**Response to NICE Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (part review of TA86)- Assessment Report**

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

NCRI/RCP/RCR/ACP/JCCO

The response has been coordinated by

[redacted]

[redacted]

# Introduction

Imatinib at a dose of 800mg daily may be considered as an alternative to imatinib at a dose of 400mg daily :-

1. As starting dose
2. For primary resistance to imatinib at 400 mg daily
3. For secondary resistance to imatinib at 400 mg daily

In each of these situations the evaluation must address:-

1. The evidence in favour of a **positive clinical impact.**
2. The **degree** of clinical benefit.
3. The **cost** of the benefit in **comparison** to alternative management.

Within the population of patients with GIST two clinically significant subgroups have been identified:-

1. Patients with common exon 11 KIT mutations (imatinib sensitive)
2. Patients with KIT exon 9, other mutations, or no detectable mutations (wild-type) (associated with reduced imatinib sensitivity)

The evaluation needs to take into account all available relevant published information.

Hislop *et al* confine themselves to analysis of escalation from 400mg to a higher dose for all patients at progression irrespective of the mutation status of the patient's tumour or other clinical factors They conclude that the cost per QALY for this intervention would be more than £45,000

# Response

## *Evidence base*

The most obvious omission in the report is the failure to reference or to consider in detail the MetaGIST analysis [1]. Although the ASCO 2007 presentation this work is referenced the full published analysis is not. This substantial work re-analysed the

joint patient level data from EORTC 62005 and S0033 which examined the outcome of patients either started on 400mg or 800mg. This paper also presents sub-group analysis of the outcome according to initial mutation status of the tumour.

## *Rationale for escalation*

The report confines itself to a numeric assessment of published data without reference to the significant amount of work regarding the rationale for a dose relationship. This leads to a flawed analysis because it ignores entirely reasonable strategies for identifying groups of patients who would benefit from dose escalation more than the whole unselected population and for whom the cost-analysis is therefore different.

The rationale for dose escalation is two-fold:-

1. The patient may have a variant mutation which can only be inhibited by a higher dose of imatinib
2. The patient has a standard mutation but the plasma level of imatinib is unusually low due to patient related factors.

Both these hypotheses have been confirmed by published data. The work on plasma level monitoring [2-5] has not been considered in the report by Hislop *et al* and this is a second major omission.

The work on mutation analysis in GIST and the differential response to imatinib [6-8] is referenced in the report but the impact of mutational analysis on the cost-effectiveness of dose escalation is omitted.

A further important observation is that the appearance of highly imatinib-insensitive secondary *KIT* mutations which heralds complete imatinib treatment failure is less frequently seen in patients with primary exon 9 mutations or wild type disease . For example, in the phase I/II study with sunitinib that preceded the randomised study that resulted in licensing [9] the incidence of secondary mutations in the exon 11 group was 73% compared with only 19% in the exon 9 group. Notwithstanding the improved progression-free survival observed with 800 mg compared with 400 mg in exon 9 mutant GIST, while dose escalation might not overcome the resistance associated with a secondary mutation, it may be effective in exon 9 and wild-type tumours that clearly use alternative mechanisms of resistance. The molecular basis for the relatively unfavourable binding of imatinib to exon 9 mutant and wild-type KIT is now better understood and future developments are likely to identify drugs which are superior to imatinib in these situations.

## *Comparisons included in Markov model*

### 600mg dose level is irrelevant

The authors spend quite a lot of time considering 600 mg daily dose. While there are a number of articles published about this dose level, particularly in the early days of the use of imatinib in the treatment of GIST, this is no longer widely considered as distinct treatment alternative to either 400 mg or 800 mg and it has largely dropped out of use except in patients where dose escalation is thought indicated and the patient is unable to tolerate the 800mg dose due to toxicity or perhaps in patients whose dose is being carefully titrated with dose level monitoring.

### Quality of life is important comparing escalated imatinib with sunitinib

In figure 5 the relevant alternatives that need to be considered are: pathway 1 (I400 → BSC), pathway 5 (I400 → I800 → S → BSC) and pathway 7 (I400 → S → BSC). Where I400 = imatinib 400mg; I800 = Imatinib 800 mg and S = sunitinib.

An important consideration that has been ignored is the comparative quality of life of patients on sunitinib compared to imatinib at 800 mg daily. While it is true that no direct head to head comparative data exists, enough data have been reported in the trials of these two treatment options and a wealth of clinical experience from both clinicians and patients to support the premise that quality of life is superior on imatinib compared to sunitinib. It is a reasonable hypothesis that I400 → S and I400 → I800 → S may have equivalent survival benefit, but the latter is likely to be better in terms of quality of life. Given that I800 and S have almost identical drug costs, the use of escalated imatinib would therefore be more cost effective when quality of life is considered.

## Summary

In summary, we would recommend that the authors are asked to review their conclusions in the light of the data provided by the MetaGIST analysis and acknowledge the impact of mutation status and plasma level monitoring on the cost-effectiveness calculation. For simplicity, we suggest that they can delete further assessment of the 600mg dose level which is no longer widely used in clinical practice.

In our opinion, while we would not argue that there is currently no basis for using an escalated dose of imatinib for the majority of patients at treatment start, there are sub-groups of patients who may definitely benefit from the higher dose and this includes:

1. Patients with confirmed exon 9 mutation at treatment start
2. Patients with low plasma levels at disease progression
3. Patients with confirmed exon 9 mutations, or no detectable mutations, at progression where they have been started on the 400 mg dose

Furthermore, due to the favourable toxicity profile of imatinib compared to sunitinib and their equivalent drug cost, it is worth a trial of escalated imatinib prior to switch to sunitinib in the majority of patients who are not progressing rapidly at first detection of tumour progression on the 400mg does and this should certainly be considered (given the arguments above) in patients progressing on 400mg where mutation status and plasma levels are not known.

Finally, in the section on recommendations for further research we would encourage the authors to support further research into the impact of plasma level monitoring and tailoring of patient dose to get the optimal benefit from this drug.

Summary assessment of escalation

| | All patients | | Exon 11 | | Exon 9 | |
|---|---|---|---|---|---|---|
| Starting dose | Impact: | MetaGIST showed a significant improvement in PFS but no difference in OS | Impact: | MetaGIST showed no improvement in PFS or OS | Impact: | MetaGIST showed a significant improvement in PFS but difference in OS not statistically significant |
| | Degree: | PFS: HR 0.89 | Degree: | None | Degree: | Approx 1 year longer PFS (statistically significant). Approx 9 months longer OS (not statistically different |
| | Cost: | Not warranted. Starting dose should be 400mg when mutation status not known | Cost: | Not warranted. Starting dose should be 400mg when mutation status not known | Cost: | Not assessed. Has become standard practice in leading centres in USA and Europe |
| Primary resistance | No specific trial data assessing this sub-group, but one common reason for primary resistance in patients where mutation status is not known is that they have a non-exon 11 KIT mutation. It is therefore reasonable to infer that the results in exon 9 patients receiving a starting dose of 800 mg daily would apply | | | | | |
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| Secondary resistance | Impact: | Observational data on patients crossing over from 400mg to 800 mg in S0033 and EORTC 62005 show 29% - 33% regain tumour control | Impact: | While no direct data exist for this sub-group, our understanding is that the impact of escalation in patients with good plasma levels of imatinib is likely to be worse than the group taken as a whole.<br>However, in patients in whom treatment failure is associated with | Impact: | While no direct data exist for this sub-group, our understanding is that the impact of escalation is likely to be better than the group taken as a whole. |

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| | | | | unusually low plasma levels then there is a (much) higher chance of re-establishing disease control through dose escalation. In fact, this chance of this should approach the same chance as for initial therapy (i.e. 85%) | | |
| | Degree: | Median duration of response ~ 5- 6 months | Degree: | Normal plasma levels: probably none<br>Low plasma levels: more than 5 – 6 months | Degree: | Likely to be more than 5 – 6 months |
| | Cost: | Over £45,000 per QALY | Cost: | Normal plasma levels: more than £45,000 per QALY<br>Low plasma levels: less than £45,000 per QALY | Cost: | Likely to be less than £45,000 per QALY |

# References


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