ACD - Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (part review of TA86)

This response is submitted by [redacted], RCP registrar on behalf of the following organisations:

Patient organisations	Professional/medical organisations
Sarcoma UK	Association of Cancer Physicians
GIST Support UK	The Institute of Cancer Research
Macmillan Cancer Support	NCRI Sarcoma Clinical Studies Group
Rarer Cancers Foundation	Royal College of Physicians
Beating Bowel Cancer	Royal College of Radiologists
Bowel Cancer UK	Joint Collegiate Council for Oncology

We are grateful for the opportunity to respond and would like to make the following comments to the questions posed.

1. Has all of the relevant evidence been taken into account?

No. We do not believe that all of the relevant evidence has been taken into account due to the restrictive interpretation of the scope of this appraisal. We find this perverse.

When imatinib was first considered by NICE for the treatment of gastrointestinal stromal tumours (GIST) in 2004, evidence for a dose response relationship for imatinib in terms of progression-free survival was not considered admissible, because it had only been published in abstract form. A large randomised clinical trial that addressed this issue was published in the Lancet later the same year. In the 2004 Technology Appraisal (TA86) it is specifically stated that a full review of imatinib in GIST would take place in October 2007.

Since 2004, a large body of evidence has been published that has not been considered by the Review Assessment Group. For example, it is known that a significant subgroup of patients with a mutation in exon 9 of the *KIT* gene benefit from the use of a larger dose of imatinib because the conformation of this altered protein is relatively unfavourable for imatinib binding [1]. This observation was confirmed in a meta-analysis of European and North American trials involving 1640 patients[2]. It is true that the meta-analysis did not show a statistically significant survival benefit, but this may be in part due to the small numbers and also to the efficacy of salvage therapy on progression. We are deeply concerned that this evidence was not considered by the Assessment Group.

In conducting this appraisal a very narrow terms of reference has been used ie ‘what is the evidence for clinical benefit from increasing the imatinib dose for patients with GIST progressing on imatinib 400 mg?’ Since most of the data available concerning imatinib in GIST are derived from studies that investigated a starting dose of either 400mg or 800mg this means that the Assessment Group has discounted all that has been learnt concerning the molecular biology and pharmacokinetics of imatinib since 2004.

The result of the above is that the promised full re-appraisal of this technology has not, in our view, been performed.

2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No.

We believe that the clinical pathway which is followed by patients with advanced GIST (as part of standard clinical practice all over the world) has not been adequately considered.

We believe that substantial effort has been wasted assessing a 600mg/d dose which is rarely used in practice, and then most often as a temporary measure to control side-effects from the higher 800mg/d dose.

The critical clinical objective for patients with advanced GIST is to be able to maintain first-line treatment on imatinib for as long as possible. Relapse indicates resistance to the drug, a situation which is not reversible. Second-line and subsequent therapies are less effective than imatinib is in first-line. It is known that some patients remain responsive to imatinib for long periods (many years) while those who develop resistance, most often typified by secondary genetic mutations and new tumour growth, do not.

In this appraisal the escalated dose issues have been reviewed in isolation, with no consideration of individual patient opportunities to benefit from provision of an escalated dose of imatinib. There is evidence from clinical experience of the benefit attained by specific sub-groups of patients defined by genetic mutation analysis, most notably those patients with a primary showing the exon 9 mutation in *KIT.*

Unfortunately, the manufacturer has not sought a product licence for the initial treatment of any particular group of patients with the 800mg/d dose of imatinib. We believe this is largely because, in the light of the almost universal acceptance that 800 mg is the appropriate dose for *KIT* exon 9 mutant GIST and the value of dose escalation on progression at the 400 mg dose, it did not appear to be commercially necessary to do so.

We believe there to be some significant inaccuracies in the ACD and its Summary.

First paragraph 4.3.3:- 'no randomized controlled trials were identified on the effectiveness of an increased dose of imatinib compared with sunitinib or best supportive care'. In fact evidence was submitted verbally that a clinical trial comparing sunitinib with imatinib at 800mg in patients progressing on 400mg had been initiated by Pfizer (Study A6181112). Unfortunately, this study failed to accrue sufficient patients, except in the UK and South Korea, the only countries where sunitinib had not yet been approved for reimbursement. It was closed shortly after sunitinib was approved for the second line treatment of GIST by NICE.

Para 4.3.9 reports that clinical specialists stated that the original criteria in TA86 remain valid, specifically:- 'continuing imatinib is recommended only if a response to initial treatment is achieved within 12 weeks'. Our experts, who attended the Committee, do not recall this being discussed as such and do not endorse the statement. Patients with exon 9 mutant GIST would appropriately receive the larger dose. In addition, it was correctly assumed by the Assessment Group (page 91 of the Evaluation Report), that imatinib can be part of best supportive care in progressing patients. This is because of the heterogeneity of the disease, even if partially resistant, and the ability of the drug to contribute greatly to symptom control in some

patients.

We believe that the development of advances in imatinib blood level testing, which allow imatinib levels in the blood to be assessed, has been ignored[3]. Ironically it is often patients whose liver function improves on treatment with imatinib whose blood levels fall. Although this is not standard clinical practice, because imatinib blood level testing facilities are not yet widespread, specialists treating GIST worldwide now recognise the importance to individual outcomes of identifying when patients' levels of active drug are falling and correcting that situation with an escalated dose. An arrangement for imatinib blood level testing for patients with GIST is now in place, funded by Novartis, as it is for patients with CML, in a laboratory at King's College Hospital, London. This is available to patients from anywhere in the UK. It is clear that low trough levels correlate with poor response and shorter response duration, hence the justification for increasing the dose. This is also being studied prospectively in the UK, at the Christie Hospital, and at the Dana Farber Cancer Center in the US.

It is true that dose escalation would not be valuable in the case of imatinib resistance due to a secondary mutation, but in about a third of cases resistance is due to other causes, including less favourable primary mutations, or the lack of a known driving mutation, but also amplification of the *KIT* gene and upregulation of drug transporter mechanisms in tumour tissue. This is the same percentage of patients that were shown to benefit from crossing over from 400 mg to 800 mg imatinib on progression in both the 62005 European-Australasian study and the S0033 North American study[4, 5].

The relative paucity of evidence is directly attributable to the rarity of this disease. However, the failure to allow clinicians to act on their knowledge serves only to condemn groups of patients to resistant and fatal disease. These patients can be individually prognostically identified and can experience high quality of extended life with, in some cases, no evidence of active disease for some years.

In particular, we would like to identify the conflicting nature of the discussion on 'end-of-life' in paragraphs 4.3.16 and 4.3.17. While not meeting the strict criteria set for an 'end-of-life' treatment a failure to prescribe escalated dose imatinib to a suitable patient will accelerate that patient's pathway to end-of-life. This conflict is not resolved by the discussion in the ACD, which we believe does not address the intent of Ministers when the 'end-of-life' review was proposed in 2008.

However, the most negative reflection on this particular technology appraisal process is to be found in the evaluation report (on which we have commented separately). Sunitinib was approved by NICE for the second line treatment of imatinib-refractory GIST on the basis of a patient access scheme agreed with the company. The technology appraisal TA179G, published in September 2009 indicates that the best estimate for the incremental cost-effectiveness ratio (ICER) for sunitinib after disease progression on imatinib was £31,800 per quality adjusted life year gained. This was based on the evidence presented to NICE by the Review Group report prepared by the Peninsula Technology Assessment Group. However, on this occasion the Assessment Group report, prepared by the Aberdeen Technology Assessment Group concludes on the basis of their modeling, that a treatment pathway that takes patients who progress on imatinib 400 mg immediately to sunitinib, pathway 7 in Fig 5, produces an incremental cost per QUALY of £272,365 (Table 16).

If the modeling is so inaccurate as to produce an estimate >8 fold higher than the one published in TA179, we wonder how a rational decision can be made not to recommend the use of imatinib 800 daily on progression on the grounds of a lack of

cost-effectiveness. We believe this threatens the credibility and consistency of the process and needs addressing. As all of the data on sunitinib were presumably available to the Aberdeen group how were they able to produce such an incredible, in the true sense of the word, result?

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

No.

We note that no other country in Europe (nor the USA) denies 800mg/d of imatinib to patients, either as first-line or second-line treatment. The numbers of patients affected is very small. Exon 9 mutation is seen in about 11% of patients with primary GIST – maybe 35-40 new patients a year in England and Wales in the advanced/metastatic setting. While one accepts that resources are not limitless and the NHS is right to have a focus on cost-effectiveness, the clinical effectiveness of imatinib in the treatment of GIST cannot be denied. It is the view of our organisations that the total cost of giving clinicians discretion in prescribing imatinib will have little overall financial impact on the NHS.

The discussion on appropriate utility scores from the EQ5D in paragraphs 4.3.13 and 4.3.14 are very unsatisfactory.

An asymptomatic GIST patient may have an EQ5D score of 1 at diagnosis and the same after five years of first-line imatinib. The cost-per-QALY would be infinite. However, without treatment this patient would have died. Similarly it is possible for a radically disabled patient to have a very low, even a minus, score at diagnosis, which is not affected by treatment, although the treatment keeps them alive. Again the cost-per-QALY may be infinite. Between these two extremes every kind of EQ5D score is possible.

Choosing a 'generic' point on which to base calculations is, we believe, a deeply flawed concept given the extreme range feasible among GIST patients. Without reliable data, and without open and transparent criteria for making a judgement on an appropriate range of scores, reviewing that range in the light of the distribution of utility scores from a real patient group, the process is open to bias and ill-informed conjecture. This is evident in para 4.3.14 where the Committee, without reference to clinical expertise and ignoring the views of expert witnesses, makes assumptions without any evidence base. We do not believe that this conjecture can be described as a 'sound and suitable base' for guidance recommendations to the NHS.

We also observe that there is a striking dissonance between the recommendations made in this ACD and the recent announcement from Cancer Research UK of active steps towards treating cancer patients on an individual genetically identified basis, rather than a histologically defined disease basis. GIST is one of a growing number of cancers for which genetic characterisation can not only provide valuable prognostic information but can also be used as a guide to the most effective therapy. We believe that this has been ignored within the appraisal.

Another aspect of GIST management with imatinib that should have been considered in a comprehensive review of the technology is the issue of CD117 negative GIST. In TA86, it is recommended that treatment with imatinib be confined to tumours expressing the antigen CD117, i.e. *KIT*. However, we now know that GIST can be driven by mutations in the *PDGFRA* gene, and in some of these tumours CD117 is

not expressed. In a minority of other cases CD117 expression is low, but a characteristic mutation in *KIT* is found, confirming the diagnosis. Additionally, another antibody, DOG1, can be used to make a diagnosis of GIST if CD117 is equivocal, as discussed by Dr Robin Reid at the appraisal meeting.

The Committee recommends, in the ACD, that further research be conducted on the use of mutational analysis to predict individual responses to treatment. However, the outcome of the ACD makes this futile with respect to imatinib. It will not be possible to collect additional data on the relationship between imatinib 800mg and survival in patients with *KIT* exon 9 mutant disease if this dose is not available. Similarly, the problem with implementing a national register and plasma level measurements has been a lack of funding.

We believe that the recommendations in this ACD, if carried forward, will deny physicians and their patients the opportunity to apply their knowledge of the driving mutations in this disease and will thus deny appropriate treatment to a rare cancer group.

4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

Discrimination on grounds of rarity of disease is not unlawful. However, we believe it to be unethical and possibly immoral by the common standards of society. There may also be a case for it being illegal if through unreasonability or irrationality a patient or group of patients is unfairly discriminated against.

We believe that the argument – 'the absence of evidence is not evidence of absence' - applies to the disease setting being examined here. The fact is that the scarcity of patients with GIST, and the even scarcer incidence of those with the less common mutations evident in the disease, makes prospective studies (even on an international scale) difficult. For NICE to make judgements on issues for which there are no studies (eg 600mg/d of imatinib) or for it to seek answers to specific questions which are not of interest outside the UK (and thus of no value to non-UK investigators), is therefore discriminatory.

However, evidence is available to be assessed, even if it is in study sub-groups, small case series, unpublished studies and, in the case of patient experience, anecdotal. In failing to pay regard to this evidence, and making judgements without taking account of this data, the recommendations could be argued to be discriminatory.

In this particular case, some of the patients who would be denied effective first-line treatment can be identified through mutation analysis. The position of receiving this prognostic information and then selectively being denied access to appropriate treatment, can also be argued as discrimination against a very rare patient sub-group.

There is one other issue about this appraisal. Imatinib was first reviewed by NICE in 2003/4. Its decision included recommendations to the NHS that a national register of GIST patients and their treatment should be established. This has not occurred. It is clear that such a register might have met some of the needs of this technology review, and the call for such a register is renewed in the ACD.

That the NHS failed to implement that recommendation in 2004, and that the failure has contributed to this decision (albeit as yet a draft), is of very serious concern.

1. Debiec-Rychter M, Sciot R, Le Cesne A et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. Eur J Cancer 2006; 42: 1093-1103.
2. Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. J Clin Oncol 28: 1247-1253.
3. Demetri GD, Wang Y, Wehrle E et al. Imatinib plasma levels are correlated with clinical benefit in patients with unresectable/metastatic gastrointestinal stromal tumors. J Clin Oncol 2009; 27: 3141-3147.
4. Blanke CD, Demetri GD, von Mehren M et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol 2008; 26: 620-625.
5. Zalcberg JR, Verweij J, Casali PG et al. Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg. Eur J Cancer 2005; 41: 1751-1757.