NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE
HEALTH TECHNOLOGY APPRAISAL
APPEAL HEARING

Advice on the Single Technology Appraisal of aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin based chemotherapy

Introduction

1. Appeal Panel was convened on 23rd January 2014 to consider an appeal against the Institute's Final Appraisal Determination, to the NHS, on the Single Technology Appraisal of aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin based chemotherapy

2. The Appeal Panel consisted of

Dr Frank McKenna	Chair
Jonathan Tross	Non-Executive Director
Prof Robin Ferner	NHS Representative
Dr Mercia Page	Industry Representative
Dr Robert Thurstans	Lay Representative

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

4. The Panel considered appeals submitted by Sanofi United Kingdom

5. The Appellants were represented by

Dr Charlie Nicholls	Head of Health Outcomes
Dr Clare Proudfoot	Senior Health Outcomes Manager
Dr Antonio Saha	Colorectal Medical Lead, Sanofi
Dr Adela Williams	Legal representative, Arnold & Porter

6. In addition the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel

Dr Amanda Adler	Technology Appraisal Committee Chair
Professor Daniel Hochhauser	Committee member
Dr Elisabeth George	Associate Director, Appraisals
Ahmed Elsada	Technical Lead
Professor John Cairns	Committee member
Dr Nicky Welton	Committee member

7. The Institute's legal adviser, Mr Stephen Hocking, was also present.

8. 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. In addition, several observers were present, but took no part in the proceedings.

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

   Ground 1: The Institute has failed to act fairly

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

   Ground 3: The Institute has exceeded its powers

10. The Chair of the Appeals Committee (Dr Maggie Helliwell) in preliminary correspondence had confirmed that: The Appellants had potentially valid grounds of appeal as follows: Grounds 1 and 2.

11. Aflibercept (Zaltrap®, Sanofi) is a recombinant human fusion protein that blocks the vascular endothelial growth factor (VGF) pathway by preferentially binding to VF-A, VF-B and placental growth factor, which play an important role in the formation of new blood vessels in solid tumours (angiogenesis). By preventing these factors from activating their endogenous receptors, aflibercept interferes with the process by which capillaries and larger blood vessels expand into tumours (vascularisation), and so inhibits tumour growth. Aflibercept in

combination with folinic acid/5-fluorouracil/irinotecan (FOLFIRI) (that is, in combination with irinotecan and fluorouracil-based therapy) has a United Kingdom marketing authorisation 'for the treatment of adults with metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin-containing regimen.'

12. The appraisal that is the subject of the current appeal provided advice to the NHS on the use of aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy.

13. Before the Appeal Panel inquired into the detailed complaints the following made preliminary statements: Dr Charlie Nicholls for the Company, and Dr Amanda Adler for the Appraisal Committee.

Appeal by Appellant Sanofi UK

Appeal Ground 1: The Institute has failed to act fairly

Appeal Ground 1.2: The Appraisal Committee's conclusions with respect to the appropriate time horizon for this appraisal are unclear and relevant evidence appears to have been disregarded

and

Appeal Ground 1.4: The Appraisal Committee has seemingly disregarded evidence indicating that improved survival in patients with metastatic colo-rectal carcinoma may be attributed to improved medical management as well as resection of metastases

14. These two appeal points were heard together as one combined point: that the Appraisal Committee did not have regard to all of the evidence on patient survival.

15. Dr Williams, for the Appellants, stated that the Appraisal Committee had made unclear decisions on the time-horizon over which the effects of treatment should be considered, and had disregarded important evidence.

16. With regard to the time-horizon, the Committee's actual conclusion on which horizon to apply was unclear. The Appraisal Committee had accepted in principle that, in order to capture all the benefits of treatment, this should be 15 years, but had in fact based its assessment (at least as far as the application of the End of Life guidance was concerned) on a time horizon of 5 years. Although there may only be a small number of patients who survived to fifteen years, it was wrong in principle to ignore them.

17. The Company understood that the Appraisal Committee had considered time horizons of 5, 10, and 15 years in order to explore uncertainty, but the Committee had not explained why it had then chosen 5 years.

18. The Appraisal Committee had commented on the evidence from the United States Surveillance, Epidemiology, and End Results Program (SEER), but not on other evidence which Sanofi had provided, even though that included patients from the United Kingdom. This evidence seemed to have been ignored. The Committee had accepted that long term survival in metastatic colo-rectal cancer was improving, but ascribed this to surgical resection, and had not examined the relevant work by Kopetz and colleagues which suggested it was also associated with better medical management.

19. Professor Cairns, for the Appraisal Committee, drew the Panel's attention to paragraph 4.13 of the Final Appraisal Determination, which stated that 'a time horizon of 15 years was, in principle, appropriate because all patients are likely to have died by 15 years…' ; however, this was not the same as saying that the Committee had to use a 15-year time horizon, and in this instance it had set out to explore the uncertainties introduced by the manufacturers assumptions in its modelling, as described in paragraph 4.24 of the Final Appraisal Determination.

20. Dr George, for the Appraisal Committee, stated that the Committee did not accept the assumptions made in extrapolating the results of the clinical trial to 15 years. In her view the issue was not the time horizon, but the shape of the curve to 15

years. Where the time horizon was much longer than the trial period or [typical] life expectancy it was particularly important to understand uncertainty.

21. Professor Hochhauser, for the Appraisal Committee, described the differences between the patients in the aflibercept trial and the patients in the United Kingdom National Cancer Intelligence Network (NCIN). He also reminded the Panel that 6.6% of that population lived for 5 years from diagnosis (his emphasis). Hepatic resection of metastatic tumour had improved survival in that cohort. In the aflibercept trial, the median time from diagnosis to trial entry was 14 months. The patients in SEER also differed from those in the aflibercept trial, as they had not received oxaliplatin, and the patients described by Kopetz had been restricted to two United States academic institutions.

22. Dr Adler told the Panel that the Appraisal Committee could not discuss every reference cited in every document submitted to it. It had read the manufacturers submission, and had discussed the SEER data, which had been raised by Dr Proudfoot at the Committee meeting.

23. Dr Nicholls accepted that the Company had seen and had the opportunity to comment on the statement in the Appraisal Consultation Document that survival had increased as a consequence of resection of liver metastases, but it had not commented. He set out the Company's calculations of the percentage of surviving patients in the aflibercept and treatment groups at 5, 10, and 15 years.

24. Dr Saha, for the Company, emphasized that the increasing numbers of survivors at and after five years were not simply a consequence of surgical treatment but also of medical advances.

25. Dr Nicholls added that Kopetz's paper gave clear evidence that the increased benefit was possibly through medical management. He accepted that the paper relied on statistical projections to reach its conclusions, and that it also stated 'other modalities besides improved medical care and hepatic resections may have contributed to the results seen.'

26. Dr Adler drew the Appeal Panel's attention to the fact that half of the patients treated with aflibercept had died by 14 months after the start of treatment, and that this made extrapolation of the trial results to a time horizon of 15 years unrealistic. Professor Cairns added that the Committee had not "chosen" a five year horizon, and they had maintained a long enough time horizon to capture all cost and benefit.

27. Dr Welton, for the Appraisal Committee, told the Appeal Panel that it was necessary to distinguish between overall survival and survival difference. There were concerns about the model that held the hazard ratio constant throughout 15 years. Professor Cairns added that the Committee hadn't accepted the way the benefits were modelled, but considered that the time horizon itself was the issue.

28. The Appeal Panel considered the arguments put forward and accepted that the need for a time horizon that adequately captured all the likely benefits of treatment had been recognized by the Appraisal Committee.

29. However, the Appraisal Committee had to balance that need against the need to use reasonable assessments of those benefits. The Panel was satisfied the Committee had done this, and that this was adequately explained in the Final Appraisal Determination and Appraisal Consultation Document.

30. The Appraisal Committee had also to consider all relevant data, but the Appeal Panel decided that this did not mean that every item of information offered by the Company had to be scrutinized in detail by the Appraisal Committee and commented upon in the Final Appraisal Determination. The Committee had clearly understood that patients could survive to five years and beyond after a diagnosis of metastatic colo-rectal cancer, and had stated this in the Final Appraisal Determination. The difficulties in comparing survival between different patient populations treated in different ways were apparent. The wording and reasoning of the Appraisal Consultation Document, committee meeting slides, and Final Appraisal Determination, and the Committee's answers to the Panel, did not support a concern that relevant information had been ignored. It may have failed to persuade but that was not a matter of procedural fairness.

31. The Appeal Panel therefore dismissed these two joined appeal points.

Appeal Ground 1.3: The Appraisal Committee's conclusion that the true mean overall survival benefit is likely to be closer to the median survival of 1.44 months, rather than Sanofi's extrapolation of 4.7 months is unexplained and the basis for the Committee's view is unclear

32. Dr Adler told the Appeal Panel that the restricted mean overall survival benefit, calculated from the data available at the end of the clinical trial, was 1.9 months. That was a conservative estimate of the true mean. The median benefit in overall survival in the trial was 1.44 months, and even that was inevitably uncertain. Treatment ceased after at most 36 months, so that none of the patients modelled as surviving to 15 years had received aflibercept for 12 years or more. Nonetheless, the model assumed that the hazard ratio for patients treated with aflibercept remained favourable for as long as they were modelled as still alive. The Appraisal Committee therefore regarded the Company's proposed mean benefit in overall survival of 4.7 months derived from this approach as unfeasibly large.

33. Dr Nicholls accepted that the Company had commented on these matters at the Appraisal Consultation stage, had read the Appraisal Committee's response and had understood the reasoning contained in the response that 'the manufacturer's extrapolation of overall survival from a population with very few patients at risk of dying after 30 months follow-up, over a further 12 years, was associated with great uncertainty.' The Evidence Review Group had suggested changes to the model. The Committee had indicated that it preferred the ERG approach. The Company's adjusted model had taken that preference on board and indicated a mean overall survival benefit of 3.4–3.7 months.

34. Professor Cairns described how the Appraisal Committee had examined other possible models in which the survival curves converged within 15 years. The Committee was concerned that the Company had fitted different survival

functions to the control and aflibercept arms, and that the treatment benefit continued. It was more likely that the two functions would converge.

35. Dr Adler stated that in this exercise the Appraisal Committee had given the Company the benefit of the doubt by constraining the hazard ratio so that it did not exceed 1.0. Even then, the mean time to progression was 6–7 months.

36. Dr George explained two relevant elements of the models, the time over which the parametric curves were extrapolated, and the value of the hazard ratio during that time. In fact, the approach the Appraisal Committee had chosen, which was to taper the hazard ratio to 1.0 at 30 months, was a less conservative approach than the Evidence Review Group had suggested.

37. Dr Nicholls directed the Panel to a warning in the Evidence Review Group's report against truncating the survival curves, but the Committee had still done so.

38. Dr Williams reminded the Appeal Panel that the appeal on this point related to fairness - the Appraisal Committee had an obligation to explain why it had reached the conclusion that the true mean benefit in overall survival was closer to 1.44 months than to 4.7 months.

39. Dr Adler pointed the Appeal Panel to paragraph 4.24 of the Final Appraisal Determination, and accepted that paragraph 4.6 would have been much clearer if it had contained a cross-reference to paragraph 4.24. In that paragraph, the Appraisal Committee indicated that with a model that allowed for the many uncertainties by restricting the time horizon to 5 years, the mean overall survival benefit from aflibercept was 2.7–2.8 months.

40. The Appeal Panel considered the appeal on this point. The Panel noted that the paragraph in question did not contain the Appraisal Committee's reasons for choosing a mean overall survival benefit below 3.07 months (that is, nearer to 1.44 months than to 4.7 months). However, the reasoning was set out elsewhere in the Final Appraisal Determination. Overall, the Panel felt that the Committee's reasoning was sufficiently clear for the manufacturer to be able to engage

properly with the issues during the appraisal, and sufficiently clear for a user of the guidance to understand the thinking behind it, and that these were the relevant requirements.

41. The Appeal Panel therefore rejected the appeal on this point.

42. The Appeal Panel also noted the possible ambiguity in the wording of paragraph 4.6 of the Final Appraisal Determination, and the lack of any cross-reference to the paragraph explaining the view set out in paragraph 4.6, and asked that the Appraisal Committee make suitable amendments before the Final Appraisal Determination is published.

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

Appeal Point Ground 2.1: The Appraisal Committee have incorrectly assumed that further follow up data from the VELOUR trial are available and this has influenced their conclusions in this appraisal

43. Dr Williams explained to the Panel that the Final Appraisal Determination stated at paragraph 4.6 that 'The Committee was aware that the cut-off date for the trial was 07 February 2011, and that the manufacturer had continued to follow-up patients for overall survival. The Committee met 18 months after this date, but the manufacturer did not present the Committee with follow-up data to support its extrapolation.' The Appraisal Committee had been misled, because there were no additional data. The manufacturer had not followed up for overall survival.

44. Dr George stated that the Appraisal Committee had requested further information at the second meeting in July 2013, and had been told by a representative of the Company that there were patients who had participated in the trial and were still alive.

45. Dr Saha stated that this was so, but there had been no formal analysis: the information came from anecdotes. He accepted that the trial protocol that was

included in the Manufacturer's Submission stipulated that 'After data cut-off for primary analysis of overall survival, patients who were still receiving study treatment and patients who were alive and had completed study treatment, and were experiencing ongoing serious adverse events or new/ongoing related adverse events, were to be followed for safety purposes until stabilisation or resolution for a maximum of 9 months after the study cut-off.' He pointed out that not all patients started treatment at the same time, and that any data would be incomplete.

46. Dr Adler told the Panel that the Appraisal Committee had naturally assumed that patients had been followed up: it had been told some were still alive, and it understood that this was a condition in which most patients survived only a short time.

47. Professor Hochhauser explained that it was not yet standard in oncology trials to follow patients up to establish mean overall survival.

48. Dr Nicholls stated that follow up was only for patients experiencing an adverse event and only for a maximum of nine months. The parent company had been asked for further analyses of the data, and he had been informed that there were none, and that he was not aware of the data that existed.

49. The Appeal Panel considered the appeal on this point. The trial protocol stated that some information would be collected on serious adverse events, and death was necessarily a serious adverse event in clinical trials. The Committee had heard from a representative of the manufacturer that some patients were alive. These facts necessarily implied to the Committee that the manufacturer was aware of the outcomes in at least some of the patients but the Panel considered that neither the trial protocol nor the assertion that some patients were still alive necessarily meant that the Company would have data on overall survival. Dr Nicholls had asked for 'analyses' but not for data, although the Panel was unclear whether he had intended to draw a distinction between the two. The Panel felt there was a miscommunication on both sides, and that the manufacturer had not provided information that the Appraisal Committee might reasonably have

thought existed (albeit which the manufacturer had now said did not exist) and which it might reasonably have considered to be relevant to the decision it was asked to make. The Panel's conclusion is that the Committee did indeed think that the manufacturer had some additional data which it could provide, and had been led to that belief by the manufacturer.

50. The Panel further concluded that the manufacturer does appear to have additional data; however, the manufacturer does not consider the data suitable to assist the Committee in its deliberations. The Panel accepts that the manufacturer does not have reliable follow-up data for overall survival. Rather, it has appears to have some data gathered for other purposes from which it might or might not be possible to add to what is known about overall survival. A discussion between the Committee and the manufacturer at the time would have been likely to clarify these issues, although the Panel does not suggest that either side is at fault.

51. The Appeal Panel also noted that Companies are asked to sign an undertaking that " *all relevant data pertinent to the [STA] [MTA] have been disclosed to the Institute"* Furthermore it was aware that this provision was strengthened for submissions made after September 2013 (i.e., after the submission in this case) to confirm that all the data necessary to address the remit and scope of the technology appraisal as issued by the Department of Health and NICE, within the Company's or any of its associated companies' possession, custody, or control in the UK or elsewhere in the world, have been disclosed to NICE. The Panel hopes that this strengthened formulation may make a misunderstanding less likely in future.

52. In addition to having been reasonable in considering that there were other data in existence, the Appeal Panel was not persuaded that the Committee's assessment of the evidence had been affected by this issue.

53. The Appeal Panel therefore rejected the appeal on this point. However it feels that it is important to state in so doing that it does not believe that the manufacturer acted improperly. In particular there is no evidence that the

manufacturer deliberately withheld data that it knew to be relevant from the Committee.

54. The Appeal Panel noted that the repeated references to the failure of the Company to provide data were unnecessary to understanding of the Guidance, and that there was a factually inaccurate reference to overall survival data. The Panel recommends that before the Guidance is published, the repeated references be removed and the inaccuracy be corrected.

Appeal point 2.2: The Committee's conclusion that the data relating to aflibercept were not sufficiently robust to accept that a three month life extension benefit was produced is inconsistent with the available evidence and therefore unreasonable

55. Dr Proudfoot, for the manufacturer, told the Appeal Panel that in order to calculate the mean overall survival benefit it was necessary to extrapolate the survival curves. Using NICE's own best practice guidelines and appropriate parametric functions, the mean overall survival benefit determined by the Company was at least 3.0 months. The manufacturer had accepted the Evidence Review Group's recommendation that the hazard ratio should taper to 1.0 after 30–36 months, and on that assumption the most plausible mean benefit in overall survival was 3.4–3.7 months. However, the Appraisal Committee had then truncated the survival curves at five years, in effect making two conservative corrections: first, that there was no benefit from treatment after 30–36 months; and secondly, that the time horizon of benefit only extended to 5 years. This double counted uncertainty, because once the hazard ratio is set to 1 any uncertainty is due to the natural history of the disease, not the effect of the drug. The manufacturer, responding to the comments in the Appraisal Consultation Document, had estimated the incremental cost-effectiveness ratio to be £42000 per quality-adjusted life year.

56. Dr George stated that on the information available to the Appraisal Committee, it was very difficult to define the most plausible incremental cost-effectiveness

ratio. The Evidence Review Group had held it to be £51,000, and the Committee decided it could plausibly lie in the range £44,000–£51,000.

57. Dr Adler added that the most reliable data came from the VELOUR trial but very small numbers contributed to the tail of the curve.

58. Mr Ahmed Elsada, for the Appraisal Committee, stated that in the original model 36% of all the benefit from aflibercept accrued beyond 5 years; in models adjusted to allow for the hazard ratio to converge, the benefit after 5 years still amounted to 22% of the total benefit.

59. Prof Cairns stated that the Committee saw the true value for mean overall survival benefit as highly uncertain, but that around 2.7–2.8 months was more likely to be correct. Dr Adler commented that this could be argued to be an overestimate, but that, on a balance of probabilities, the value was below three months and the manufacturer's assumptions were not realistic.

60. Dr Proudfoot commented that uncertainty was normal in oncology. VELOUR was a large trial and a good basis for extrapolation. Dr Nicholls drew the Panel's attention to a statement in the Evidence Review Group report that 'where there exists uncertainty concerning both the magnitude and duration of OS benefits, a more appropriate basis for informing decision making would be to consider alternative scenarios concerning the treatment effect itself (or the shape of the survival functions) whilst maintaining a lifetime time horizon.'

61. The Appeal Panel considered this point, and noted that there were many uncertainties in the extrapolation of overall survival benefit from limited data gathered during a clinical trial. The Panel was aware that in order to satisfy the End of Life criteria the estimates of the extension to life needed to be robust and could be shown or reasonably inferred from either progression free survival or overall survival. The Appraisal Committee had adopted one approach to allow for these uncertainties. While others may have adopted a different approach, the approach adopted by the Appraisal Committee was not outside the range of responses open to it and so was not unreasonable.

62. The Appeal Panel therefore dismissed the appeal on this ground.

Appeal point 2.3: The Appraisal Committee has provided no explanation for the inconsistencies in its approach to the assessment of the overall survival benefit associated with aflibercept in this appraisal and that for panitumumab in TAG 242: in the absence of an explanation, these inconsistencies suggest an arbitrary approach which is unreasonable

63. Dr Nicholls stated that the Final Appraisal Determination offered no explanation for the differences between the Appraisal Committee's approach to the problem of aflibercept and to the problems of cetuximab and panitumumab. In Technology Appraisal 242, it was accepted that the trial of panitumumab showed no improvement in overall survival, but that the results were made more difficult to interpret because of cross-over between treatments, and attempts had been made to control for this. The Appraisal Committee had accepted a corrected mean overall survival benefit of 2.8–3.1 months, and had noted that the progression-free survival with panitumumab and cetuximab was similar. It had therefore accepted that panitumumab satisfied this criterion for consideration of the End of Life adjustments to thresholds. This was despite the uncertain relationship between progression-free survival and overall survival.

64. Dr Adler stated that the Appraisal Committee was not obliged, in this Single Technology Appraisal of aflibercept, to consider any comparison with panitumumab. In any event, the incremental cost-effectiveness ratio for panitumumab was at least £100,000, so that the End of Life criteria were irrelevant to that decision.

65. Dr George explained to the Appeal Panel that cetuximab and panitumumab had similar mechanisms of action, while the mechanism of action of aflibercept was different. The Institute had considered several related applications, for example, TA227, TA209, and TA202, but each had a different set of uncertainties and they were not comparable on the relevant facts.

66. Professor Cairns told the Appeal Panel that the Committee judged the medicines by consistent criteria applied consistently.

67. Dr Williams expressed the concern that where decisions between Assessments apparently differed, then the criteria to reach them might be arbitrary.

68. The Appeal Panel considered the point. It accepted that there was an overall requirement of consistency, between relevantly similar cases. It observes that this requirement must be reasonably applied, in particular having regard to the fact that NICE has four appraisal committees who cannot be expected to be familiar with the minutiae of each others' work. (In this case the same committee was involved in both appraisals, but the Panel does not feel that can impose a higher obligation of consistency.) The details of each appraisal will differ, and the details are usually important. Further there has to be room for committees to exercise their judgment afresh in each case. Therefore for guidance to be unreasonable on the grounds of inconsistency the Panel feels the inconsistency needs to be very clear indeed. The Panel noted that there were important differences between the case of aflibercept and the cases of panitumumab and cetuximab. It was not unreasonable for the Committee to reach a different conclusion for aflibercept than for panitumumab and cetuximab.

69. The Appeal Panel therefore dismissed the appeal on this ground.

70. Although it does not affect the outcome of this appeal the Appeal Panel wishes to comment on Dr Adler's suggestion that less rigour may have been brought to bear on the application of the End of Life Criteria in the panitumumab appraisal because it was already clear that the ICER for that treatment would be too high to be recommended in any event. The Appeal Panel considered that this is not the best approach. There is an interest in reaching a robust conclusion on End of Life criteria even if the ICER as calculated at the time of the appraisal remains excessive. Manufacturers and others need to know whether a treatment does or does not meet the criteria: this may be relevant to submission of any patient access scheme or for other purposes. Appraisal Committees are asked to consider the End of Life criteria with the same rigour independent of any consideration of

the likely incremental cost-effectiveness ratio. Appraisal Committees should always record their consideration of the End of Life criteria. If the Appraisal Committee was clear that a technology failed on one or more criteria, it should state the reasons why this was so. In such a case the Committee is not required to consider the remaining criteria, but should state explicitly whether or not it had done so.

Appeal Ground 3: The Institute has exceeded its powers

71. There was no appeal under this ground.

Conclusion and effect of the Appeal Panel's decision

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

73. The Appeal Panel has, however, suggested changes to the wording of the Final Appraisal Determination, and made recommendations for future Appraisal Committees.

74. 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.