Comments submitted by Professor Ian Judson, clinical expert to the Appraisal Committee. Endorsed by [redacted], RCP Registrar on behalf of:

NCRI/RCP/RCR/ACP/JCCO

NICE ACD on sunitinib in GIST issued in February 2009

Thank you for giving me the opportunity to respond to the ACD. I appreciate that additional information has been requested from the manufacturer and that this is a provisional decision that might be altered in response to new information.

Do you consider that all of the relevant evidence has been taken into account?

Yes, I believe that all the available data have been made available and have been reviewed.

Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?

No, I have serious concerns about the interpretation of the evidence, as discussed below:

1. Clinical benefit

1.1 I am pleased to see that the Appraisal Committee concluded that sunitinib was an effective treatment with a likely survival benefit for patients with GIST progressing on or intolerant of imatinib (4.2, page 13). This is certainly consistent with my own experience as a treating physician with a large population of patients with GIST, many of whom appear to have benefited greatly from this agent. Similarly, although serious side effects can occur, the fact that in the randomised clinical trial (RCT) the quality of life (QoL) as measured by the EQ-5D tool did not differ between the treatment and placebo groups (section 3.6, page 8 of the ACD) is consistent with the

fact that most side effects are mild and can be managed with symptomatic treatment or by modifying the dose of the drug. Any drug-related detriment to QoL is compensated for by a decrease in disease-related symptoms. This is a point to which I will return when considering the definition of QUALY in relation to this agent.

1.2 What is clear from the ACD and the discussion I took part in at the STA meeting on February 5, is that owing to the design of the RCT used to support the licence application there are some uncertainties regarding the magnitude of the benefit of sunitinib owing to the study being unblinded at the time of the interim analysis and the subsequent cross-over to active treatment of the majority of patients who were taking placebo at that time. The additional data considered concern an expanded access programme (EAP), termed the cohort study by the company, which was designed to make the drug available for patients who were ineligible for the RCT or without access to it. I think the key value of the EAP is that it confirms that sunitinib is safe and effective in this setting in a much larger group of patients. The differences in eligibility criteria and response assessment between the RCT and the cohort study may explain some of the differences observed in progression-free and overall survival between the two.

1.3 Median survival in the cohort study was 75 weeks, similar to the 73 weeks for the RCT (summarised in Table 16 on page 63 of the Expert Review Group (ERG) report) but that median time to progression (TTP) was 41 weeks rather than 29 weeks for the overall RCT and 27 weeks for the interim analysis. This seems a little surprising, since median performance status (PS) was slightly worse in the cohort study owing to less strict entry criteria. However, the figure of 29 weeks PFS for the entire study includes those patients allocated to placebo who crossed over to active treatment after unblinding but may have begun to progress prior to cross-over. By the time the study was reported in full the ITT analysis was effectively a comparison of early versus delayed sunitinib therapy.

1.4 A sub-analysis, as described in the ERG report in section 4.2.3 on page 61, in which patients with similar PS, i.e. 0-1, treated in the cohort study and the RCT were compared, gave figures of 88 weeks for OS in the expanded access study (EAP), otherwise known as the cohort study, versus 73 weeks for the RCT and for PFS 41 weeks versus 29 weeks respectively. This again suggests that there is a systematic bias based on disease burden in favour of the EAP. The discrepancy cannot be explained by the cross-over since the ITT interim analysis, which is not confounded by cross-over gives a figure of 27 weeks PFS on sunitinib.

1.5 An additional confounding factor when comparing these studies is that to be eligible for the RCT patients had to have demonstrated disease progression using the strict size criteria of RECIST, whereas one of the eligibility criteria for the cohort study was not being eligible for the RCT, which could have been on the basis of disease measurability. This means that different criteria for assessment of progression might apply between the two studies. Perhaps in spite of the strict PS entry criteria the requirement for proof of disease progression by RECIST may have selected patients with bulkier, more rapidly progressive disease for the RCT.

2. Cost-effectiveness

2.1 When considering benefit, not in terms of disease control, or survival, which does not appear to be in doubt, but in terms of cost-effectiveness, what I think clinicians and patients find hard to accept is the apparent implication from some of the discussion in the ACD that the better a drug works, the worse its cost-effectiveness would be. This appears to be contrary to the normal rules by which we estimate the value of anything, especially a new drug. In particular, emphasis was placed on the fact that 22% of patients continued on sunitinib in the RCT after they had “progressive disease” according to RECIST as they were still experiencing clinical benefit (e.g. section 4.5, page 14 of the ACD). If the cost of treating these patients is taken into account the cost per QUALY increases, albeit only by £2,237

(section 5.4.1.2 page 87 of ERG report). I think it is reasonable to take this into account, since, as I explained on February 5, disease progression may occur according to RECIST owing to the development of a single new lesion, even when the overall disease burden is reasonably stable and under control of a drug such as imatinib or sunitinib. Thus treatment may continue while a patient is "benefiting clinically", in other words, while their disease-related symptoms are being controlled and areas of non-progressive disease are still responding to treatment. What patients sometimes describe when treatment is stopped in this situation is a rapid escalation in symptoms with deterioration in appetite, an increase in pain and abdominal distension, fatigue and weight loss. This "tumour flare" phenomenon may occur when all treatment is withdrawn, hence the entire tumour burden progressive, rather than simply the component that has become resistant to the tyrosine kinase inhibitor being administered.

2.2 Although the ERG accepted that it was an appropriate thing to do, I realise that there are difficulties in understanding how the rank preserved structural failure time (RPSFT) model was applied by the manufacturer. Whatever the drawbacks of the RPSFT it seems clear that it is more appropriate than using the ITT analysis of the entire study including the subsequent open label treatment with sunitinib in the absence of censoring. This is acknowledged in the submission by PenTAG on page 61. They actually state that the RPSFT is more appropriate than censoring the data at the primary endpoint yet this is specifically recommended as something to be explored in section 4.9, page 19 of the ACD.

2.3 At the time of the interim analysis, when the trial was unblinded on the advice of the IDMC, there was a highly statistically significant difference in survival. This occurred in spite of the fact that patients were allowed to cross-over to sunitinib on progression if they were found to be on placebo and were still fit enough to receive the drug. The criteria for allowing cross-over did, however, include RECIST assessable progression and maintenance of performance status 0-2 (not 0-1, I apologise if I misled the committee on this point). In other words their performance status was permitted to have

deteriorated somewhat, since study entry demanded a PS of 0-1. The difference in survival must indicate either that a significant percentage of patients on placebo died before their disease status could be determined objectively or that they were no longer fit enough to receive sunitinib by the time it was proven that they had progressed. This latter problem could in part be due to the use of RECIST which is now acknowledged to be suboptimal in assessing response status in patients with GIST. The fact that the difference between the 2 arms dissipated over a further year of follow-up (Fig 4, page 45 or ERG report) is hardly surprising, given that the majority of patients who had been assigned to placebo and were still alive and well were given the active drug. As acknowledged, an intention to treat analysis of the entire study period up to the time that median survival had been reached in both arms merely compares immediate with delayed sunitinib therapy.

2.4 I was present in the open part of the STA meeting when the RPSFT model was discussed and strongly criticised. It seemed surprising to me as an observer was that the representatives from PenTAG did not seem to be expressing such negative views. A lot of the discussion had been prompted by the fact that an independent expert on the model had challenged certain assumptions and in particular the narrow confidence intervals for the hazard ratio proposed by Pfizer. A comment was made that these confidence intervals were impossibly narrow. Again from the naïve perspective of a treating physician I find this puzzling. It can be seen that according to intention to treat at the time of the interim analysis, the sunitinib and placebo arms were diverging, both for PFS and OS. This occurred in spite of the fact that patients were allowed to cross-over to sunitinib on progression within the RCT. What the RPSFT does is assume that patients remained on the allocated treatment and then looks to see what would have happened to them. This does not really mimic what would have happened if the trial had not been unblinded in January 2005. What if we examine another hypothesis? Whatever determined the death of the patients in the placebo arm, as discussed above in 2.3, it would have continued to happen if the trial had continued to accrue patients in a blinded fashion for, let us say, another year. In this situation it is surely not unreasonable to assume that the curves would

have continued to separate because a proportion of placebo patients would have failed to cross-over on progression or would not have been salvaged owing to the extent of disease progression and would have died earlier than if they had been on active treatment from the time of randomisation. In this case while the hazard ratio may have been the same, the confidence interval (CI) would surely have been narrower and the HR even more significant than it was at the time of the interim analysis, when it was 0.491 (CI 0.29 – 0.833) P = 0.007 (Fig 2, page 43 of the ERG report). It seems very unlikely that the survival benefit observed was due to chance when the PFS curves are considered (Fig 1, page 42 of the ERG report). It is unfortunate if it is deemed that the RPSFT is not able to produce a more reliable figure for the survival benefit of sunitinib than that seen at the time of the interim analysis which is only perhaps thought to be suspect because median survival had not yet been reached. To me, this seems arbitrary and unnecessary.

2.5 This brings me to the application of this discussion to the economic model. Section 3.12 it states that if instead of using the base-case ICER supplied by the manufacturer, which gave a figure of £27,365 per QUALY gained, if one uses the unadjusted ITT data the figure was £77,107. I presume, on the basis of the previous discussion, that this means the ITT analysis of the whole study. It then discussed using these data to model the placebo plus best supportive care overall survival curve. However, we know that the only data that can reasonably be used to model that curve are the data up to the time of the interim analysis. What I find the most disturbing statement of all is at the end of section 3.12. It is stated that on the basis of comparing the most favourable with the least favourable cost-effectiveness calculations there is a 50% chance of sunitinib being cost-effective. Is this a basis for not approving its use? Patients would willingly accept a 50% chance of a treatment being successful!

Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

No, I do not for the following reasons:

1. Sunitinib is an effective and reasonably well tolerated medication that usefully extends survival and maintains quality of life in patients with GIST after imatinib failure.
2. The magnitude of benefit is under-estimated by the registration trial. A significant increase in overall survival was observed at the time of the interim analysis in spite of patients being allowed to cross-over to active treatment on progression.
3. Whatever the strengths or weakness of the method proposed by Pfizer for calculating cost-effectiveness (RPSFT), it appears superior to using the data from the whole trial and was acknowledged by the ERG to be appropriate if used correctly.
4. According to recent supplementary advice, within the scope of which sunitinib was approved for the treatment of renal cancer, a medicine could be approved for use if the following conditions apply
    a. It be used for treating a population of less than 7000 new patients a year
    b. It would be indicated for patients with a terminal illness and a life expectancy of less than 24 months
    c. There are no alternative treatments available with comparable benefit via the NHS
    d. Assessment of cost-effectiveness places it above the upper end of the range normally considered to be cost effective, i.e. £30,000 per QUALY gained.

    It would seem that sunitinib fits these criteria very well.

It is clear that if sunitinib is not approved for use in imatinib-refractory GIST this will be a step backwards in the management of this rare disease. Access to the drug via the exceptional use prescribing route would become even more difficult, if not impossible, and access to other new drugs would also become very difficult. This is because the standard treatments for GIST worldwide following progression on imatinib 400 mg daily are imatinib 800 mg daily and sunitinib. Certain clinical trials now about to start in the UK are restricted to patients who have received these interventions.

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