SHTAC model outputs and Professor Craddock said that there is widespread clinical concern that the model does not adequately reflect the disease. Responding, Professor Stevens explained that in so far as the SHTAC model was used it was rectified to accommodate the problem with progression free survival, clinical experts views were listened to, and reliance was not placed upon the SHTAC model but virtually relied on the BMS model corroboration; the problem with the BMS models being that they had far higher savings than others.

68. In addition to the oral material summarised above the Appeal Panel took account of BMS's written submission. The Appeal Panel considered the contribution of the different economic models in the decision-making processes of the Appraisal Committee and concluded on the basis of what it had heard, and contrary to the apparent emphasis placed on the SHTAC model in paragraph 4.3.19, that the Appraisal Committee had taken into account the outputs of all of the economic models in reaching its recommendations. The Appeal Panel accepted that there are significant weaknesses in the SHTAC model, but noted that, given the available data, there were particular challenges in modelling the disease and its outcomes. However, the Appeal Panel were persuaded that, as all of the economic models were relied upon, the specific weaknesses of the SHTAC model should not be given undue emphasis. The Appeal Panel concluded that the Appraisal Committee had been aware of the limitations of all models, and of the evidence base, and had reasonably exercised its judgment in relying on all of this material to come to an overall conclusion. All of the options open to the Appraisal Committee had drawbacks. Having been asked to perform the appraisal, the Appraisal Committee would understandably have considered it a last resort to report that it could reach no conclusion. A refusal to have any regard at all to the models would seem an extreme reaction. The decision that further input from the Decision Support Unit would be unlikely to help appeared reasonable, having regard to the underlying weakness in the evidence base, and the fact that a number of modelling teams (including BMS's) had already grappled with these problems with limited

success. In these circumstances, the Appraisal Committee's approach, to have had cautious regard to all models alongside other considerations was within the range of reasonable responses.

69. The Appeal Panel therefore dismissed this appeal point.

70. Given the comments of Professor Stevens that the wording in paragraph 4.3.19 of the FAD is infelicitous, and given the explanation to the Appeal Panel of the key considerations with respect to the economic models on which the Appraisal Committee relied in reaching its decisions, the Appeal Panel suggest that the wording within the FAD be clarified on this particular point.

Appeal Ground 2.2: The choice of hydroxycarbamide as the most appropriate comparator is perverse.

71. Miss Jemima Stratford QC for BMS stated that, in choosing hydroxycarbamide as the most appropriate comparator, the Appraisal Committee perversely set its face against all expert clinical advice. Hydroxycarbamide is not recommended as a 2nd line drug in any clinical guidance and NICE processes are that a comparator must be in routine use and represent NHS best practice; this is not so. Referring to the opening statement by Professor Stevens that NICE processes are intended to be inclusive as regards comparators, Miss Stratford QC said that that does not hold in this case; only one product is used as the comparator in the ICERs used in the FAD. There is significant and cumulating clinical evidence that HDI can result in a cytogenic response so to go back to the situation that pertained when the previous appraisal of imatinib, TA 70, was published is not pertinent. This is a case where not just one specific expert but all clinical experts and guidance point in one way. That is why it is so illogical for the Appraisal Committee to rely on hydroxycarbamide.

72. The significant question is what would a clinician do? The Royal Colleges and others all agree that hydroxycarbamide is the wrong comparator. In choosing hydroxycarbamide the Appraisal Committee also restricted data on which it could rely because establishing trials to compare hydroxycarbamide would be unethical. For all of these reasons the choice of comparator is perverse.

73. Professor Stevens for the Appraisal Committee explained that hydroxycarbamide is not the selected comparator. All treatments were considered but HDI was not selected as the only comparator because it is a very expensive and not very effective treatment and it would be wrong to ignore TA 70 (which stated that HDI should only be used in the context of clinical trials). Professor Stevens referred to slide 10 in a set of slides presented at Appraisal Committee meetings for discussion of dasatinib to illustrate the range of comparator treatments and why HDI would be a desirable comparator from industry perspectives.

74. In contrast, what the Appraisal Committee asked was 'what is the base intervention'? In their economic models BMS and PenTAG use interferon while SHTAC uses hydroxycarbamide. This resulted in a base treatment – not what people want to choose but a reasonable starting point. Hydroxycarbamide is in

the frame as one of a basket of treatments – all of which give much the same result – that are appropriate to use as comparators.

75. Ms Jenny Griffiths asked Professor Craddock to explain the status of hydroxycarbamide in clinical practice. He explained that, if a patient were resistant to standard dose imatinib, then HDI would be introduced because there is robust clinical experience of its effectiveness. In such circumstances no clinician would ever use hydroxycarbamide. Later in the discussion Professor Stevens indicated that, while clinicians argued for HDI as the comparator, this was not reasonable when wider NHS interests are taken into account, as using as a comparator a treatment that costs £38K is how a drug that costs £30K would get approved.

76. Responding to a question on the importance of comparators in the appraisal process Professor Stevens explained that this is a central issue but one that must be correctly understood. Of course HDI would be the clinician's treatment choice. But this is not the NICE perspective; NICE must take into account the consequences for the NHS in terms of displacement costs. HDI is very expensive and its use results in a net health loss. NICE has to stand on a scale of fairness – what would be used if none of them (imatinib, dasatinib, nilotinib) were around? In such circumstances hydroxycarbamide would be in play as much as interferon or SDI. Dasatinib would be cost ineffective against all of these. Responding to this point, Miss Stratford QC said that what NICE has to consider in selecting comparators is what is best and routine practice in the NHS. In further discussion Professor Stevens indicated that hydroxycarbamide is in a sense a part of a package of best supportive care. Ms Griffiths inquired about the approach Appraisal Committees adopt when, as in this case, none of the comparator drugs in play are in routine NHS use and in this case a layman might have thought best supported care might have been considered as a comparator. Professor Stevens explained that there are no good set of rules to deal with a comparator which was a standard treatment at a higher dose which had not been appraised, but luckily in this case the 'escape valve' was that one of the new drugs came in as cost effective.

77. Miss Stratford QC said that the BMS issue is not with the fact that hydroxycarbamide is included as one in a long list of comparators. Rather, that at the end of the day the Appraisal Committee selected hydroxycarbamide as the comparator it was going to rely on – the wrong comparator in terms of NICE's own guidance.

78. The Appeal Panel were mindful of the difficulties in selecting comparators in circumstances when drugs under consideration are in use in clinical practice but not in line with extant NICE guidance. This was the case with HDI. That is, the potential comparator favoured by some stakeholders, HDI, had itself not been recommended as cost effective. Additionally, the Appeal Panel noted that, in deciding which comparators to use, the Appraisal Committee had taken into account both the view of clinicians and the responsibilities of NICE with respect to the impact on the NHS as a whole of the adoption into clinical practice of treatments that are not cost effective. The Appeal Panel considered the NICE methods guide. It noted however that, whilst it would be contrary to the guide (and arguably unreasonable) <u>not</u> to take into account a treatment that was in

routine use or was best practice in the NHS, the guide does not exclude also taking account of treatments that are not in routine use. An appraisal which does so may or may not reach a reasonable conclusion, but that would be a separate question.

79. The Appeal Panel considered whether sole or undue reliance had been placed on hydroxycarbamide as a comparator. However, bearing in mind the explanations it had heard of the process that had been followed, it concluded that this was not so. Rather, while hydroxycarbamide had been an important comparator, it had been one of several used in the various economic models, which had included treatments in routine use. The Appeal Panel noted the concern about using HDI as a sole comparator, having regard to its unappraised status, apparently poor cost effectiveness, and the Institute's past statement that it should be appraised. If HDI is in routine use, the Panel felt that these factors could not have justified the Appraisal Committee in not taking it into account at all. However, the Panel also felt that the Appraisal Committee could reasonably take HDI into account and then have concluded (having regard to the purpose of technology appraisals of issuing guidance on the clinical and cost effective use of resources) that it would be wrong to issue guidance on that basis, if the effect might be to recommend a treatment for being "less cost ineffective", rather than cost effective. The slides of data presented to the Appraisal Committee and Professor Stevens' explanation suggested this was the view taken. The Appeal Panel also noted that, while hydroxycarbamide is not used as a 2nd line therapy, it is in clinical use as an element of supportive care. It understood and accepted Professor Craddock's evidence that no clinician would freely choose hydroxycarbamide in place of a TKI (including HDI), and on exclusively clinical criteria that must be correct. But this presupposes a choice free of cost effectiveness concerns, which is not the Appraisal Committee's perspective. Given the Appraisal Committee's reasonable concerns about HDI, it was reasonable to ask what patients would be offered if no second line TKI at all were available, and the "basket" of treatments used (hydroxycarbamide, interferon, SDI) was a reasonable attempt to do that. In a sense, hydroxycarbamide could be seen as part of supportive care to which it was indeed linked in the scope for treatment for those resistant to standard dose imatinib in respect of the accelerated phase. The Appeal Panel also noted (FAD 4.3.27) that hydroxycarbamide was not referred to as a comparator in the blast phase.

80. The Appeal Panel considered the approach it had taken to a similar issue in past appeals relating to the use of lapatinib for the treatment of women with previously treated advanced or metastatic breast cancer. An argument had been advanced in those appeals that lapatinib should be recommended, although cost ineffective in absolute terms, because its use would achieve an overall improvement in cost effectiveness by replacing a still less cost effective alternative. The panels in those appeals had rejected this argument. Those panels had said a committee could not ignore a treatment in routine use, even if that treatment was of uncertain cost efficacy, but that it was doubtful whether "*it would have been open to the Committee in a Single Technology Appraisal to make a recommendation based only on relative improvements in cost-effectiveness against one comparator, where the technology appraised was not*

cost-effective when set against other comparators". The current appeal concerns an MTA and not an STA, but the underlying principle, that it is not enough to be relatively more cost effective than a treatment whose own use is, at best, in doubt, remains a reasonable position for an Appraisal Committee to adopt.

81. The appraisal was clearly difficult, but the decision could not be said to be "robbed of logic".

82. The Appeal Panel noted the view of Professor Stevens that NICE processes are intended to be inclusive of possible comparators and concluded that the use of hydroxycarbamide and other comparators in the various economic models was in keeping with this intention of the process and the ambit of the scope.

83. The Appeal Panel therefore dismissed this appeal point.

Appeal Ground 2.3: The decision not to apply the End-of-Life criteria to blast crisis patients is perverse

84. Miss Jemima Stratford QC for BMS stated that BMS readily acknowledges that the evidence is not ideal and that it has not been possible given the small number of patients to conduct randomised control or blinded trials but it is perverse of the Appraisal Committee to dismiss the available trial evidence (the START trials) when it was considered sufficiently robust by the European Commission, in line with the positive opinion of the Committee for Medicinal Products for Human Use, to approve marketing authorisation for dasatinib in the blast stage. The Servier case (Servier Laboratories Limited v National Institute for Health (2010)) indicates that the Appraisal Committee needs to give clear reasons for arriving at a different view from the European Commission. Additionally, all clinical guidelines support the use of dasatinib in the blast stage. Dasatinib was designated an orphan drug by the European Union in 2005 and is in use to treat what is a rare disease and in the blast stage exceptionally rare.

85. Data from a clinical trial with two year follow up showed median survival of eight to eleven months when compared with historical data that shows median survival of three to six months. That is, a five to six month gain or almost a doubling of life expectancy for blast stage patients. This cannot be dismissed by referring to the quality of life as the end-of-life guidance only refers to the length of life extension.

86. In relation to the chronic phase of CML in this appraisal the Appraisal Committee was prepared to base its recommendations on trial data that is similarly deficient. And with respect to other appraisals NICE based its recommendations on data that is similarly curtailed, for example for trabectedin.

87. Professor Andrew Stevens for the Institute explained that the end-of-life rules are an exception to the general rule and this needs to be emphasised. The rules for applying the end of life criteria include that the evidence is robust and the initial data from BMS were not. Subsequently the Appraisal Committee heard that for the START B study the results were 'promising'. But none of the

modelling information provided by BMS got to the heart of the issue as to whether the data were robust and none of it was particularly good. The example of trabectedin is given but there are other examples where the data were better than here but were not judged good enough.

88. Mr Andrew Jones outlined the evidence that BMS had and when this was made available to the Appraisal Committee. He explained that despite the very small numbers the BMS data referred to the longest follow up study to date involving about 200 patients in the blast stage randomised for comparison of different drug doses. This is where the median survival came from. Mr Tross asked whether the Appraisal Committee was aware of but not convinced by the BMS data and why if the material available was sufficient for licensing why not for the Appraisal Committee. Professor Stevens indicated that the Appraisal Committee was aware of the data and that while it is adequate for licensing, the Appraisal Committee is considering evidence of cost effectiveness, which is not a factor for the licensing authority. Miss Stratford QC observed that the Court of Appeal decision in the Servier case requires NICE to give its reasons if it reaches a different view from the licensing authority.

89. From the arguments and explanations it had heard, the Appeal Panel concluded that the key consideration for the Appraisal Committee in reaching its conclusion was the robustness of the data presented by BMS. Little data had been presented at the time. The Appeal Panel noted that the evidence on median survival had been contained in a reference in BMS' evidence submitted to the Appraisal Committee covering two year patient survival but the Appraisal Committee had not been specifically alerted to its potential significance in relation to consideration of the end of life criteria. What had been highlighted was the percentage two year survival. It was for BMS to make the best case they felt able to advance. The Appraisal Committee could not be held responsible if there was data included in a reference which had not been picked out. The Appeal Panel was mindful of the difficulties of developing robust trial findings in circumstances such as the blast stage of CML and of the arguments comparing the robustness of data in this case with other examples, but was satisfied that the Appraisal Committee had taken such considerations into account in reaching its decision. Furthermore, although it would expect the Appraisal Committee to have regard to whether it was plausible to expect the data to be improved in the future, where this was not plausible, it could not follow that the Appraisal Committee had for that reason to regard such data as there was as robust. That was not the policy the Institute had adopted. Dealing with the Servier decision, it is correct that the Appraisal Committee and the EMEA consider different questions. In the Servier case, it had been asserted that the EMEA and the relevant committee had reached a different conclusion on precisely the same study for essentially the same issue, and it was undeniably the case that the EMEA had turned its attention specifically to the analysis in question. Here, the connection was less direct. The EMEA was satisfied that the evidence justified a marketing authorisation including the blast phase, but this is a different question to whether the evidence of incremental benefit compared to the benefits of what other treatment might be offered in the NHS is sufficiently robust to justify a departure from the Institute's usual expectations on cost effectiveness. The EMEA's perspective is patient specific:

do the clinical benefits to the patient outweigh the possible risks to the patient? The Institute's perspective is system wide: does the benefit to this patient outweigh the certain loss to other patients elsewhere in the system. Mr Boysen had also been correct to draw attention to the difference between efficacy, established by the EMEA, and effectiveness, of interest to NICE. It would not be unreasonable to expect a higher standard of evidence in this context, particularly in the context of the end of life criteria where usual standards of cost effectiveness are relaxed. The Appeal Panel accepted that the Appraisal Committee has to apply considerations other than those that are appropriate for marketing authorisation and had done so in this case. Furthermore, the Appeal Panel would question how far it is possible to give reasons for a judgment that evidence is insufficiently robust. In Servier, the analysis in question was said to have specific methodological flaws, which could be and subsequently were articulated and explored. Here, there is an overall failure to be convinced. There is a limit to how much elaboration is possible.

90. The Appeal Panel therefore dismissed this appeal point.

Appeal Ground 2.4: The conclusion that dasatinib is not innovative is perverse

91. Miss Jemima Stratford QC for BMS stated that imatinib was recognised as a step change in the treatment of CML when it was introduced in 2003. For patients intolerant of imatinib dasatinib is just as much a step change in 2nd line treatment as imatinib was in 1st line treatment. It is a fact that dasatinib is a second generation drug but this is not determinative of whether it is innovative. For patients taking dasatinib it is an innovative treatment, improving the way a current clinical need is met. It should be accepted as a step change in the management of CML.

92. Professor Andrew Stevens for the Institute explained that the Appraisal Committee had given serious consideration as to whether dasatinib and nilotinib were innovative. They would have been willing to give a positive recommendation at the upper end of the usual cost effectiveness range. But the drugs are further tyrosine kinase inhibitors that fill a diminishing gap. The Appraisal Committee did not regard that as "innovation". On balance the Appraisal Committee concluded that recognising dasatinib as innovative is not justified for the reasons stated in the FAD.

93. The Appeal Panel concluded that due consideration had been given by the Appraisal Committee to whether dasatinib should be recognised as an innovative therapy, that it had considered despite being a 2nd generation tyrosine kinase inhibitor it could still be considered to a degree innovative, and that the argument that it is should be seen as innovative for imatinib intolerant patients had been taken into account. The Appraisal Committee had reasonably rejected the argument that filling a gap after the first TKI, or as a first TKI for those who could not take imatinib, constituted innovation requiring special treatment in the appraisal process. There is not enough of a step change or creative step to require special credit to be given.

94. The Appeal Panel therefore dismissed this appeal point.

CML Support Group

Appeal Ground 2.1: In relation to FAD section 4.3.3 the Committee's conclusion is flawed. Relevant inhibitor technologies, including standard dose imatinib, are available and are proven to be able to induce cytogenetic responses at high rates in patient populations resistant or intolerant to standard dose imatinib. Hydroxycarbamide, on an in principle basis, cannot do so, interferon has minor efficacy and low tolerability and stem cell transplantation is available to only a minority.

95. The CML Support Group had agreed earlier in the proceedings that this point is sufficiently similar to the BMS Appeal Ground 2.2 that the CML Support Group appeal be included in consideration of the latter. In that discussion Mr Ryner had requested that the Appeal Panel hear from Professor Craddock how hydroxycarbamide is actually currently used in clinical practice.

    The relevant sections above are 71 – 83.

96. The Appeal Panel therefore dismissed this appeal point.

BMS

Appeal Ground 3: The Institute has exceeded its powers

Appeal Point Ground 3.1: The FAD recommendations are in breach of the Human Rights Act 1998

97. The Appeal Panel had the benefit of written submissions from BMS, the Appraisal Committee, and its legal advisor. Those submissions were taken into account, but will not be repeated here. It was established that it was also common ground that the issues reacted to the blast phase crisis not to earlier stages of the progression of the disease.

98. Miss Stratford QC elaborated that she agreed that, if Art 8(1) was engaged, as BMS had argued and the Appeal Panel's legal advisor had advised, then the issue became one of necessity under Art 8(2). However, in contrast to the Appeal Panel's legal advice, when asking whether the guidance was "necessary" the Appeal Panel were not obliged to allow a margin of appreciation. The reason was that, as the Appeal Panel's legal advice had noted in a different context, an Appeal Panel of NICE need not show the same deference to an Appraisal Committee as a court of law might show (on non-legal issues, at any rate). She also elaborated that for stem cell matching, whereas c.90% of north European Caucasian patients might find a match, for

BME patients the figure was c.40%, and for some minorities as low as 10%. This was relevant to the challenge under Art 14.

99. The Chairman questioned Miss Stratford QC as to the applicability of Art 8(1). In reply she said that Strasbourg has brought a relatively wide range of concepts of physical and moral integrity within Art 8(1), as the Appeal Panel's legal adviser had also indicated.

100. The Appeal Panel concluded as follows: Although it has applied its understanding of the law to the facts of this appraisal, it has already considered very similar arguments in the azacitidine appeal decision. It does not want to repeat the material in that decision in this decision, and so regard should be had to that decision for a full understanding of its views on these issues.

101. As regards Art 2 and Art 3, the Appeal Panel agrees with and adopts the reasoning given in the azacitidine appeal, and the advice of its legal advisor. The obligations under Art 2 and 3 are essentially negative, and do not extend to an obligation to make a particular treatment (or, in any event, dasatinib) available within the National Health Service.

102. As regards Art 8, the Appeal Panel accepted that the guidance was within the ambit of Article 8, in the sense that its application needed to be considered in the context of this appeal but noted that Article 8 is itself (as are Articles 2 and 3) framed in terms of interference with rights that might otherwise be enjoyed. The Appeal Panel did not agree that the threshold for application of Art 8 (1) had been met in this case of access to a particular medical treatment (and specifically, dasatinib). The Appeal Panel felt questions of access to such particular medical treatments were matters of social policy, going to the level of resources to be devoted to healthcare as opposed to other competing areas of spending, and within the healthcare budget going to the priority to be given to competing needs. These were not best addressed through legal process. A "direct" or "special" link between the desired treatment and an individual's private or family life is needed. The Appeal Panel could see no special link here, over and above a link applying to any treatment for a life threatening illness.

103. Interference was within Art 8(2), as the NICE appraisal process is prescribed and regulated by law, and the guidance is necessary for the economic well being of the country (by seeking to maximise the health benefit generated by the health budget) and for the protection of health (again, by seeking to maximise health benefit in the population as a whole).

104. However the Appeal Panel accepts that access to treatment is within the ambit of Art 8, and therefore Art 14 is engaged. In considering Art 14, the panel also had regard to its and the Institute's obligations under s.149 of the Equality Act 2010.

105. The Appeal Panel rejects the argument that the guidance is discriminatory on the grounds of age. The guidance itself is age-neutral. NICE's cost effectiveness thresholds are similarly age neutral. In common with many conditions CML has a particular age profile, but the Appeal Panel does not accept that the application of a standard appraisal process and common

thresholds to a condition which affects one age group more than another constitutes either a breach of Art 14 or a circumstance requiring any special action under s.149.

106. The evidence before the Appeal Panel suggests that some BME patients with CML will have fewer treatment options than Caucasian patients (though not all patients, BME or otherwise, are suitable for stem cell transplantation). The problem is a lack of donors, which is not an effect of the guidance. The Appeal Panel did not consider that this could put the guidance in breach of Art 14. The Appeal Panel does consider that s.149 requires the position of BME patients to be taken account of, and it notes that the FAD makes reference to this issue. The FAD observes, correctly, that it does not limit access to the technology to any specific protected group, but that may not be a sufficient analysis. It is necessary to consider whether the position of BME patients requires positive action, having in mind that the positive action cannot be conduct that is itself prohibited on equality grounds. The Appeal Panel has therefore asked itself that question. It notes that patients of all ethnicities may receive nilotinib, including therefore BME patients who cannot have a stem cell transplant. It also notes that some BME patients will be eligible for stem cell transplantation, and some Caucasians will not. Therefore in the context of a very small overall patient population the scale of any problem in absolute numbers is open to question. It is, clearly, not possible to recommend dasatanib only for certain racial groups, as this would be direct (and unlawful) racial discrimination. It would presumably be possible to recommend dasatinib as an option for a patient (of any ethnicity) who was unable to receive a stem cell transplant or treatment with nilotinib. However the Appraisal Committee's finding is that the use of dasatinib is cost ineffective, ie, that such a recommendation would deny more benefit (to patients unknown) than it would confer on CML patients. The Appeal Panel believes that achieving equitable health outcomes across different ethnicities is an important objective, but having regard to the uncertain, but on any view very small, number of patients affected, and the cost ineffectiveness of the technology, it is not necessary to adjust the recommendations at this time.

107. However the Appeal Panel notes the FAD recommendation that registry data be collected and it urges that the registry be established so as to allow this issue to be re-evaluated with real-world data in due course.

108. The Appeal Panel therefore dismissed this appeal point.

Appeal Ground 3.2: The acceptance of the Novartis Patient Access Scheme is in breach of the PPRS

109. Miss Stratford QC observed that the issues under this heading had been considered under ground 1, but added that, even if NICE does not operate a presumption against accepting a PAS late in an appraisal, and does not require consultation, then in any event this is contrary to the clear terms of the PPRS.

110. The Appeal Panel concluded that both accepting a proposed PAS for consideration, and deciding that a PAS should be adopted, are matters for the Department of Health over which NICE has no influence (save to the extent that

the PASLU advises on the feasibility of a PAS, which is a different point). It is for the Department of Health to operate and police the PPRS, and NICE would not be entitled to look behind a communication that a PAS had been considered and had been accepted. NICE does have discretion as to whether or not a PAS should be incorporated into an appraisal which is under way, and the Appeal Panel has given its views on that question at section above.

111. The Appeal Panel therefore dismissed this appeal point

The CML Support Group

There were no grounds raised

Conclusion and effect of the Appeal Panel's decision

112. The Appeal Panel has dismissed all the grounds for appeal in this appraisal.

113. There is no possibility of further appeal against this decision of the Appeal Panel. However, this decision and NICE's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of publishing the final guidance.