NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

APPEAL HEARING

Advice on the Single Technology Appraisal of Renal cell carcinoma for locally advanced and/or metastatic (2nd line) - axitinib

Decision of the Panel

Introduction

1. An appeal Panel was convened on 10 June 2013 to consider an appeal against the Institute's Final Appraisal Determination of axitinib for the treatment of advanced renal cell carcinoma after failure of prior systemic treatment.

2. The Appeal Panel consisted of Dr Frank McKenna, Chair, Prof Rona McCandlish, Non-executive Director, Dr Lindsay Smith, NHS representative, Mr Uday Bose, Industry representative, Mr Colin Standfield, Lay representative.

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

4. The Panel considered appeals submitted by Pfizer Limited, James Whale Fund for Kidney Cancer, Kidney Cancer UK and the Royal College of Physicians.

5. Pfizer Limited (PL) was represented by Mr Apostolos Charos, Mr Ben Osborn, Ms Grace Foley and Dr Adela Williams (legal representative).

6. James Whale Fund for Kidney Cancer (JWF) was represented by Dr Thomas Powles, Mr Neil Cameron and Ms Sharon Deveson

7. The Royal College of Physicians (RCP) was represented by Dr Robert Hawkins and Dr Thomas Powles.

8. Kidney Cancer UK (KCUK) was represented by Dr Pat Hanlon, Ms Jackie Lowe and Prof Timothy Eisen.

9. Dr Powles, Dr Hawkins and Prof Eisen declared research funding interests. None of the other participants declared any interests.

10. In addition the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel: Prof Andrew Stevens, Chair Appraisals Committee, Prof Gary McVeigh, Vice Chair, Appraisals Committee, Mr Meindert Boysen, Programme Director, CHTE, Dr Frances Sutcliffe, CHTE and Ms Nwamaka Umeweni, Technical Lead.

11. All the above declared no conflicts of interest.

12. The Institute's legal adviser, Eleanor Tunnicliffe of DAC Beachcroft LLP, was also present.

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

- Ground 1: The Institute has failed to act fairly
- Ground 2: The Institute has formulated guidance which cannot reasonably be justified in the light of the evidence submitted
- Ground 3: The Institute has exceeded its powers

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

PL had potentially valid grounds of appeal summarised as follows:

Ground 1:

1.1 The fact that Pfizer had no adequate opportunity to respond to the additional matters raised by the pharmaceutical industry commentator in response to the ACD is unfair

1.2 The lack of transparency in relation to a submission relied upon for the purposes of the guidance is procedurally unfair

1.4 The Appraisal Committee's refusal to find that use of axitinib in post-cytokine patients satisfied the "end of life" criteria on the basis that no comparison with sunitinib or pazopanib had been provided was inconsistent with the Scope for this appraisal

1.7 The Appraisal Committee's final conclusions in relation to the cost-effectiveness of axitinib are not stated and its reasons for failing to recommend second-line treatment in patients with advanced or metastatic RCC are therefore unclear, in circumstances where the ICER values appear to fall within the range generally regarded as acceptable in other appraisals

Ground 2:

2.1 (originally 1.5) The Committee's approach to the assessment of QALY gains occurring in the post-sunitinib group following disease progression and its conclusion that the post-progression model outputs lacked "clinical plausibility" was not transparent

The JWF had potentially valid grounds of appeal summarised as follows:

Ground 1:

1.1 Uncertainty and ICERS

The RCP had potentially valid grounds of appeal summarised as follows:

Ground 1:

1.2 No explanation of where the most plausible ICER sat

KCUK had potentially valid grounds of appeal summarised as follows:

Either Ground 1 or Ground 2:

1.2 Uncertainty concerning OS and ICERS

15. Axitinib (Inlyta®, Pfizer) is an oral multi-targeted kinase inhibitor (TKI) with anti-tumour activity. Axitinib selectively inhibits vascular endothelial growth factor receptors 1, 2 and 3, platelet-derived growth factor receptor, and c-kit, which may inhibit angiogenesis in tumours. Axitinib has a marketing authorisation for 'the treatment of adult patients with advanced renal cell carcinoma, after failure of prior treatment with sunitinib or a cytokine'. The manufacturer has agreed a patient access scheme with the Department of Health. The clinical-effectiveness evidence presented in the manufacturer's submission was based mainly on the AXIS trial, but because that trial had no best supportive care comparator as defined in the scope, additional studies were used for an indirect comparison of axitinib with best supportive care. The economic evaluation was based on the 2 separate populations specified in the marketing authorisation for axitinib – the group of people in whom prior treatment with sunitinib has failed (also referred to as the prior-sunitinib group) and the group of people in whom prior treatment with cytokines has failed (also referred to as the prior-cytokine groups). For the prior-cytokine group an indirect comparison was undertaken; for the prior-sunitinib group a simulated treatment comparison was undertaken.

16. The appraisal that is the subject of the current appeal developed advice to the NHS on axitinib for the treatment of advanced renal cell carcinoma after failure of prior systemic treatment.

17. Before the Appeal Panel inquired into the detailed complaints all of the following made preliminary statements: Ben Osborn on behalf of PL, Mr Neil Cameron for the JWF, Dr Pat Hanlon for KCUK, Dr Thomas Powles for the RCP and Prof Andrew Stevens for the Appraisal Committee (AC).

Appeal by Pfizer Limited (PL)

Appeal Ground 1: The Institute has failed to act fairly

Appeal Ground 1.1: The lack of transparency in relation to a submission relied upon for the purposes of the guidance is procedurally unfair

18. Dr Adela Williams stated that there was a lack of transparency in the appraisal because PL did not know the identity of a particular commentator. The compilation of ACD consultation responses did not give the identity of the commentator, who was simply classified as pharmaceutical industry. Nor was it clear whether that commentator had a conflict of interest (COI).

19. Dr Williams submitted that the identity was a relevant factor when deciding what weight to give to a submission and also that any potential conflict of interest should be made obvious. She asked what weight was attached by the AC to this submission, and whether the AC were aware the commentator was likely to have a COI. This commentator had provided detailed criticism of the comparator that PL had used. PL considered that, given the nature of the comments, it was likely that the comments had been made by one of their commercial competitors. Such a competitor would have an interest in ensuring that axitinib was not recommended for use in the NHS but that interest had not been identified.

20. Dr Williams pointed out that slides 13 and 16 of the presentation made to the second AC meeting referred to the substance of the comments made by this commentator. Slide 13 does not mention the pharmaceutical commentator as the source; neither does slide 16 mention the source of the adverse comments. In the FAD, paragraph 4.8, much of these adverse comments are reproduced and are attributed to a commentator but not their type. As this paragraph has been expanded compared to the ACD, this implies that the AC relied heavily on these anonymous critical comments from a likely commercial competitor when coming to their conclusions. The AC should have clearly been told the source of the criticism, of the likely COI, and indeed the identity of the commentator.

21. In the absence of a proper declaration of interest, a fair minded observer would not be clear whether the source of the comment had been properly taken into account. Dr Williams referred the Panel to the case of Re Medicaments.

22. The Panel confirmed with the AC that the NICE website does ask commentators: *"Do you work for, or are projects you work on funded by, the manufacturers of this technology?"* The Panel noted that this would not identify those with an interest in the outcome of the appraisal due to their interest in a competing product. The AC explained that NICE did not reveal the identity of members of the public who commented on the ACD.

23. PL reiterated that it is the impression given by documents that is of key importance, based on case law, and what the AC was aware of is of secondary concern.

24. Prof Stevens for the AC stated that the AC was very aware of the likely COI highlighted by PL. He stated that maintaining anonymity of individuals who are commentators is standard procedure and said that the AC took the probable source and likely COI into account in their deliberations. He noted that while it was important for decision-makers (such as the AC) to declare COIs this was not the case for commentators responding to the ACD.

25. The Panel asked the AC to explain how they had considered and weighed these pharmaceutical industry comments and how had they verified the accuracy of the comments.

26. The AC stated that these specific comments raised by the pharmaceutical industry commentator had simply corroborated previously known and stated concerns (ACD 3.14-16, 3.39 et seq, 4.7) and that on balance they had decided to add them to the FAD but they could just as easily have omitted them as they had not influenced their final decision.

27. PL asserted that because the FAD included detailed comments which match this commentator's points then the AC must have been strongly influenced by this commentator.

28. The AC did not confirm that they had verified the facts that the commentator had made.

29. In discussion, the Appeal Panel noted that maintaining anonymity of commentator comments from individuals on ACDs is a standard part of existing NICE procedures. It noted that commentators are asked to declare interests in the product being appraised but not in any competing technologies.

30. The Panel noted that this was a ground 1 point and therefore the issue for them to consider was whether the anonymity of the commentator meant that the Institute had failed to act fairly.

31. The Panel noted the *Medicaments* case but considered that case related to the appearance of bias on behalf of a decision-maker. This appeal point is not concerned with the failure of any decision-maker (the AC) to make public an interest but whether the failure to make public the identity of a contributor to the consultation made that consultation unfair.

32. As the COI that PL referred to did not belong to a member of the AC but to a contributor to the consultation, the Panel was not persuaded that the anonymity of the commentator and the limited extent of the declaration requested by the Institute would lead a fair minded and informed observer to conclude that there was a real possibility the AC was biased towards a particular outcome.

33. The Panel noted that although PL did not know the identity of the individual concerned they had been identified as being from the pharmaceutical industry, so the possibility that the comments might come from a competitor had effectively been highlighted.

34. Under the Institute's procedures, consultees do not have a general right to comment on the submissions made by other commentators, so PL did not have a procedural right to comment on the submissions from the pharmaceutical industry commentator (this is expanded upon further below in relation to Ground 1.2).

35. Furthermore, it was clear that the AC was aware that this commentator was likely to have been a commercial competitor of PL. The AC took this into account when assessing the comments.

36. In these circumstances, the Panel was not persuaded that the fact that the individual's name had not been disclosed had made the appraisal unfair – there was appropriate transparency and procedures were correctly followed.

37. The Appeal Panel therefore dismissed this appeal point

Appeal Ground 1.2: The fact that Pfizer had no adequate opportunity to respond to the additional matters raised by the pharmaceutical industry commentator in response to the ACD, is unfair.

38. The Panel began by referring to paragraph 3.5.35 of the Guide to the Single Technology Appraisal Process. This sets out that when consultees and commentators submit comments and/or new evidence that lead to a substantial revision of the ACD, involving a major change in the recommendations, considerations and/or evidence base, the Centre Director and the Chair of the Appraisal Committee will decide whether it is necessary to prepare another ACD. If so, the consultation process will be repeated. The Panel then invited PL to explain their position regarding this ground of appeal.

39. Dr Adela Williams outlined PL's concerns. She stated that the ACD criticised PL and that PL had responded to all criticisms raised in the ACD. However PL was not given the opportunity to rebut the new critical points by the pharmaceutical industry commentator. It was clear these points were significant as otherwise they would not have been put into para 4.8 of the FAD. PL asserted that the points raised by the commentator were new substantive issues regarding a key issue in the appraisal. PL should have been given the opportunity to comment on them by NICE issuing a second ACD and it was unfair that this was not done. Irrespective of the wording of

the Institute's procedures, the Institute had a general obligation to act fairly, and this required PL to be given a further opportunity to comment.

40. The Panel asked the AC why a second ACD had not been issued. The AC stated that second ACDs are rarely issued and when they are it is because there is either substantial new information submitted during consultation on the ACD or when there is a major change to the AC's recommendations. Prof Stevens emphasised that neither was the case here. Manufacturers are now present at all AC meetings including those where the FAD is finalised and so PL had the opportunity to comment on any factual errors and no factual errors were raised by PL at that time. Mr Meindert Boysen for the AC stated that there is a presumption against a second ACD if new information is not material. The issues raised by the consultee in this case were neither new nor material.

41. The Panel noted that under the Institute's procedures the AC can amend the ACD in light of comments received during the ACD consultation to produce a FAD. PL asserted that in this case the guidance mandates a second ACD because new material evidence had been introduced. This heightened the obligation on NICE to do so.

42. The Panel asked PL to outline the evidence which they believed was new and meant that for the appraisal to be fair a further ACD had to be issued. PL stated that the evidence was that submitted on the web by the pharmaceutical commentator which then appeared with little modification in para 4.8 of the FAD, which was an expanded paragraph compared to its equivalent in the ACD.

43. The Panel asked PL why they had not raised this at the FAD meeting. PL explained they are only allowed by NICE methods to raise factual errors at AC meetings. In PL's experience, the type of submission they wished to make would not have been permitted. Furthermore, in this case the comments were detailed, involving complex statistics and maths, and so it would be unfair to expect PL to raise the issue "on the hoof" at the meeting. As the pharmaceutical commentator

comments had made a difference to the FAD final wording, so a second ACD should have been issued to permit PL to rebut them.

44. In considering this point, the Panel did not consider that the comments made by the pharmaceutical industry commentator had led to a major change in the recommendations, considerations or evidence base as described by paragraph 3.5.35 of the Guide to the Single Technology Appraisal Process. Rather they elaborated upon issues regarding the reliability of the simulated treatment comparison (STC) which was already a live issue in the appraisal – see e.g. ACD paragraphs 3.20 and 4.7.

45. The fact that the ACD had been amended did not alone mean that the comments prompting that amendment should themselves have been consulted upon.
The Appeal Panel agreed with the view of the AC that the points raised by the commentator were not sufficiently new or significant to justify a further ACD. The Panel noted Dr Williams' comments regarding the requirement that all appraisals be conducted fairly, irrespective of the requirements of the Institute's procedures. The Panel considered whether regardless of the Institute's procedures, fairness required an opportunity for PL to comment on the pharmaceutical industry commentator's points.

46. The Panel concluded that the issues raised by the commentator were not sufficiently new or significant for the general principles of fairness to require a further round of consultation. The Institute's procedures struck a fair balance between consultation and the need to issue guidance in a timely way. By acting in accordance with these procedures the AC had acted fairly.

47. The Appeal Panel therefore dismissed this appeal point

Appeal Ground 1.4: The Appraisal Committee's refusal to find that use of axitinib in post-cytokine patients satisfied the "end of life" criteria on the basis that no comparison with sunitinib or pazopanib had been provided was inconsistent with the Scope for this appraisal

48. In explaining this appeal point, PL noted that under the scope for this appraisal axitinib is to be compared to best supportive care (BSC). PL stated that at paragraph 4.18 of the FAD, the Appraisal Committee criticised the axitinib submission on the basis that no comparison with sunitinib or pazopanib was provided in relation to the post-cytokine group and, seemingly for this reason, declined to find that axitinib had been shown to be a life-extending end-of-life treatment for the purposes of the end of life advice.

49. The Panel read out the FAD paragraph in question – 4.18 – and then asked the AC to explain why they decided that the prior-cytokine group did not meet the End of Life (EoL) criteria.

50. Prof Stevens for the AC responded by stating that the appraisal was not really about the prior-cytokine group and that all those involved knew this: the AC, PL, stakeholders and commentators. Patients treated with cytokines would today not move on to best supportive care but would receive treatment with sunitinib and pazopanib notwithstanding previous treatment with cytokines. As a result the post-cytokine group is small and dwindling. Therefore the AC decided not to ask PL to do the work to seek to demonstrate that treatment with axitinib offers an extension to life of at least three months for the prior cytokine group.

51. The AC stated that the scope is there to assist, not limit, a common sense approach, and agreed, when asked specifically by the Panel, that the comparison they considered for the prior-cytokine group (axitinib vs active comparator) was outside the scope for this appraisal but was a pragmatic approach.

52. KCUK stated that in some parts of the country patients do not have access to sunitinib and pazopanib. Such patients belong to the prior-cytokine group that the AC asserts is very small and dwindling.

53. The Panel asked if the AC had effectively modified the scope by introducing a new comparator – treatment with cytokines followed by sunitinib/pazopanib rather

than treatment with cytokines followed by BSC. The AC accepted that they had adhered to the scope for the prior-sunitinib group only.

54. The Panel then asked the AC if PL had agreed to this change in comparator. The AC considered that in reality the prior-cytokine group does not exist anymore. In addition during the appraisal the AC did not hear that axitinib was ever used as treatment for prior-cytokine patients without an earlier active treatment. Mr Meindert Boysen for the AC stated that advice on the NICE website since 2009 on use of tyrosine-kinase inhibitors (TKIs) for renal cell carcinoma (RCC) meant that all PCTs/CCGs should be funding the first line NICE recommended care for RCC so patients should not be moving to BSC following treatment with cytokines.

55. PL stated that the prior-cytokine group did exist in the NHS and the two drugs that the AC mentioned in the FAD were not approved by NICE and had not been stated to be the comparator in the scope. PL stated that although NICE was told this at the time the scope was agreed, this advice was ignored. Although the prior-cytokine group is small, procedures must be fair when developing recommendations for this group and the group should be considered adequately.

56. Dr Powles supported this view by stating that the London cancer care group do not automatically approve first line TKI treatments and so there are post-cytokine group patients in the London area.

57. PL stated that the AC had not asked them to undertake the work to produce an ICER for axitinib versus the TKIs mentioned in the FAD so questioned how the AC could reject axitinib in this situation when an ICER had not been presented.

58. In discussion, the Appeal Panel considered the point raised by the AC that the prior-cytokine group were no longer an appropriate consideration as patients received other therapy; therefore it was sensible to modify the scope during the appraisal to adopt a comparator other than BSC for the prior-cytokine group.

59. The Panel also considered the information from clinical experts that some patients do not receive funding for other treatment following treatment with cytokines. The Panel considered that although the prior-cytokine group might be uncommon, it was the responsibility of the AC to produce recommendations using the comparators set out in the scope

60. If the AC wished to change the comparator used in this appraisal it had to do this by formally amending the scope. This had not been done. As a result of this PL did not have an opportunity to make an appropriate and detailed submission regarding the performance of axitinib in comparison to the new comparator.

61. The Appeal Panel therefore upheld this appeal point.

Appeal Ground 1.7: The Appraisal Committee's final conclusions in relation to the cost-effectiveness of axitinib are not stated and its reasons for failing to recommend second-line treatment in patients with advanced or metastatic RCC are therefore unclear, in circumstances where the ICER values appear to fall within the range generally regarded as acceptable in other appraisals

62. Mr Apostolos Charos for PL stated that they believe that the post-sunitinib group meets the EoL criteria because the ICER estimates vary between £33.5 and £53K. £50K is the approximate threshold at which treatments meeting the EoL criteria have been recommended by the Institute for use in the NHS. Furthermore the highest estimate of £53K includes no survival gain (ratio used 1:1) so if any gain were permitted (the FAD states this was likely) then the ratio would rise and the top ICER estimate would fall to below £50K. In addition, the AC gave no final point estimate of the ICER and gave no clear reasons as to why they rejected axitinib as not fulfilling the EoL criteria. It appeared to PL that the ICER was at or below the normally acceptable threshold – the lack of explanation as to why axitinib had not been recommended was therefore unfair.

63. The Panel asked the AC to explain their reasoning. Prof Stevens stated for the AC that the process was transparent: the ERG had estimated both (prior-cytokine

and prior-sunitinib) ICERs as over £50K and NICE had never approved a drug with an ICER over £50K, or had only done so where the ICER was very close to £50K. For the prior-cytokine group PL's submitted ICER was more than £50K so there was no case to consider as even on PL's submission the 50K threshold was exceeded. For the prior-sunitinib group the ICER estimates varied in both the PL and ERG estimates but the AC preferred the ERG's estimate.

64. Prof Stevens explained to the Panel that in order to meet the EoL criteria, the ICER needed to be below £50K and in addition the AC needed to be confident that the data was robust. For the post-sunitinib group although the ICERs were in the EoL range there was extreme uncertainty with the data and so it failed the EoL criteria.

65. The Panel were referred by the AC to the scatter plot on p16 of PL's updated PAS submission. The AC stated that this was the most variable one they had ever seen. PL countered by stating that the AC has to establish which clinical scenario is most plausible and not just statistically possible and they asserted that 65% of possible ICERs were less than £50K. PL argued that the clinically plausible scenarios were much less scattered. The AC stated that the scatter plot does not include the ratio progression free survival to overall survival (PFS:OS) uncertainty which would increase the scatter even more and concluded that there was just too much uncertainty in the ICER estimates for axitinib to be recommended under the EoL criteria.

66. The Panel asked PL how the AC could have treated this appraisal differently. PL asserted that NICE had previously approved drugs where the ICERs were in the £45-53K range which had similarly wide confidence intervals (CIs) and could give specific examples. PL stated that the AC should have given a clear final ICER in the FAD which they had not done. The AC responded that they had given no precise figure because it was not possible to do so from the evidence submitted by the manufacturer nor by the ERG as the data were too imprecise. Their best guess was a point estimate somewhere between £45 and £53K with an upper end of £120K.

67. In considering this point the Appeal Panel considered that the AC had discussed the ICER in detail and that its point estimate lay towards the top end of the range presented to it by PL and the ERG. The Panel also considered that it was appropriate that the AC had concluded that there was much uncertainty around all ICER estimates it had considered.

68. The Panel concluded that the AC is not obliged to always provide an exact point estimate and in this case the uncertainty in the data presented meant that it was not appropriate to do so. The Panel also accepted the reasoning of the AC that the further an estimated ICER is above the usual 20-30K ICER threshold the more certain they must be about its exact value to approve it under the EoL rules.

69. However, the Panel agreed with PL that the AC is obliged to give clear reasons in the FAD as to why a technology has failed to be recommended under the EoL criteria. The Panel noted that in this case the FAD at paragraph 4.19 gives an ICER range of £33,500 to £52,900 and states that the most plausible valuations are *"at the higher end of this range"*. As other treatments have been recommended by the Institute with ICERs of approximately £50K, the reasons for the AC's conclusion not to recommend the use of axitinib need to be made particularly clear.

70. The Panel concluded that the reasons for the AC not recommending axitinib for use in the NHS under the EoL criteria were not sufficiently clear in the FAD and that this lack of clarity was unfair to the appellant.

71. The Appeal Panel therefore upheld this appeal point.

Appeals by JWF and RCP

JWF Appeal Ground 1.1: Uncertainty and ICERs

RCP Appeal Ground 1.2: No explanation of where the most plausible ICER sat

72. The JWF and RCP agreed to the Panel's suggestion that their grounds of appeal were considered together as they were essentially arguing similar points.

73. Dr Powles, representing both the JWF and the RCP, stated that the scope meant that uncertainty, due to the economic modelling used in this appraisal, was unavoidable as no alternative to the modelling was suggested. The FAD for the post-sunitinib group quoted ICERs of £33.5-53K with the AC choosing the top of the range, which is a conservative figure but clinically less plausible. The true point estimate is likely to be in the middle and it was unfair to accept £53K as the estimate. The inability to assess this (and other) renal cell carcinoma second line treatments because of the inherent uncertainty in the economic modelling is a result of NICE's requirement to compare them individually to BSC. This discriminates against UK renal cell carcinoma patients (compared to other European sufferers).

74. The RCP stated that the trial data NICE needs in order for the uncertainty to be reduced are not possible to obtain as trials comparing axitinib to BSC will not receive ethical approval.

75. The Panel enquired if the RCP had made any of these points at the scoping meeting but none of the RCP nor JWF representatives had been at the scoping meeting so could not respond to this question.

76. The RCP went on to argue that a plausible survival benefit should have been allowed for in the AC's analysis. The RCP considered that the use of the top estimate of the ICER was incorrect and a figure in the middle of the range should have been used.

77. The Panel indicated that issues about the reasonableness of conclusions drawn from the data were ground 2 points. This appeal ground was about the fairness of the appraisal. The Panel asked the AC if NICE's previous decisions regarding therapy for renal cell carcinoma effectively amounted to discrimination against such patients.

78. The AC responded by stating that the ICER range had been clearly stated and explained. The AC had to use data given to them by PL and the AC has to decide the best point ICER estimate and the degree of uncertainty associated with this point

estimate. Any treatment recommended for use with a most plausible ICER over £30K would displace care from other NHS patients and discriminates against other NHS patients. To reduce uncertainty in NICE's technology appraisal (TA) processes, manufacturers need to do better trials and to reduce the point estimate manufacturers need to reduce the cost of their drugs further.

79. The Panel asked whether it was inevitable to have high levels of uncertainty in the STA process where simulated treatment comparisons were used. The AC agreed but emphasised that greater uncertainty could be accepted by NICE if the point ICER estimate were less than 30K.

80. The JWF asked what price would be acceptable to NICE. The AC replied that NICE is prohibited at present from such discussions.

81. In discussion the Panel was not persuaded that the Institute had discriminated unlawfully against patients with RCC – either when compared with other patient groups or in comparison with RCC patients elsewhere in Europe.

82. Recommending a treatment with a high ICER and high levels of uncertainty would divert resources from treatments whose benefits are more certain and that would not be fair to those other patient groups.

83. The Institute provides guidance to the NHS in England and Wales. The fact that this may result in patients receiving different treatment to patients living elsewhere in Europe does not in itself make the recommendations unfair.

84. The Appeal Panel therefore dismissed this point.

Appeal by KCUK

KCUK Appeal Ground 1.1: Uncertainty concerning OS and ICERs

85. KCUK asserted that the FAD states that for the post-cytokine group the ICER is overestimated and all involved in this appraisal agreed that survival in the best

supportive care (BSC) group in reality is much nearer six than the 24 months used to calculate the ICER. Using a survival period for the BSC group of less than 24 months would reduce the ICER.

86. The Panel asked the AC why they did not reduce the ICER for the post-cytokine group to allow for the over-estimation of survival in the BSC group. The AC responded that the FAD also mentions other factors which would increase the ICER, as indicated in the sensitivity analysis in PL's patient access scheme submission template. In this tornado diagram all the ICERs remain greater than £30K whatever optimistic assumptions the AC might have made and many have very high top end ICER values. Although the over-estimate of survival on BSC would push the ICER down the other factors would push it up. The AC conceded however that the tornado plot had not been adjusted to allow for a more realistic BSC survival figure. This was because the effect of the over-estimation of BSC was a second order issue and it was clear that the ICER figures were well past the relevant threshold.

87. KCUK said that because of crossover issues and the artificial comparator the BSC survival estimate was too high in the model used by the AC. PL stated that it had been impossible in their original submission to use a better estimate of BSC in their model. KCUK further asserted that drug resistance to first line therapy always develops and so the disease progression in the model used was unrealistic and should be much shorter.

88. The Panel reminded KCUK that at the scrutiny stage they had been given the option of making their arguments under ground 1 or ground 2. The Panel Chair indicated that the arguments sat more comfortably under ground 2. KCUK confirmed they were happy to proceed on that basis.

89. The Panel asked the AC where the ICER for more realistic BSC survival estimate is provided. The AC responded that it had not been presented. They had expected to be presented with a cost-effective ICER by PL but this did not occur. However, the AC reasoned that no ICER estimate would ever take the ICER below £30K.

Furthermore, this issue was seen as peripheral as the prior-cytokine group is so small and falling in number and it is not a realistic comparator.

90. In discussion, the Appeal Panel considered that the AC had correctly used the data provided to them by PL in their evaluation of the ICER for the post-cytokine group. It was clear from the FAD (paragraph 4.12) that the AC was aware of the issue of the plausibility of the survival gains estimated for the prior-cytokine group for those receiving BSC. The Panel was satisfied that the AC's handling of these uncertainties was reasonable.

91. The Appeal Panel therefore dismissed this appeal point.

Appeal Point Ground 2.1: (originally 1.5) The Committee's approach to the assessment of QALY gains occurring in the post-sunitinib group following disease progression and its conclusion that the post-progression model outputs lacked "clinical plausibility" was not transparent.

92. Grace Foley for PL stated that the PFS:OS gain ratio should be 1:1.6 as in PL's base case which then generated an ICER of £33.5K. This ratio had been criticised by the AC and despite PL and the clinical experts' responses to rebut this criticism, the FAD had simply repeated the ACD with no reasons given as to why the AC had ignored these rebuttals. No specific ICER was reported in the FAD. PL asserted that just a small change in the ratio would bring the ICER under £50K and the ratio accepted by the AC was not consistent with previous AC decisions which utilised this ratio. The clinical experts for the RCP then gave an explanation as to why OS is better after disease progression if a patient has had active therapy, thus justifying the higher ratio.

93. Earlier in the hearing KCUK stated that the AC had been inconsistent in their use of PFS:OS ratios across different appraisals. They gave the example of everolimus for second line treatment of renal cell carcinoma (the same clinical scenario as the current appraisal). The everolimus appraisal had accepted a different ratio from that used in the current appraisal.

94. The Panel noted that this AC had conducted the everolimus appraisal and had accepted a PFS:OS ratio of 1:1.4 and asked the AC why they did not do so with the present appraisal. The AC stated that assumptions can change in either direction and each AC decision must be taken on the merits of the case at the time. Prof McVeigh for the AC agreed that the ratio had been a contentious point. PL had introduced the Delea meta-analysis as a way of externally validating their choice of ratio. The abstract referenced at the time of the previous AC decision provided a ratio of 1:1.4 but the subsequent full paper gave a ratio of 1:1.04. In view of this the AC used the more mature data for the current appraisal.

95. PL then stated that an updated Delea review gave a ratio of 1:1.3 after allowing for crossover and at the FAD stage it had been argued that even if the AC had used 1:1.04 then the ICER would be below £50K with a point estimate of between £48-49K.

96. The Panel asked the AC why they had not accepted that the likely ICER was below £50K. The AC stated that this proposed ICER of £48-49K was new evidence not previously presented to the AC by PL. Even if this figure had been presented, it would not have changed the AC's decision, which was based on excessive uncertainty that was clearly demonstrated by the scatter plot referred to earlier.

97. The AC considered whether a different AC would make a different decision. They stated that the only other AC with a similar dilemma had said 'no' and that even PL had recognised the high level of uncertainty with the data in its response to the ACD; STAs had to rely on manufacturers' data.

98. PL stated that they hoped that the AC would ask a manufacturer for additional analyses if the AC believed further work was important and not just rely on their submission. The AC confirmed that if it had wanted more information then it would have asked for more work to assist with its decision from a number of sources including the manufacturer.

99. PL had responded to the AC's ACD criticisms but PL still do not know why their rebuttals were apparently ignored and why the AC did not use the 1:1.3 Delia crossover corrected ratio? The AC re-affirmed their view that the data was inherently uncertain.

100. In discussion, the Appeal Panel considered whether the AC had been unreasonable in not adopting a more favourable PFS:OS ratio. The Panel noted the explanation provided by the AC at paragraph 4.15 of the FAD concluding that the PFS:OS relationship was probably closer to the ERG's estimate. The panel also noted that the PFS:OS ratio was uncertain and that there was not an accepted ratio by clinical experts. The Panel concluded that it was reasonable for the AC to use the ratio that it did, for the reasons outlined by the AC.

101. The Appeal Panel therefore dismissed this appeal point.

Appeal Ground 3: The Institute has exceeded its powers
There was no appeal under this ground.

Conclusion and effect of the Appeal Panel's decision

102. The Panel upheld the appeal under two ground 1 points.

Point 1.4 (The Appraisal Committee's refusal to find that use of axitinib in post-cytokine patients satisfied the "end of life" criteria on the basis that no comparison with sunitinib or pazopanib had been provided was inconsistent with the Scope for this appraisal) was upheld because the AC did not act in accordance with the scope for this appraisal, resulting in unfairness to PL.

Point 1.7 (The Appraisal Committee's final conclusions in relation to the cost-effectiveness of axitinib are not stated and its reasons for failing to recommend second-line treatment in patients with advanced or metastatic RCC are therefore unclear, in circumstances where the ICER values appear to fall within the range generally regarded as acceptable in other appraisals) was upheld because the AC

did not provide sufficiently clear reasons for not recommending axitinib for use in the NHS under the EoL criteria.

103. The appeal is dismissed on all other grounds.

104. The appraisal is remitted to the AC who must now take all reasonable steps to address the issues on which the appeal has been allowed.

105. 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.