Response to NICE ACD on Sunitinib for the treatment of GIST – February 2009

This is a joint submission by Sarcoma UK, GIST Support UK

and the Rarer Cancers Forum.

We address the four general questions on which comments are requested.

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

We believe that all the available data have been made available and have been reviewed. However we do not believe that all relevant evidence, in the form of expert clinical interpretation from specialists treating GIST, and from patient submitted information, has been taken fully into account.

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?

1. The summary of clinical efficacy concludes that sunitinib is an effective treatment for this group of patients. We welcome this conclusion.

2. We do however wish to clarify and comment on points made in the Evaluation Report.

    a. In the additional notes on page 2, the first assumption, that treatment has the same effect on everyone, is untrue. We know that a proportion of patients get no benefit from sunitinib, but since this can be determined during the first cycle, funded by Pfizer under current arrangements, there is no risk to the NHS. We also know that about the same proportion of patients gain between 5 and 15 months of PFS. A small but very important group of patients gains long-term PFS. We do not know yet how long this can be: the longest we know of has now passed the 4-year mark. We also do not know in detail how to predict which patients will fall into which of these groups. We do know that the mutation type is a valuable predictor: patients with exon 9 mutations or those with wild type GIST, including the very rare but very important paediatric GIST patients, generally respond less well than other patients to imatinib, but better to sunitinib.

    b. In the same paragraph it is stated that, “This is not necessarily true, but minor departures probably won’t matter much.” It may not matter very much to the analyst, but it matters a great deal to patients, especially if they belong to one of the groups of patients who stand to benefit most from sunitinib, or are parents of a child or teenager with GIST.

    c. On page 2 of the pre-meeting briefing, third bullet point, the issue of the 54 patients who continued to take sunitinib after progression is discussed. Today these patients would most probably be entered into a Phase I/II clinical trial, and not continue on sunitinib. We know that there is often clinical benefit in staying on sunitinib after

progression, because some of the tumour(s) are still responding. However new treatments and combinations of drug treatments are being studied. We suspect that the proportion of patients who stay on sunitinib after progression has already decreased markedly, and will continue to do so. The issue in the paragraph is now of less significance.

d. The question is raised about whether patients take more than the NICE approved 400mg dose of imatinib. We know that in the UK, there are a number of patients who are taking escalated doses under a compassionate support programme funded by Novartis. Many of these have the rare exon 9 mutation, wild type GIST or paediatric GIST. Some of these are still receiving the 800mg dose to which they were randomized on the trial starting in 2001. Most receive it because of disease progression. We believe that most oncologists will increase the dose of imatinib after progression on 400mg, before moving the patient onto sunitinib. A Phase 3 randomized trial is now underway to examine this choice.

3. The summary of cost effectiveness gives us cause for great concern. We applaud the committee's request for further information from Pfizer, the manufacturer.

   a. It is clear from the ACD, and from the public session of the Committee's meeting, that the Evidence Review Group (from Peninsula) was unable to address the Committee's questions about how Pfizer applied its choice of the Rank Preserved Structural Failure Time (RPSFT) model in analyzing comparators for cost effectiveness.

   b. This raises questions about the procedures employed by NICE in this Appraisal. If the ERG is to act as expert adviser to the Committee they should be in the position of addressing the committee's concerns to the manufacturer <u>prior to the meeting</u>, not afterwards. It is worth noting that Pfizer's health economist working on this Appraisal was in the room, albeit as a member of the public. Her presence would have been known about by NICE personnel in the room as all public attendance is pre-registered. She was not called upon to respond to questions which could have been addressed, and possible resolved, quickly. While such a step may be unusual, we believe the Committee faced an unusual problem – lack of competence by the ERG. The failure to adapt to this unusual situation reflects badly on NICE. Although we cannot know what took place during the Techonology Appraisal committee's secret session it was quite apparent in the public session that the malfunctioning of procedure was creating a blockage for the Committee. This is reflected by the extensive discussion of this issue in the ACD.

4. We have availed ourselves of NICE's offer to inspect the Pfizer economic model.

   a. This model comprises 17 interconnected Excel spreadsheets. It is complex and difficult to penetrate, especially considering the absence of adequate internal commenting. It is a case of trying to deduce what the question was by examining the answer. However we did detect one glaring error in cell K64 of the Budget Impact sheet, where the total has omitted the BSC cost of £334,771. This in turn

results in an overstated Budget Impact of £334,771 for year 2011. In other words the Sutent route is made to appear more expensive than it should be for 2011.

b. It is easy to understand how errors of this kind can be made by the original builders of the model, but what really concerns us is that the error was not spotted in the course of all the subsequent analysis, and that the error has been carried forward verbatim on to page 87 of the Pfizer submission in the Evaluation Report. If errors of this kind can slip through, it can only sap our confidence in the ERG as independent experts in examining the more complex aspects of the model.

5. The number of patients in the RCT was small (235 on treatment, 115 on placebo – numbers vary according to the point reported).

   a. The comparison of TTP was so significant that the trial was stopped and remaining placebo patients crossed over to active treatment. Of the 99 patients who had crossed over prior to the trial being stopped 13 achieved an objective partial response. Overall survival (OS) is the most robust measure for assessing cost effectiveness and median OS for patients who received sunitinib through randomsation or cross-over was similar. Eliminating the effect of cross-over is the purpose of analysis using the Rank Preserved Structural Failure Time (RPSFT) model.

   b. The analysis of RPSFT on overall survival data was presented at ASCO in 2008[1]. It demonstrated correlation with the interim analysis of the trial using Kaplan-Meier methods, suggesting a valid approach to estimating OS for the placebo group should the trial have remained blinded. The critical group of patients in this analysis is therefore the group of 13 who extended the overall survival of the placebo group by responding to sunitinib following cross-over.

   c. We do not believe it is valid, in any scientific or moral sense, to determine the future of this treatment in the NHS on suppositions about statistical models, however academically robust they may be, based on a group of 13 patients.

6. One further consideration which needs to be taken into account, when considering the availability or non-availability of Sutent, is the psychological well-being of the patient. How a patient feels about his future, and whether he can see some sort of hope for his condition, is a very important part of how he will assess his quality of life when he is asked to do so. In the A6181004 trial all the patients, whichever arm they were in, would have known that they were participating in a trial aimed at improving their outcome. This knowledge in itself would have put a positive bias on how they reported their EQ-5D status. If patients in the UK, who have failed on Imatinib, know that there is a drug which might help them, but

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[1] Novel statistical analysis of long-term survival to account for crossover in a phase III trial of sunitinib (SU) vs. placebo (PL) in advanced GIST after imatinib (IM) failure. *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 10524). Authors: G. D. Demetri, X. Huang, C. R. Garrett, P. Schöffski, M. E. Blackstein, M. H. Shah, J. Verweij, V. Tassell, C. M. Baum, P. G. Casali

which is not available, this fact in itself will adversely impact their quality of life, because of the negative emotions engendered. No account of this appears to have been taken in the course of NICE's deliberations so far.

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 - for the following reasons:

1. Sunitinib is an effective and generally well tolerated medication that usefully extends survival and maintains quality of life in patients with GIST after failing imatinib. The ACD recognises this clinical benefit.

2. The magnitude of benefit seen in the registration trial has been exceeded in clinical practice. Owing to the rarity of this disease gathering retrospective data and publishing case series is problematical. To support this assertion we note that an increase in overall survival was observed at the time of the interim analysis of the registration study, including data on patients allowed to cross-over to active treatment following progression on placebo.

3. The ERG/PENTAG group acknowledged that Pfizer's method for calculating cost-effectiveness (RPSFT) was superior to using the data from the whole trial, even though it failed to defend this expert opinion to the Appraisal Committee.

4. NICE now accepts the principle that a medicine can be approved for use if certain rarity criteria apply and the medicine can be seen to be applicable to 'end-of-life'. This was applied in the recent FAD for sunitinib for renal cell cancer.

    a. The technology is used for treating a population of less than 7000 new patients a year (we estimate the relevant GIST population here to be 120-150)

    b. It is indicated for patients with a terminal illness and a life expectancy of less than 24 months (untreated median survival with GIST is <40 weeks)

    c. There are no alternative treatments available with comparable benefit via the NHS (this is the situation for patients with GIST resistant to imatinib)

    d. Assessment of cost-effectiveness places it above the range normally considered to be cost effective.

    We conclude that it is appropriate to consider sunitinib for GIST as an 'end-of-life' exception to the £30,000 cost per QALY gained benchmark.

5. Failure to approve sunitinib for GIST patients who have relapsed on imatinib will effectively bring to an end all treatment options in the NHS for this small group of patients. Clinical trials (currently running and planned) of new technologies have entry criteria which require failure on sunitinib, a fully authorized standard treatment in 84 countries. Patients who have not received sunitinib are ineligible for these trials. Future marketing authorisation of

such new technologies will reflect these criteria if current authorization practice is applied. Failure to approve sunitinib will therefore close future treatment options to GIST patients within the NHS.

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

Equality is not often discussed in the context of rarity of disease. The cohort of patients with relapsed GIST treated by imatinib is approximately 250 per annum in the whole UK. Accurate data is not available, despite NICE TAG86 (2004) recommending to the NHS that data are gathered. Of those resistant to imatinib at 400mg/d some are prescribed sunitinib. An estimate indicates that this is about 120 patients in England/Wales. Again, no data are available.

At every turn the GIST community encounters the problem of numbers, an inescapable result of rarity. We can accept that NICE makes no allowance for rarity when developing its procedures. However we believe that Technology Appraisals must acknowledge extreme rarity (ultra-orphan conditions), and make allowances for the problems it presents to clinicians, patients and manufacturers in making a case for approval.

Demonstration of that understanding would be appreciated, and matters just as much as any demonstrations of the understanding of issues concerning the ethnic, religious, cultural or sexual realities of life.

Signed:

For GIST Support UK – Judith Robinson (Expert witness)

For Rarer Cancers Forum – Stella Pendleton (Expert witness and Stakeholder Patient Organisation)

For Sarcoma UK – [redacted] (Stakeholder Patient Organisation)

(Note: GIST Support UK is a sub-group of Sarcoma UK and following its pending registration as an autonomous charity will be seeking independent stakeholder status with NICE).